Principles and Practice of Maternal Critical Care

Sharon Einav
Carolyn F. Weiniger
Ruth Landau
Editors

Springer

Principles and Practice of Maternal Critical Care

Sharon Einav • Carolyn F. Weiniger
Ruth Landau
Editors

Principles and Practice of Maternal Critical Care

Springer

Editors
Sharon Einav
Intensive Care Unit
Shaare Zedek Medical Center
and Hebrew University Faculty
of Medicine
Jerusalem
Israel

Ruth Landau
Department of Anesthesiology
Columbia University Medical Center
New York, NY
USA

Carolyn F. Weiniger
Division of Anesthesia
Critical Care and Pain
Tel Aviv Sourasky Medical Center
Tel Aviv
Israel

ISBN 978-3-030-43476-2 ISBN 978-3-030-43477-9 (eBook)
https://doi.org/10.1007/978-3-030-43477-9

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Foreword

I begin this foreword with a personal story. For 26 years of residency training and academic clinical practice, I provided care for high-risk obstetric patients at three major tertiary care academic medical centers. I took care of my fair share of complex obstetric patients, and I thought that I acquired reasonable expertise in the care of critically ill parturients. In 2005, I became the chief academic officer/associate medical school dean at a mid-sized, community-based academic medical center in a small upper Midwestern town. I continued to practice clinical anesthesiology as my schedule permitted, but the obstetric service was small, and it included mostly low-risk patients.

In 2014, I returned to my professional roots as a full-time obstetric anesthesiologist, and I became Chief of the Obstetric Anesthesia Division at Vanderbilt University Medical Center, which is the major high-risk obstetric referral center for a wide geographic area, and where we have almost 5000 deliveries each year. I naively thought that the transition would not be too difficult. I had done this type of work before, and surely, I thought, it would not be too challenging to do it again. But soon I was stunned and at times overwhelmed by the complexity and acuity of our high-risk obstetric population. As I discussed my experience with obstetric anesthesia colleagues around the country and abroad, I learned that this phenomenon was not unique to Vanderbilt. I have now concluded that the complexity of obstetric practice has drastically changed over the last two decades. Obstetric patients in developed countries have more complicated problems, are often sicker, and are more likely to require critical care than ever before. Sadly, maternal mortality has increased in some developed countries, especially the United States. Likewise, indices of maternal morbidity also reflect the escalating severity of maternal illness.

For these reasons, I was delighted to learn of the timely publication of this new textbook, which is focused on maternal critical care. The book is thoughtfully and skillfully edited by three prominent critical care medicine physicians and obstetric anesthesiologists. The chapters are written by a multidisciplinary group of anesthesiologists, critical care medicine (CCM) physicians, maternal–fetal medicine (MFM) physicians, pain medicine physicians, epidemiologists, and fetal pharmacology experts from around the globe, including Australia, Austria, Canada, Denmark, Finland, France, India, Ireland, Israel, Italy, Singapore, the United Kingdom, and the United States. By design, this book was written for a worldwide audience. All authors were asked to especially consider the care of the mother who is receiving care in an

intensive care unit (ICU) or who needs ICU care and is managed by CCM physicians as part of a multidisciplinary team. This book specifically focuses on the care of the critically ill mother, and the severe aspects of her disease or condition.

This book is designed for all healthcare professionals who provide care for critically ill pregnant (or recently pregnant) women. The content was included to help those physicians and other providers who infrequently take care of critically ill obstetric patients. Some chapters discuss the timing for surgery during pregnancy according to maternal needs, and what drugs may be safely given to pregnant women. The chapter on cardiac disease in pregnancy states that bridging therapy—given for fetal benefit—endangers mothers with a mechanical heart valve. The chapter on acute fatty liver of pregnancy emphasizes that the decision to deliver the baby is often life-saving for the mother. Likewise, the discussion of perimortem cesarean delivery emphasizes that this procedure is done not only to save the baby's life, but also as a critically important, often life-saving part of maternal resuscitation.

I want to add some personal editorial comments, as well as some suggestions for present and future training and clinical practice. First, not all sick parturients who need a higher level of care are admitted to an ICU. The American College of Obstetricians and Gynecologists [1] has stated that "some patients can be successfully monitored in an intermediate care unit … sometimes referred to as Obstetric Intermediate Care Units," ideally located as part of—or immediately adjacent to—the Labor and Delivery Unit. This unit may handle invasive monitoring, but typically does not provide mechanical ventilation. It helps reduce the frequency of moving sick laboring women far away from the preferred location of vaginal or cesarean delivery. Meanwhile, we badly need clinical validation of obstetric-specific screening tools that help identify what patients are likely to need an advanced level and location of ICU care (e.g., what mothers are at high risk for sepsis/septic shock and/or organ failure). This book includes a chapter dedicated to that subject, and the senior author of that chapter has developed a comorbidity index for use in obstetric patients [2]. Maternal early warning criteria have also been described; these criteria may need some refinement, and they need to be implemented more widely [3].

Second, we desperately need to improve both obstetrician and obstetric anesthesiologist training in CCM worldwide. At present in the United States, a 3-year MFM fellowship requires only one month of CCM training. In 2010, the American Board of Anesthesiology (ABA) and the American Board of Obstetrics and Gynecology (ABOG) began a partnership, so that ABOG diplomats could complete a 1-year anesthesiology CCM fellowship and then take the ABA CCM certification exam, and if successful, obtain certification in CCM. At the time of writing this foreword, a total of 10 ABOG diplomats have obtained CCM certification through this pathway [4]. The ABOG also has a partnership with the American Board of Surgery (ABS), and over the last three decades, approximately 16 ABOG diplomats have obtained certification in surgical critical care (SCC) from the ABS [5]. On the obstetric anesthesiology side, the ACGME-accredited obstetric anesthesiology fellowship program curriculum currently does not require a single month of CCM experience. In the future, I hope that more anesthesiology trainees will choose to

complete 2 years of fellowship training—1 year in obstetric anesthesia, and the second year in CCM. Approval of a pathway for subspecialty certification in obstetric anesthesia would then allow those physicians to obtain dual certification in both obstetric anesthesia and CCM. In the meantime, obstetric anesthesiologists and MFM physicians would do well to acquire expertise in new bedside diagnostic tools, such as point-of-care echocardiography and ultrasonography, whether performed on the Labor and Delivery Unit or in the ICU. These and other new assessment tools (e.g., minimally invasive cardiac output monitoring) need to be studied, validated, and refined for use in pregnant women.

Finally, given the shortage of CCM physicians in many places, consideration may be given to selected use of telemedicine to assist local physicians in the care of critically ill obstetric patients who cannot be transferred to a center with greater resources. Greater emphasis should be made on identifying those pregnant women who are at high risk for critical illness, so that advance preparations can be made to ensure that they receive peripartum care in centers with the resources needed to provide optimal care [6].

Notwithstanding the efforts to provide a higher level of maternal care on the Labor and Delivery Unit, it seems likely that an increasing number of critically pregnant women will require care from a multidisciplinary team in an ICU setting. This book was created with those patients in mind. I congratulate the editors and authors for preparing this comprehensive, resource-rich text. It should be accessible to all those who provide care for critically ill pregnant women.

David H. Chestnut
Division of Obstetric Anesthesiology
Vanderbilt University Medical Center
Nashville, TN, USA

References

1. American College of Obstetricians and Gynecologists. Critical care in pregnancy. ACOG technical bulletin no. 211. Obstet Gynecol. 2019;133:e303–19.
2. Bateman BT, Mhyre JM, Hernandez-Diaz S, et al. Development of a comorbidity index for use in obstetric patients. Obstet Gynecol. 2013;122:957–65.
3. Mhyre JM, D'Oria R, Hameed AB, et al. The maternal early warning criteria: a proposal from the National Partnership for Maternal Safety. Obstet Gynecol. 2014;124:782–6.
4. Personal communication, the American Board of Anesthesiology and the American Board of Obstetrics and Gynecology, 14 June 2019.
5. Personal communication, the American Board of Surgery and the American Board of Anesthesiology, 31 May 2019.
6. Clapp MA, James KE, Kaimal AJ. The effect of hospital acuity on severe maternal morbidity in high-risk patients. Am J Obstet Gynecol. 2018;219:111.e1–7.

Foreword

It is a privilege to have been asked to write the foreword for this textbook on maternal and obstetric critical care, edited by a leading authority in this field, Dr. Sharon Einav, co-edited by two experts in obstetric anesthesiology, Dr. Carolyn Weiniger and Dr. Ruth Landau, and written by an international team of almost 100 experts.

Maternal/obstetric critical care concerns only a relatively small minority of critically ill admissions overall although there is some evidence that demand for maternal/obstetric critical care is increasing, particularly in the developed world, in part related to the increasing numbers of older pregnant mothers with higher rates of comorbidities. This is a highly challenging population of patients, especially as conditions can be life-threatening not only for the mother but also for the child(ren) she carries. However, although much has been written about the critically ill neonate, there are few articles and even fewer textbooks dedicated to coverage of the critically ill mother, making this endeavor all the more impressive and important.

This comprehensive volume covers all aspects of maternal/obstetric critical care, from complications associated with early pregnancy, through to puerperal sepsis and postpartum hemorrhage. After the first section on epidemiology the editors have grouped chapters according to seven organ systems: the coagulation system, cardiovascular system, immune system, respiratory system, neuromuscular system, renal system, and endocrine and metabolic systems. There is a separate section on cardiac arrest during pregnancy, including ethical considerations, one on surgical considerations, and one on issues of medication and its complications. Importantly, the book includes chapters covering key challenges and relevant topics of particular current interest, including extracorporeal membrane oxygenation, viral infection, point-of-care ultrasound, and disaster management. The book finishes with a summary chapter on general aspects of intensive care for all pregnant ICU patients.

The topics covered in this comprehensive volume are important for all involved in taking care of obstetric patients and all responsible for the

management of acutely ill patients. I congratulate Dr. Einav for her initiative in drawing together this useful book on a very important subject that is poorly covered in the current literature.

Jean-Louis Vincent
Université Libre de Bruxelles
Brussels Belgium
Department of Intensive Care
Erasme University Hospital
Brussels Belgium

Preface

Pregnancy is viewed as joyous period, a time spent looking forward to good things to come. So when things go wrong during pregnancy, a chasm opens between expectations and reality. Unfortunately, this gap needs to be bridged by the treating physicians, not just the family. Awareness of this cognitive dissociation is a major step towards improved medical care of these women. Pregnant women can get critically ill. Pregnant women are still dying because of suboptimal medical care worldwide. This book, we hope, will be another step, among many being made around the world, to make pregnancy safer.

Creating this book was a challenge. Not for lack of willing authors. On the contrary—each and every one of the wonderful authors of this book immediately stepped up to the task and did so professionally and with grace. Creating a book is always a challenge, one would think. But creating this book entailed more than just the regular challenge of deciding on the table of contents and finding outstanding authors. This book on maternal critical care was a challenge because it required that each and every one of those contributing to this book undergo a paradigm shift in terms of how we view critically ill pregnant or peripartum women. It required that focus be shifted from the pregnancy to the woman carrying the pregnancy. And this was no simple task.

The chapters in this book underwent rigorous screening by the editors to ensure that the patient being discussed within always remains the woman, not her pregnancy. As a result, some of the chapters were written and then rewritten entirely. All of the chapters were revised several times. To our sorrow, two chapters had to be left out entirely. It was a slow process during which all of us, editors and authors together, not only created a book but also learned to change the way we think of our pregnant patients. The presence of a pregnancy distracts attention away from the woman carrying it, and it was our role to return the spotlight to the patient before us.

This book would never have come to fruition without the perseverance and constant support of my co-editors. My profound thanks to Carolyn Weiniger. Without her professional input, organizational skills, optimism, and tact, this book could never have been finished. I could not have chosen a better right-hand woman for making this ambitious project a reality. My thanks also go to Ruth Landau for her elegant writing, her ability to coax the best out of any text, and her ever tactful yet piercingly observant comments. To Nechama Kaufman for diligently checking and rechecking the references, dotting the i's and crossing the t's. Nechama—your hard work, candid comments, insightful ideas, and (brilliant) English edits are invaluable. But most invaluable is your

friendship. To Liat Lerner-Geva and her team at the Gertner Institute who hosted me graciously for the (too brief) sabbatical of 3 months that gave this book the initial push it needed. They not only gave me place in their offices but also a place on their team. To Andrea Ridolfi from Springer—who proposed this textbook after hearing me lecture on maternal intensive care in Brussels. To all of the authors, who kindly bore our comments and generously found the time and invested the effort required to create this book from nothing.

I also owe my mother—who talked me through the difficult periods that occurred during the creation of this book. Dear mom: thanks for telling me that I am a scion of generations of midwives many years after I finished my medical training and found an interest in this specific topic in intensive care. With you a teacher and dad an engineer, I thought my being a doctor (and one interested in maternity to boot) is original… Well, it turns out it was in my genes all along.

My greatest thanks however to my daughters—who grew up with a mother that spends more time with her laptop than with her children. Ron, the best feedback I ever received regarding my work was on the day you told me you never resented it because you understood its importance. So to my beloved Ron, Gal, and Shai—this book is dedicated to you. May you never benefit from it in any way other than a means of taking some pride in your mother.

Jerusalem, Israel Sharon Einav

Preface

"But she's pregnant" is heard so often, when a woman carrying a fetus presents for medical care that is not directly related to the pregnancy. This mantra leads to refused, reduced, delayed, and even missed care for the critically ill pregnant woman. Our concern for the fetus may override our concern for the woman. Writing this book was not simple, as all authors and we, the editors too needed to reevaluate the standard approach of mother and fetus, and focus on the care for the mother. It is my hope that when faced with a critically ill pregnant woman, readers of this book will not be drawn magnetically to the uterus and the magical life-form growing inside it, but focus instead on the woman herself.

I am grateful to my wonderful and supportive family, Paul, Shahar, Ariel, Libi, and Elinor for tolerating my disappearance to work on all those little projects that never seem to end. Thank you for your love and laughs.

Tel Aviv, Israel — Carolyn F. Weiniger

Preface

This book is the culminating result of a vision to optimize care for the growing body of sickest women before, during, and immediately after childbirth.

How could one create recommendations on maternal critical care when best practices most often have not yet been established? Each chapter is the product of meaningful discussions between us, authors and editors, and incorporates evidence-based and expert-opinion tactics. We hope to help save one woman at a time, around the world.

I would like to thank my husband, Alex, for his ever support, and Mya, for inspiring me to be a better mom every day.

New York, NY, USA Ruth Landau

Contents

Contributors

Gillian Abir Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, CA, USA

Avraham Abutbul Medical Intensive Care Unit, Hadassah-Hebrew University Medical Centre, Jerusalem, Israel

Arash Afshari Department of Anaesthesia, Copenhagen University Hospital Rigshospitalet, Juliane Marie Centret, Copenhagen, Denmark

Cande V. Ananth Division of Epidemiology and Biostatistics, Department of Obstetrics, Gynecology, and Reproductive Sciences, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA

Cardiovascular Institute of New Jersey, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA

Environmental and Occupational Health Sciences Institute (EOHSI), Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA

Department of Biostatistics and Epidemiology, Rutgers School of Public Health, New Brunswick, NJ, USA

Rosaleen Baruah NHS Lothian, Edinburgh, UK

Brian T. Bateman Department of Anesthesiology, Perioperative, and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Itai Bendavid Department of General Intensive Care and Institute for Nutrition Research, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel

Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

Federico Bilotta Neurocritical Care Unit, Addenbrookes Hospital, Cambridge, UK

Department of Neuroanaesthesia, University La Sapienza, Rome, Italy

Intensive Care Unit, Policlinico San Martino, Genova, Italy

Evgeni Brotfain Department of Anesthesiology and Critical Care, Soroka Medical Center, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Erin J. Ciampa Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Benjamin Cobb Department of Anesthesiology, University of North Carolina, Chapel Hill, NC, USA

Yitzhak Cohen Post Anesthesia Care Unit, Chaim Sheba Medical Center, Tel Hashomer, Israel

Faculty of Medicine, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv-Yafo, Israel

Andreea A. Creanga Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Department of Gynecology and Obstetrics, Johns Hopkins School of Medicine, Baltimore, MD, USA

Tim M. Crozier, MBBS, FRACP, FCICM, MPH Intensive Care Unit, Monash Medical Centre, Monash Health, Clayton, VIC, Australia

Kay Daniels Department of Obstetrics and Gynecology, Stanford University School of Medicine, Stanford, CA, USA

Nicola M. Dobos, MBBS, MPH, FCICM Intensive Care Unit, Western Health, Melbourne, VIC, Australia

Gary Duclos Department of Anesthesiology and Intensive Care Medicine, Aix Marseille Université, Assistance Publique Hôpitaux de Marseille, North Hospital, Marseille, France

Chundamannil Eapen Eapen Hepatology Department, Christian Medical College, Vellore, Tamil Nadu, India

Sarah Rae Easter Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Sharon Einav Intensive Care Unit, Shaare Zedek Medical Center and Hebrew University Faculty of Medicine, Jerusalem, Israel

Kim Ekelund Department of Anaesthesia, Copenhagen University Hospital Rigshospitalet, Juliane Marie Centret, Copenhagen, Denmark

Emma Roche-Kelly Department of Intensive Care, King's College NHS Foundation Hospital, London, UK

Lui G. Forni Department of Intensive Care Medicine, Royal Surrey County Hospital NHS Foundation Trust, Guildford, UK

Department of Clinical & Experimental Medicine, Faculty of Health Sciences, University of Surrey, Guildford, UK

Surrey Peri-Operative Anaesthesia and Critical Care Collaborative Research Group (SPACER), Guildford, UK

Alexander M. Friedman Department of Obstetrics and Gynecology, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY, USA

Ashish Goel Hepatology Department, Christian Medical College, Vellore, Tamil Nadu, India

Sorina Grisaru-Granovsky Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Shaare Zedek Medical Center, Hebrew University Jerusalem, Jerusalem, Israel

Christophe Guervilly Aix-Marseille Univ, APHM, URMITE UMR CNRS 7278, Hôpital Nord, Réanimation des Détresses Respiratoires et Infections sévères, Marseille, France

Malik Haddam Department of Anesthesiology and Intensive Care Medicine, Aix Marseille Université, Assistance Publique Hôpitaux de Marseille, North Hospital, Marseille, France

Elsje Harker Department of Anesthesiology, University of North Carolina, Chapel Hill, NC, USA

Philip E. Hess Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Raghad A. Hussein Department of Critical Care Medicine, Geisinger Medical Center, Danville, PA, USA

Alexander Izakson Department of Anesthesia and Operating Rooms, Ziv Medical Center, Safed, Israel

Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel

Davinder S. Jassal Section of Cardiology, Department of Internal Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada

Nechama Kaufman Department of Emergency Medicine, Shaare Zedek Medical Center, Jerusalem, Israel

Moti Klein Department of Anesthesiology and Critical Care, Soroka Medical Center, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Ruth Landau Department of Anesthesiology, Columbia University Medical Center, New York, NY, USA

Stephen Earl Lapinsky Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, ON, Canada

Mount Sinai Hospital, Toronto, ON, Canada

Lisa Leffert Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, MA, USA

Marc Leone Department of Anesthesiology and Intensive Care Medicine, Aix Marseille Université, Assistance Publique Hôpitaux de Marseille, North Hospital, Marseille, France

Nadav Levy Division of Anesthesiology, Critical Care and Pain Medicine, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA

Shuangbo Liu Section of Cardiology, Department of Internal Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada

D. N. Lucas London North West University, Healthcare NHS Trust, London, UK

Marlies Ostermann Department of Intensive Care, King's College London, Guy's & St Thomas' NHS Foundation Hospital, London, UK

Ignacio Martin-Loeches St James's Hospital, Dublin, Ireland

Ryan C. Maves Infectious Diseases Division, Naval Medical Center, San Diego, CA, USA

Critical Care Medicine Service, Naval Medical Center, San Diego, CA, USA

Uniformed Services University, Bethesda, MD, USA

Paul McConnell Anaesthesia and Intensive Care Medicine, Royal Alexandra Hospital, Paisley, UK

Claire McLintock, ONZM, MB, ChB, FRACP, FRCPA National Women's Health, Auckland City Hospital, Auckland, New Zealand

Marie-Louise Meng Department of Anesthesiology, Columbia University Medical Center, New York, NY, USA

Eliza Cushman Miller Department of Neurology, Division of Stroke and Cerebrovascular Disease, Columbia University College of Physicians and Surgeons, New York, NY, USA

Orsolya Miskolci St Georges University Hospital, London, UK

Vivek Kumar Moitra Division of Critical Care Medicine, Department of Anesthesiology, College of Physicians and Surgeons of Columbia University, New York, NY, USA

Morten Hylander Møller Department of Intensive Care, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark

Deirdre Morley Department of Genito Urinary Medicine and Infectious Diseases, St James Hospital, Dublin, Ireland

Leslie Moroz Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, New York Presbyterian/Columbia University Medical Center, New York, NY, USA

K. J. Murray London North West University, Healthcare NHS Trust, London, UK

Bhaskar Narayan NHS Health Education England, London, UK

Cathy Nelson-Piercy Guy's and St Thomas' NHS Foundation Trust, London, UK

Amiram Nir Pediatric Cardiology and Adult Congenital Heart Disease, Shaare Zedek Medical Center, Jerusalem, Israel

Asher Ornoy Laboratory of Teratology, Department of Medical Neurobiology, Canada-Israel Medical Research Institute, Hebrew University Hadassah Medical School, Jerusalem, Israel

Cesar Padilla Department of Anesthesiology, Perioperative, and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Laurent Papazian Aix-Marseille Univ, APHM, URMITE UMR CNRS 7278, Hôpital Nord, Réanimation des Détresses Respiratoires et Infections sévères, Marseille, France

Samir N. Patel Englewood Health, Englewood, NJ, USA

Laura Peltola Department of Anaesthesia, Queen Charlotte's & Chelsea Hospital, London, UK

Jonathan D. Perez Department of Critical Care Medicine, Medical Center Navicent Health, Macon, GA, USA

Felicity Plaat Department of Anaesthesia, Queen Charlotte's & Chelsea Hospital, London, UK

Romain Rambaud Aix-Marseille Univ, APHM, URMITE UMR CNRS 7278, Hôpital Nord, Réanimation des Détresses Respiratoires et Infections sévères, Marseille, France

Mary Jane Reed Department of Critical Care Medicine and Surgery, Geisnger Medical Center, Danville, PA, USA

Elena Reitman Department of Anesthesiology, Columbia University Medical Center, New York, NY, USA

Philippe Richebé Department of Anesthesiology of Maisonneuve-Rosemont Hospital, CIUSSS de l'Est de l'Ile de Montréal, University of Montréal, Montréal, QC, Canada

Chiara Robba Neurocritical Care Unit, Addenbrookes Hospital, Cambridge, UK

Department of Neuroanaesthesia, University La Sapienza, Rome, Italy

Intensive Care Unit, Policlinico San Martino, Genova, Italy

Misgav Rottenstreich Department of Obstetrics and Gynecology, Shaare Zedek Medical Center in Jerusalem, Hebrew University School of Medicine, Jerusalem, Israel

Rachel Savine Department of Intensive Care Medicine, Royal Surrey County Hospital NHS Foundation Trust, Guildford, UK

Hen Y. Sela Department of Obstetrics and Gynecology, Shaare Zedek Medical Center in Jerusalem, Hebrew University School of Medicine, Jerusalem, Israel

Aryeh Shander Department of Anesthesiology, Critical Care Medicine, Hyperbaric Medicine and Pain Management, Englewood, NJ, USA

Team Health Research Institute, Englewood, NJ, USA

Department of Anesthesiology, Medicine and Surgery at Icahn School of Medicine, Mount Sinai, New York, NY, USA

Department of Anesthesiology at Rutgers New Jersey Medical School, Newark, NJ, USA

Henry Shapiro Department of Neurosurgery, Shaare Zedek Medical Center, Jerusalem, Israel

Pierre Singer Department of General Intensive Care and Institute for Nutrition Research, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel

Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

Markus B. Skrifvars Department of Emergency Care and Services, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

Joseph L. Smith Department of Critical Care Medicine and Infectious Disease, Geisinger Medical Center, Danville, PA, USA

Valeria Spennati Neurocritical Care Unit, Addenbrookes Hospital, Cambridge, UK

Department of Neuroanaesthesia, University La Sapienza, Rome, Italy

Intensive Care Unit, Policlinico San Martino, Genova, Italy

Robert Strony Geisinger Commonwealth School of Medicine, Danville, PA, USA

Lewis Katz School of Medicine Temple University, Philadelphia, PA, USA

Geisinger Health System, Danville, PA, USA

Subramani Kandasamy Surgical Intensive Care Department, Christian Medical College, Vellore, Tamil Nadu, India

Arvind Kalyan Sundaram Department of Clinical Science (Education), Geisinger Commonwealth School of Medicine, Geisinger Medical Center, Danville, PA, USA

Sigal Sviri Medical Intensive Care Unit, Hadassah-Hebrew University Medical Centre, Jerusalem, Israel

Wendy H. Teoh Private Anaesthesia Practice, Wendy Teoh Pte. Ltd., Singapore, Singapore

College of Anaesthesiologists Singapore, Singapore, Singapore

Singapore Society of Anaesthesiologist's Airway Special Interest Group, Singapore, Singapore

Julien Viau-Lapointe Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, ON, Canada

Hôpital Maisonneuve-Rosemont, University of Montreal, Montreal, QC, Canada

Carolyn F. Weiniger Division of Anesthesia, Critical Care and Pain, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

Valerie Zaphiratos Department of Anesthesiology of Maisonneuve-Rosemont Hospital, CIUSSS de l'Est de l'Ile de Montréal, University of Montréal, Montréal, QC, Canada

Carolyn M. Zelop The Valley Hospital, Ridgewood, NJ, USA

NYU School of Medicine, New York, NY, USA

Laurent Zieleskiewicz Department of Anesthesiology and Intensive Care Medicine, Aix Marseille Université, Assistance Publique Hôpitaux de Marseille, North Hospital, Marseille, France

Alexander Zlotnik Department of Anesthesiology and Critical Care, Soroka Medical Center, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Part I

Epidemiology

1 Maternal Deaths in Developed Countries: Epidemiology and Preventable Causes

Alexander M. Friedman and Cande V. Ananth

Bullet Points

- Maternal mortality from obstetrical hemorrhage and hypertensive diseases of pregnancy may be preventable in a majority of cases.
- Cardiovascular and non-cardiovascular causes are responsible for a growing proportion of maternal mortality.
- Reduction of mortality risk from medical causes may be dependent on multidisciplinary coordinated care on an outpatient, inpatient, and preconception basis.
- Maternal deaths solely attributable to complications with anesthesia are rare.
- Early warnings systems may facilitate early identification of women with sepsis and impending critical illness.

1.1 Introduction

The profile of maternal mortality has changed substantially over the past three decades in the United States, Europe, Australia, and New Zealand. Deaths from hemorrhage have declined, while risks associated with cardiovascular and non-cardiovascular medical complications have increased substantially [1–7]. Pregnancy-related hypertensive diseases, stroke, sepsis, and venous thromboembolism remain the leading causes of maternal death. These trends have contributed to a maternal mortality rate that in the United States is either stable or rising and limited reduction of maternal mortality risk in other countries.

This chapter reviews the epidemiology of maternal mortality in the United States, the United Kingdom and Ireland, France, Australia, the Netherlands, Scandinavia, and New Zealand, with a description of its incidence, temporal

A. M. Friedman
Department of Obstetrics and Gynecology, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY, USA

C. V. Ananth (✉)
Division of Epidemiology and Biostatistics, Department of Obstetrics, Gynecology, and Reproductive Sciences, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA

Cardiovascular Institute of New Jersey, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA

Environmental and Occupational Health Sciences Institute (EOHSI), Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA

Department of Biostatistics and Epidemiology, Rutgers School of Public Health, New Brunswick, NJ, USA
e-mail: ananthcv@rwjms.rutgers.edu

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_1

trends, and risk factors. Included in this review is an overview of reported preventable causes of maternal deaths from the ten leading causes of maternal mortality as identified by the Centers for Disease Control and Prevention (CDC) (Box 1.1). Data from several sources are presented: (1) reports from the United Kingdom's (UK) Confidential Enquiry into Maternal Death [2, 4–7]; (2) findings from United States (US) state-level maternal mortality reviews [1, 8], as well as the Hospital Corporation of America (HCA) [9, 10]; and (3) maternal death reviews from France, the Netherlands, Australia, Scandinavia, and New Zealand [11–14]. The focus of this chapter is on maternal death in high-resource settings and differs significantly from a global view of preventable maternal mortality that includes low- and medium-resource settings, which can be found elsewhere [15].

1.2 Epidemiology of Maternal Mortality

Maternal mortality does not have a homogeneous definition in the literature. It has been defined as death occurring during pregnancy, childbirth, or the postpartum period, [16] as well as deaths as those occurring within 42 days of the end of pregnancy. However, varying maternal death criteria, including different time intervals, up to 1 year postpartum, may be included, thus affecting reported maternal risk. In many reviews, including those from the United Kingdom [4], maternal deaths are classified as direct versus indirect; the former resulting from obstetrical complications and the latter resulting from underlying disease aggravated by pregnancy. Coincidental maternal deaths may be defined as deaths from unrelated causes which occur in pregnancy such as trauma. Late deaths are often classified as those occurring from >42 days up to 1 year after the end of pregnancy [17]. The World Health Organization (WHO) classifies all deaths occurring within 42 days of delivery or termination of pregnancy as maternal deaths but excludes those attributable to incidental causes (i.e., seemingly unrelated to the pregnancy such as trauma or non-puerperal sepsis). The CDC defines a "pregnancy-related death" as the death of a woman while pregnant or within 1 year of pregnancy termination—regardless of the duration or site of the pregnancy—from any cause related to or aggravated by the pregnancy or its management and also excludes accidental or incidental causes [18]. Additionally, ascertainment of maternal death differs significantly by country which may affect reporting. For example, in the United States reporting of death by the CDC is based in part on administrative data [1], whereas in the United Kingdom, in-depth maternal depth reviews are performed [4]. When data is collected by dedicated maternal death review systems, the maternal mortality rate is generally found to be higher than by using administrative data alone [5, 14].

1.2.1 Incidence and Trends of Maternal Mortality

The maternal mortality ratio (MMR) per 100,000 births in developed countries has undergone decline since the turn of the twentieth century when in the United States close to 1% of births resulted in maternal death (Fig. 1.1). However, in more recent decades the CDC's Pregnancy-Related Mortality Surveillance System (PMSS) demonstrated an increase in the MMR from 7.2/100,000 live births in 1986, the first year the system was implemented, to 17.8/100,000 live births in 2009, with consistently high MMRs ranging from 15.9 to 17.4 from 2010 through 2018 [19]. While some of this increase has been attributed to improved case identification, a real increase in maternal risk in the United States appears likely [1, 18–20]. Data from other countries regarding increasing risk varies. The United Kingdom similarly demonstrated possible increases in maternal mortality from the 1980s to the 2000s followed by a recent decline [4]. Other countries such as Australia and France have demonstrated stable mortality risk over recent years [11, 13]. In the Netherlands, maternal mortality appeared to increase from 1983–1992 to 1993–2005 [12].

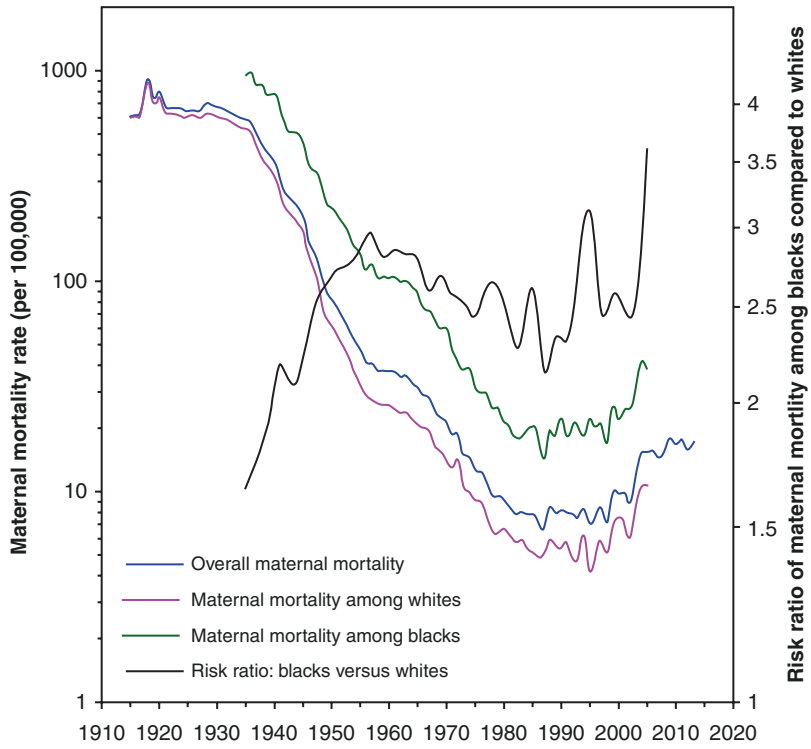


Fig. 1.1 Maternal mortality rates in the United States since the turn of the twentieth century. In the United States, the maternal mortality ratio (per 100,000) has declined since the turn of the century; it was close to 1000 per 100,000 births (or 1%) in 1910–1920 and has sharply declined since. While the mortality ratio showed a strong temporal decline overall, the decline was disproportionate between black and white women. Although the maternal mortality ratio has been consistently higher among black than in white women, the risk ratio of maternal mortality among black women actually increased sharply from 1930 to 1960 (from about 1.6 to 3.0). Thereafter, the risk ratio declined to a nadir of 2.1 up to 1990, but more recent data shows an increase in the risk ratio. These data underscore the persistent black-white race disparity in maternal mortality ratios in the United States

1.2.2 Risk Factors for Maternal Deaths

Disparities based on race, ethnicity, and national origin may play an important role in increased mortality risk [14, 21]. In the United States, racial disparities are likely an important factor in increasing maternal mortality rates (Fig. 1.2). In a report on maternal deaths from 2006 to 2010, the CDC demonstrated an MMR for black women 40 or older approaching 150/100,000 live births [8]. Recent data from the United Kingdom show substantial disparities in maternal mortality rates across different ethnic, age, and socioeconomic groups [22]. For instance, there was a widening of the disparity in maternal mortality rates between black and white women (RR 2.59 in 2009–2011 compared with 5.27 in 2015–2017, ratio of the relative risks 2.03, 95% CI 1.11, 3.72) [22]. In a review of deaths in New Zealand from 2006 to 2015, Maori and Pacific mothers were found to have twice the mortality risk of women of European origin [14]. In France, after adjusting for risk factors, odds of maternal death were more than 5 times higher for women of sub-Saharan African nationality compared to French women, and more than 3 times higher for women from Asia, North America, and South America [11]. In the Netherlands, nonwestern immigrant populations had an increased risk for maternal mortality [12].

The risk profile for maternal death has changed significantly over the last three decades. While incidences of direct obstetric conditions such as

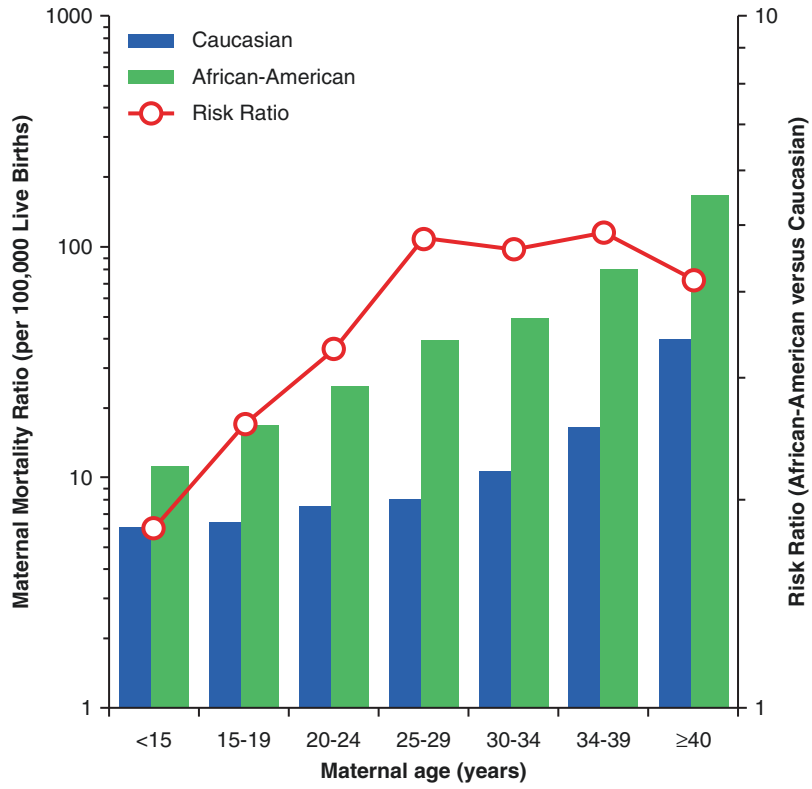


Fig. 1.2 Maternal mortality ratio among black and white women by maternal age and risk ratio of mortality among black compared to white women. Mortality rates for black versus white women, by maternal age with the red line representing the risk ratio for mortality, depicted on axis on the right. Maternal mortality ratios are generally 3- to 4-fold higher for black women than white women

obstetrical hemorrhage and preeclampsia—historical leading causes of maternal death—are rising, these conditions are resulting in death less frequently. In the United Kingdom in the 1980s, direct maternal deaths due to pregnancy-specific causes accounted for approximately 60% of overall maternal deaths. By 2009–2014, direct causes accounted for less than one third of maternal deaths, with indirect causes accounting for the remaining two thirds [4]. These data are in sharp contrast to those in the United States: in 2018, the direct causes accounted for 77.4% of all maternal deaths (and 22.6% attributable to indirect causes) [19].

In the United States during the most recent maternal mortality reporting period 2011–2016, hypertensive disorders and hemorrhage accounted for 17.9% of maternal deaths combined, with cardiovascular disease (15.7%), other medical non-cardiovascular (13.9%), and infection/sepsis (12.5%) the three new leading causes of maternal death [1, 18, 19]. In comparison, from 1987 to 1990 hemorrhage and hypertensive disorders of pregnancy accounted for 34.1% of maternal deaths with medical conditions accounting for only 18.2% of deaths [23]. Maternal death reports from other countries have demonstrated indirect maternal deaths to represent large portions of overall maternal death including Denmark (50.0%) [17], France (30.8%) [11], New Zealand (61.0%) [14], and Australia (47.5%) [13].

1.3 Leading Causes of Preventable Maternal Deaths

The CDC lists ten leading causes that accounted for 93.6% of maternal deaths from 2011 to 2016 in the United States (Box 1.1) [1, 19]. Mortality reviews from other countries categorize maternal deaths similarly. While reports vary by country regarding the proportionate role of individual causes of maternal mortality, there are commonalities with regard to preventability,

Box 1.1 Leading Causes of Maternal Death in the United States 2011–2016

1. Cardiovascular disease (15.7%)
2. Other medical non-cardiovascular disease (13.9%)
3. Infection/sepsis (12.5%)
4. Hemorrhage (11.0%)
5. Cardiomyopathy (11.0%)
6. Thrombotic pulmonary embolism (9.0%)
7. Cerebrovascular accidents (7.7%)
8. Hypertensive disorders of pregnancy (6.9%)
9. Amniotic fluid embolism (5.6%)
10. Anesthesia complications (0.3%)
11. Unknown cause (6.4%)

with hemorrhage deaths most often classified as preventable, and deaths from amniotic fluid embolism classified as least likely to be preventable.

Determining the preventability of maternal deaths involves multiple challenges. First, the degree to which a death may have been preventable is a qualitative judgment that is to some degree subjective [9]. Second, in scenarios where preventability of maternal death can be objectively assessed, criteria for what is appropriate care are in flux and a matter of debate for many leading causes of maternal mortality. For example, recommendations for appropriate VTE prophylaxis differ significantly between major societies [24, 25]. Third, in-depth maternal mortality reviews involve considerable resource utilization. While some countries have a nationwide means of investigating the preventability of maternal deaths comparable to the United Kingdom's Confidential Enquiries, others such as the CDC's PMSS rely on vital statistics data precluding determining the degree which deaths are preventable [1, 26]. Given that city, state, and regional maternal death review committees are proliferating in the United States, a more granular national picture of preventability may become available in the near future. Overall, reported preventability ranged from half of French maternal deaths [11], up to 49% of deaths in Australia [13], up to 30% of deaths in Denmark [17], 38% of deaths in California [27], 40% of deaths in North Carolina [28], and 21% of deaths in New York State [29]. A review of deaths from the Netherlands found that in 55% of cases, substandard care was provided [12].

1.3.1 Cardiovascular Disease and Cardiomyopathy

Cardiovascular conditions represent an increasing cause of maternal deaths over recent decades both absolutely and proportionately [1]. The ability to improve outcomes for women with these conditions will be a major determinant in overall maternal mortality trends.

From 2006 to 2008, the 2011 UK Confidential Enquiries report found 53 women died of heart disease associated with or aggravated by pregnancy. Care was substandard in 27 of the 53 deaths, and in 13 deaths the outcome may have been preventable. Substandard care included not recognizing symptoms and signs of myocardial infarction and aortic dissection, and not optimizing and coordinating care prepregnancy and early in pregnancy [2]. The California Pregnancy-Associated Mortality Review found that for 19 deaths that occurred because of cardiomyopathy and other cardiac causes, seven (37%) deaths would have had a good chance of being prevented with improvements in care [30]. A review of pregnancy-related mortality in North Carolina found that 22% of deaths related to cardiomyopathy and 40% of deaths related to other cardiovascular conditions were preventable [28]. In comparison, none of the ten cardiac deaths in the HCA cohort were deemed preventable [9].

To prevent cardiac mortality, the UK Confidential Enquiries report includes the following recommendations: (1) co-location of and close co-management by obstetric and cardiac specialists for women with known cardiac disease, (2) early involvement of team involving cardiac and obstetric specialists particularly when a patient presents emergently, and (3) thorough evaluation and diagnostic testing for

patients with concerning symptoms or physical exam findings and abnormal vital sign parameters are present [4].

1.3.2 Other Medical Non-cardiovascular Disease

Non-cardiovascular diseases represent a rising, heterogeneous, and often preventable cause of maternal death. The 2014 UK Confidential Enquiries report detailed 10 deaths attributable to respiratory disease, 10 deaths due to liver disease, 10 deaths due to diabetes, 2 deaths due to lupus, 4 deaths due to hematological disorders, and 3 women who died from intra-abdominal aneurysm rupture over a 4-year period [5]. In some cases, deaths were preventable either by improved, coordinated care early in pregnancy or by more timely and appropriate diagnosis of acute complications. The preceding 2011 report also demonstrated a heterogeneous group of conditions with opportunities for care improvement with earlier diagnosis and improvements in care coordination [2]. The CDC PMSS demonstrated medical non-cardiovascular diseases to be an increasing cause of maternal mortality over recent decades and a major determinant of overall mortality trends [1]. A review of pregnancy-related mortality in North Carolina found that 89% of deaths related to chronic medical conditions were preventable [28]. Many of these deaths could have been prevented with appropriate preconception care.

While clinical heterogeneity to some degree precludes specific management recommendations to avoid mortality, the 2017 UK Confidential Enquiries makes the following recommendations reducing risk from medical complications: (1) women with significant medical preexisting conditions should undergo prepregnancy counseling by doctors with experience in managing their disorder in pregnancy and have access to specialist contraceptive services, (2) transfer to facilities with critical care capabilities should be expedited if indicated, and (3) postpartum care for women with medical conditions should be carefully coordinated [6].

1.3.3 Infection and Sepsis

A significant proportion of maternal mortality from sepsis may be preventable. In a review of 26 deaths related to sepsis, the 2011 UK Confidential Enquiries report found that death might have been averted in 12 cases if infection had been diagnosed and treated more promptly [2]. The 2014 iteration of the UK Confidential Enquiries report found major concerns with sepsis and infectious management to be related to delays in diagnoses, prompt administration of appropriate antibiotics, timely identification of clinical deterioration, and communication shortcomings [5]. The 2017 UK Confidential Enquiries role found that maternal death from influenza decreased substantially from 2009 to 2011, and from 2012 to 2015, one woman died from influenza. Of the 23 women who died from sepsis during this later period (2012–2015), 4 women died from urinary tract sepsis or wound infections following cesarean, 7 from genital tract sepsis, and 12 women died from other causes of infection, 9 of whom died between 6 weeks and 1 year after pregnancy. Of the three women who died within 6 weeks postpartum, one died from pneumococcal meningitis, one from pneumonia, and one from clostridium difficile infections [6]. The California Pregnancy-Associated Mortality Review found that for 8 deaths that occurred because of infection/sepsis, 5 (63%) deaths would have had a good chance of being prevented with improvements in care [27]. Review of deaths within the HCA determined that 1 of 14 of deaths related to infection were preventable [9]. A review of pregnancy-related mortality in North Carolina found that 43% of deaths related to infection were preventable [28].

Identification of women at risk for critical illness from sepsis may be possible by evaluating abnormal vital signs (maternal early warnings scoring systems) and providing timely intervention. The 2017 UK Confidential Enquiries report recommends the following to reduce maternal risk from infection: (1) evaluate risk based on maternal early warnings score; (2) timely initiation of critical care; and (3) identifying patients at risk for sepsis such as those with immunosuppression or chronic disease [5, 6, 31].

1.3.4 Obstetrical Hemorrhage

Obstetrical hemorrhage is cited as one of the most frequently preventable causes of maternal death. Many cases involved inadequate monitoring, failure to escalate care in the setting of abnormal vital signs, communication problems, suboptimal coordination with consultants, and lack of timely involvement of senior clinicians. The 2011 UK Confidential Enquiries report substandard care was a factor in 66% of maternal deaths from hemorrhage from 2006 to 2008 [2]. The following UK Confidential Enquiries report (2009–2012) reviewed direct maternal deaths due to obstetrical hemorrhage and found that both provider and systems issues were implicated in maternal deaths [5]. Severity of hemorrhage was not recognized in 61% of deaths. The California Pregnancy-Associated Mortality Review found that for 10 deaths that occurred because of hemorrhage, 7 deaths would have had a good chance of being prevented with improvements in care [27]. Review of deaths within the HCA determined that 8 of 11 (72.7%) of deaths related to hemorrhage were preventable [9]. A review of pregnancy-related mortality in North Carolina found that 93% of deaths related to hemorrhage were preventable [28].

Most surgical and medical strategies for prevention of hemorrhage and optimizing maternal outcomes during and after massive hemorrhage have yet to be elucidated in the obstetric population (see also Chaps. 5 and 6).

1.3.5 Thrombotic Pulmonary Embolism

The 2011 Confidential Enquiries reviewed 18 thrombosis or thromboembolism deaths (2 from cerebral vein thrombosis and 16 from pulmonary embolism) from 2006 to 2008 and found substandard care in 56% of cases [2]. Poor quality care involved inadequate risk assessment, inadequate thromboprophylaxis (seven women), and failure to investigate chest symptoms (six women). The California Pregnancy-Associated Mortality Review found that for eight deaths that occurred because of thromboembolism, three deaths would have had a good chance of being prevented with improvements in care [27]. A review of pregnancy-related mortality in North Carolina found that 17% of deaths related to thromboembolism were preventable [28]. Review of deaths within the HCA determined that zero of nine deaths related to pulmonary embolism were preventable; however, this assessment was performed prior to recommendations supporting broader thromboprophylaxis strategies [9, 10].

There are two primary means by which death from thrombotic pulmonary embolism (PE) can be prevented: (1) use of venous thromboembolism (VTE) prophylaxis and (2) timely identification and treatment of acute VTE events. Because shortness of breath, other respiratory symptoms, and tachycardia related to pregnancy are common and may be difficult to differentiate from symptoms related to PE, systematic improvement in VTE prophylaxis may represent the best means of reducing population-based maternal death risk from VTE. Use of perioperative cesarean mechanical prophylaxis is supported by a large case series from the HCA in which universal use of pneumatic compression devices for all women undergoing cesarean delivery resulted in a statistically significant reduction of pulmonary embolism deaths from 7 in 458,097 prior to implementation to 1 in 465,880 after implementation [9, 10].

Data from the United Kingdom demonstrates success in reducing deaths from VTE that may be related to aggressive pharmacologic thromboprophylaxis advocated by RCOG recommendations released in 2004 [26, 32]. Maternal deaths from VTE in the United Kingdom decreased by more than half, from 1.94 maternal deaths per 100,000 deliveries in 2003–2005 to 0.79 maternal deaths per 100,000 in 2006–2008 [2]. Subsequent iterations of the Confidential Enquiries report have also demonstrated decreased risk for death from thromboembolism in comparison to triennial periods preceding the release of the initial 2004 thromboembolism guidelines that made recommendations for expanded risk factor-based prophylaxis [4–7].

1.3.6 Hypertensive Disorders of Pregnancy and Cerebrovascular Accidents

Overall, maternal death reviews support that a significant proportion of maternal mortality from hypertensive disorders of pregnancy is preventable via timely administration of antihypertensive medications.

In a review of direct maternal deaths due to hypertensive diseases of pregnancy, the 2011 UK Confidential Enquiries report found that 22 women died, 14 from intracranial hemorrhage and 5 from anoxia following cardiac arrest in association with eclamptic seizures [2]. Overall, substandard care was present in 20 of 22 cases and in 14 cases this was classified as "major." The cases of intracranial deaths were found to be secondary to inadequate administration of antihypertensive therapy. Data from California's maternal mortality review found that 60% of deaths (9 of 15) had a strong or good chance of being averted with improved care [27].

A review of deaths within the HCA from 2000 to 2006 determined that 5 of 15 (33.3%) deaths related to complications of preeclampsia were preventable [9, 10]. However, a subsequent post-intervention analysis of an antihypertensive protocol found that only three deaths occurred post implementation over a subsequent 6-year period suggesting that a larger proportion of hypertension-related stroke deaths might be averted [9, 10]. A review of pregnancy-related mortality in North Carolina found that 60% of deaths related to pregnancy-induced hypertension were preventable, while none of the cases of stroke were considered to be preventable [28].

1.3.7 Amniotic Fluid Embolism

Deaths from amniotic fluid embolism (AFE) are most difficult to prevent. AFE deaths occur despite prompt resuscitation, treatment of cardiac arrhythmias, intensive care unit care, and transfusion to counteract coagulopathy. This makes determination of AFE preventability also challenging [33].

The UK Confidential Enquiries review of direct maternal deaths due to amniotic fluid embolism from 2006 to 2008 reviewed 13 cases of AFE. The authors identified substandard care in 8 cases but noted that maternal death may have been inevitable even with appropriate care [2]. The following report of deaths from AFE occurring from 2009 to 2012 noted that all 11 women collapsed either before or within minutes of delivery. No women had bleeding prior to collapse, and most women could not be resuscitated even by experienced clinical personnel who were present at the event [5].

The California Pregnancy-Associated Mortality Review found that among the 14 deaths that occurred because of AFE, it was improbable that any could have been prevented by improving care [27]. Similarly, none of the deaths attributed to AFE in the North Carolina review were considered preventable [28], and none of the 13 AFE-related deaths in the HCA mortality review cohort were considered to be preventable [9, 10].

1.3.8 Anesthesia

The rate of maternal complications and death attributed directly to anesthesia varies by country. In the UK report, 3 of 253 deaths from 2009 to 2011 and 4 of 243 deaths from 2010 to 2012 were associated with anesthesia causes [7]. A review of maternal cardiac collapse in the UK Obstetric Surveillance System, identified 17 of 59 cases that were associated with an anesthesia-related cause; however, while the mortality rate was 37.3%, none of the 17 women who suffered anesthesia-related cardiac collapse died [34]. In the Australian cohort, two maternal deaths were related to anesthesia [13]. In the CDC PMSS report from 2011 to 2013, 3 of 2009 maternal deaths were due to anesthesia complications [12]. Conversely the New Zealand death review [14] and the Danish cohort [17] had no deaths related to anesthesia.

While data on preventability of maternal deaths related to anesthesia is limited due to the small sample size available, the 2017 UK Confidential Enquiries report includes the following recommen-

dations for obstetric anesthesia care: (1) medically complex obstetric patients should have timely multidisciplinary planning including an experienced obstetric anesthesiologist; (2) in cases of massive hemorrhage, resuscitation must be adequate and bleeding stopped prior to extubation; and (3) vigilance for pulmonary aspiration is required for obstetric patients requiring general anesthesia [6].

1.4 Conclusions

Maternal mortality review data is consistent in indicating that some causes of maternal death are more preventable than others (e.g., hemorrhage compared to AFE). Clinical resources, based in part on death review findings, are being developed and disseminated with the goal of reducing risk from the most preventable causes of maternal death. For example, the US National Partnership for Maternal Safety's obstetric hemorrhage bundle centers around improved readiness for and recognition and management of large obstetric hemorrhage with the goal of addressing shortcomings in care identified in mortality reviews [35]. The United States National Partnership's VTE bundle, acknowledging divergent VTE prophylaxis recommendations, makes general recommendations for risk assessment. A bundle has also been released regarding management of hypertension [36]. To reduce severe morbidity and mortality from cardiovascular and non-cardiovascular medical conditions, a parallel model of regionalized perinatal care for medically complicated mothers has been proposed [37]. The degree to which these initiatives will successfully reduce preventable mortality in the United States or in other countries that follow US recommendations remains to be seen. In California, which has been a leader in implementation of maternal safety initiatives, maternal mortality, which historically tracked with the national average, has decreased significantly over recent years [27]. Data from the United Kingdom's most recent reports supports that overall maternal mortality due to some causes may be decreasing [6]. Improved granularity and ascertainment of maternal death, development of quality measures to assess implementation, and standardized outcome measures will be required to measure progress and identify important safety gaps.

References

1. Creanga AA, Syverson C, Seed K, Callaghan WM. Pregnancy-related mortality in the United States, 2011–2013. Obstet Gynecol. 2017;130(2):366–73.
2. Cantwell R, Clutton-Brock T, Cooper G, et al. Saving Mothers' lives: reviewing maternal deaths to make motherhood safer: 2006–2008. The eighth report of the confidential enquiries into maternal deaths in the United Kingdom. BJOG. 2011;118(Suppl):1:1–203.
3. Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. Lancet. 2006;367:1066–74.
4. Knight M, Nair M, Tuffnell D, Kenyon S, Shakespeare J, Brocklehurst P, Kurinczuk JJ, editors. On behalf of MBRRACE-UK. Saving lives, improving mothers' care—surveillance of maternal deaths in the UK 2012–14 and lessons learned to inform maternity care from the UK and Ireland confidential enquiries into maternal deaths and morbidity 2009–14. Oxford: National Perinatal Epidemiology Unit, University of Oxford; 2016.
5. Knight M, Kenyon S, Brocklehurst P, Neilson J, Shakespeare J, Kurinczuk JJ, editors. On behalf of MBRRACE-UK. Saving lives, improving mothers' care—lessons learned to inform future maternity care from the UK and Ireland confidential enquiries into maternal deaths and morbidity 2009–12. Oxford: National Perinatal Epidemiology Unit, University of Oxford; 2014.
6. Knight M, Nair M, Tuffnell D, Shakespeare J, Kenyon S, Kurinczuk JJ, editors. On behalf of MBRRACE-UK. Saving lives, improving mothers' care—lessons learned to inform maternity care from the UK and Ireland confidential enquiries into maternal deaths and morbidity 2013–15. Oxford: National Perinatal Epidemiology Unit, University of Oxford; 2017.
7. Knight M, Tuffnell D, Kenyon S, Shakespeare J, Gray R, Kurinczuk JJ, editors. On behalf of MBRRACE-UK. Saving lives, improving mothers' care—surveillance of maternal deaths in the UK 2011–13 and lessons learned to inform maternity care from the UK and Ireland confidential enquiries into maternal deaths and morbidity 2009–13. Oxford: National Perinatal Epidemiology Unit, University of Oxford; 2015.
8. Creanga AA, Berg CJ, Syverson C, Seed K, Bruce FC, Callaghan WM. Pregnancy-related mortality in the United States, 2006–2010. Obstet Gynecol. 2015;125:5–12.
9. Clark SL, Belfort MA, Dildy GA, Herbst MA, Meyers JA, Hankins GD. Maternal death in the 21st century:

causes, prevention, and relationship to cesarean delivery. Am J Obstet Gynecol. 2008;199:36.e1–5. discussion 91–2 e7–11.
10. Clark SL, Christmas JT, Frye DR, Meyers JA, Perlin JB. Maternal mortality in the United States: predictability and the impact of protocols on fatal postcesarean pulmonary embolism and hypertension-related intracranial hemorrhage. Am J Obstet Gynecol. 2014;211:32.e1–9.
11. Saucedo M, Deneux-Tharaux C, Bouvier-Colle MH, French National Experts Committee on Maternal M. Ten years of confidential inquiries into maternal deaths in France, 1998–2007. Obstet Gynecol. 2013;122:752–60.
12. Schutte JM, Steegers EA, Schuitemaker NW, et al. Rise in maternal mortality in the Netherlands. BJOG. 2010;117:399–406.
13. Australian Institue of Health and Welfare. Maternal deaths in Australia 2012–2014. 2017. https://www.aihw.gov.au/reports/mothers-babies/maternal-deaths-in-australia-2012-2014/contents/table-of-contents. Accessed Feb 2018.
14. Health Quality and Safety Commission New Zealand. Eleventh annual report of the perinatal and maternal mortality review committee: reporting mortality 2015. Wellington: Health Quality & Safety Commission; 2017. https://www.hqsc.govt.nz/assets/PMMRC/Publications/2017_PMMRC_Eleventh_Annual_Report.pdf. Accessed Feb 2018.
15. Alkema L, Chou D, Hogan D, et al. Global, regional, and national levels and trends in maternal mortality between 1990 and 2015, with scenario-based projections to 2030: a systematic analysis by the UN Maternal Mortality Estimation Inter-Agency Group. Lancet. 2016;387:462–74.
16. Hogan MC, Foreman KJ, Naghavi M, et al. Maternal mortality for 181 countries, 1980–2008: a systematic analysis of progress towards Millennium Development Goal 5. Lancet. 2010;375:1609–23.
17. Bodker B, Hvidman L, Weber T, et al. Maternal deaths in Denmark 2002–2006. Acta Obstet Gynecol Scand. 2009;88:556–62.
18. Centers for Disease Control and Prevention. Pregnancy mortality surveillance system. www.cdc.gov/reproductivehealth/maternalinfanthealth/pmss.html. Accessed 4 Mar 2020.
19. Centers for Disease Control and Prevention. Maternal mortality. https://www.cdc.gov/nchs/maternal-mortality/index.htm. Accessed 5 Mar 2020.
20. Callaghan WM. Overview of maternal mortality in the United States. Semin Perinatol. 2012;36:2–6.
21. Philibert M, Deneux-Tharaux C, Bouvier-Colle MH. Can excess maternal mortality among women of foreign nationality be explained by suboptimal obstetric care? BJOG. 2008;115:1411–8.
22. Knight M, Bunch K, Kenyon S, Tuffnell D, Kurinczuk JJ. A national population-based cohort study to investigate inequalities in maternal mortality in the United Kingdom, 2009–17. Paediatr Perinat Epidemiol. 2020. https://doi.org/10.1111/ppe.12640.
23. Berg CJ, Atrash HK, Koonin LM, Tucker M. Pregnancy-related mortality in the United States, 1987–1990. Obstet Gynecol. 1996;88:161–7.
24. Palmerola KL, D'Alton ME, Brock CO, Friedman AM. A comparison of recommendations for pharmacologic thromboembolism prophylaxis after caesarean delivery from three major guidelines. BJOG. 2016;123:2157–62.
25. Sibai BM, Rouse DJ. In reply. Obstet Gynecol. 2017;129:382–3.
26. The Royal College of Obstetricians and Gynaecologists. Thrombosis and embolism during pregnancy and the puerperium, reducing the risk. Green-top guideline no. 37a, vol. 2015. London: The Royal College of Obstetricians and Gynaecologists; 2015.
27. California Maternal Quality Care Collaborative. California pregnancy-associated mortality review 1999–2013. https://www.cmqcc.org/research/ca-pamr-maternal-mortality-review. Accessed Feb 2018.
28. Berg CJ, Harper MA, Atkinson SM, et al. Preventability of pregnancy-related deaths: results of a state-wide review. Obstet Gynecol. 2005;106:1228–34.
29. The New York State Department of Health. New York state maternal mortality review report 2012–2013. 2017. https://www.health.ny.gov/community/adults/women/docs/maternal_mortality_review_2012-2013.pdf.
30. The California Pregnancy-Associated Mortality Review. Report from 2002 and 2003 maternal death reviews. Sacramento: California Department of Public Health, Maternal Child and Adolescent Health Division; 2011.
31. Shields LE, Wiesner S, Klein C, Pelletreau B, Hedriana HL. Use of maternal early warning trigger tool reduces maternal morbidity. Am J Obstet Gynecol. 2016;214:527 e1–6.
32. The Royal College of Obstetricians and Gynaecologists. Thrombosis and embolism during pregnancy and the puerperium, reducing the risk. Green-top guideline no. 37a. London: The Royal College of Obstetricians and Gynaecologists; 2009.
33. Clark SL, Romero R, Dildy GA, et al. Proposed diagnostic criteria for the case definition of amniotic fluid embolism in research studies. Am J Obstet Gynecol. 2016;215:408–12.
34. Beckett VA, Knight M, Sharpe P. The CAPS study: incidence, management and outcomes of cardiac arrest in pregnancy in the UK: a prospective, descriptive study. BJOG. 2017;124:1374–81.
35. Main EK, Goffman D, Scavone BM, et al. National Partnership for maternal safety: consensus bundle on obstetric hemorrhage. Obstet Gynecol. 2015;126:155–62.
36. D'Alton ME, Friedman AM, Smiley RM, et al. National partnership for maternal safety: consensus bundle on venous thromboembolism. Obstet Gynecol. 2016;128:688–98.
37. D'Alton ME, Bonanno CA, Berkowitz RL, et al. Putting the "M" back in maternal-fetal medicine. Am J Obstet Gynecol. 2013;208:442–8.

2 Identifying the Critically Ill Parturient

Cesar Padilla, Sarah Rae Easter, and Brian T. Bateman

Bullet Points

- Much of the increased maternal mortality in the last 25 years in the United States is likely attributable to a higher burden of maternal medical illness.
- Admission of a pregnant or postpartum patient to the intensive care unit (ICU) is estimated to occur in 1 in every 300 deliveries.
- Early identification of those at risk may accelerate care, including transfer and timely intervention, thereby reversing these trends in morbidity and mortality.
- The vital signs of normal pregnancy often overlap with abnormal vital signs, further challenging the development of a physiology-based tool with adequate sensitivity and specificity.
- The Modified Obstetric Early Warning System (MOEWS), tailored for obstetric vital signs, and obstetric-focused Sepsis in Obstetrics Score (SOS) require further assessments for improved outcomes.
- The Obstetric Comorbidity Index (OCI) is a clinical calculator using underlying comorbidities to predict need for ICU admission and the likelihood of severe maternal morbidity at delivery.
- The relatively low absolute rate of critical illness among obstetric patients remains a significant challenge for achieving validity with any scoring system.
- Early referral of women with specific comorbidities, such as abnormal placentation, severe preeclampsia, and maternal cardiac disease, is encouraged, to appropriate facilities.
- Multidisciplinary collaboration constitutes the optimal model for coordinating care and delivery planning in high-risk pregnant women.

C. Padilla · B. T. Bateman (✉)
Department of Anesthesiology, Perioperative, and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
e-mail: BBATEMAN@mgh.harvard.edu

S. R. Easter
Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

2.1 The Modern Parturient: A Changing Demographic

In the United States (USA), maternal mortality has increased in the last 25 years. Much of this increase is likely attributable to a higher burden of maternal medical illness [1–6]. Maternal morbidity and "near miss" events have also markedly

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_2

increased during the same interval, by as much as 75% by some estimates [6]. Maternal critical illness, defined by end organ dysfunction, need for advanced treatment (need for ventilation, vasopressor requirement) or diagnostic criteria (see Chap. 1), is now relatively common in the obstetric population [7]. Admission of a pregnant or postpartum patient to the ICU is estimated to occur in 1 in every 300 deliveries [8], accounting for 12.1% of all ICU admissions for women aged 16–50 [9]. Obstetric patients requiring ICU-level care are also being treated outside of the formal critical care setting, with studies showing that 1–3% of parturients require ICU-level care or are at risk of developing maternal critical illness [10, 11]. Identifying obstetric patients at risk of clinical deterioration and critical illness, therefore, represents an important component of a comprehensive strategy to address the needs of increasingly ill pregnant and postpartum women. Early identification of those at risk may accelerate transfer to high-risk centers and/or allows timely intervention, thereby reversing these trends in morbidity and mortality.

2.2 Maternal Hemodynamic Screening Tools: Balancing Sensitivity and Specificity

Many public health organizations recommend routine use of validated tools to identify women at high-risk of morbidity during pregnancy [4, 12, 13]. In the United Kingdom, Confidential Enquiry into Maternal and Child Health (CEMACH) reports have led to the introduction and integration of criteria to identify derangements in physiologic parameters in pregnant women [13]. In the United States, the multidisciplinary National Partnership for Maternal Safety has also suggested that tracking several physiological parameters is a key component of identifying morbidity (Table 2.1) [4, 14].

The use of vital signs and other physiologic parameters as indicators of critical illness is well described in the general medical and surgical populations [15]. The ideal screening tool should be sufficiently sensitive to predict development of critical illness. However, it should also have a threshold of specificity that avoids overdiagnosis and recurrent false alarms (which lead to clinical fatigue) [16]. Therein lies the problem. Critical illness is less common in the obstetric population than in the general medical and surgical populations, and infrequent signals are more often missed [17]. In addition, the vital signs of normal pregnancy often overlap with abnormal vital signs. These issues challenge the development of a physiology-based tool with adequate sensitivity and specificity [18].

Table 2.1 Maternal early warning criteria from the National Partnership for Maternal Safety

Parameter	Value
Systolic blood pressure (mmHg)	<90 or >160
Diastolic blood pressure (mmHg)	>100
Heart rate (beats per minute)	<50 or >120
Respiratory rate (breaths per minute)	<10 or >30
Oxygen saturation on room air, at sea level (%)	<95
Oliguria (mL/h for ≥2 h)	<35
Maternal agitation, confusion, or unresponsiveness; Patient with preeclampsia reporting a non-remitting headache or shortness of breath	Present

Mhyre JM, D'Oria R, Hameed AB, Lappen JR, Holley SL, Hunter SK, Jones RL, King JC, D'Alton ME. The maternal early warning criteria: a proposal from the national partnership for maternal safety. Obstet Gynecol 2014;124:782–6

2.3 Predicting Adverse Outcomes in Infection

Though the etiology of severe maternal morbidity and mortality continues to evolve in the contemporary obstetric population, sepsis remains a leading cause of obstetric critical illness [19]. Early recognition and intervention during sepsis improve outcomes [20]. Therefore, the validity of many screening tools has been tested in the context of maternal infection (Table 2.2).

The systemic inflammatory response syndrome (SIRS) and modified early warning system (MEWS) are two physiology-based tools commonly used to screen for the presence of sep-

Table 2.2 Test characteristics of scoring systems for sepsis in an obstetric population

Score	Author	Population	Outcome	Components	Threshold	Characteristics
Maternal Early Warning System (MEWS)	Lappen et al., 2010	Chorioamnionitis at single-center in the United States	Severe sepsis [3] ICU admission Death	Temperature HR RR WBC count	≥5	Sensitivity 100% Specificity 90.4% NPV 100% PPV 0.05%
Modified Obstetric Early Warning Scoring Systems (MOEWS)	Edwards et al., 2015	Chorioamnionitis at single-center in the United States	Severe Sepsis [3] ICU transfer death	Temperature HR SBP DBP RR SpO_2 Mental state	≥2	Sensitivity 40–100% Specificity 3.6–96.9% PPV 1.42–15.4 NPV 99.1–100
Sequential Organ Failure Assessment (SOFA)	Jain et al., 2016	Obstetric ICU admissions in India	Death	PaO_2/FiO_2 ratio GCS score Vasopressors Creatinine/ urine output Bilirubin Platelet count	≥2 ≥8	Sensitivity 100% Specificity 3.3% Sensitivity 96.7% Specificity 78.3%
Sepsis in Obstetrics Score (SOS)	Albright et al., 2017	Pregnant or postpartum women meeting ≥2 SIRS criteria at single-center in the United States	ICU transfer	Temperature SBP HR RR SpO_2 WBC count % immature neutrophils Lactic acid	≥6	Sensitivity 64% Specificity 88% PPV 15% NPV 98.6%

HR heart rate (beats/min), *RR* respiratory rate (breaths/min), *WBC* white blood cell (10^9/L), *NPV* negative predictive value, *PPV* positive predictive value, *SBP* systolic blood pressure (mmHg), *DBP* diastolic blood pressure (mmHg), *SpO_2* peripheral oxygen saturation (%), *GCS* Glasgow Coma Scale, *MAP* mean arterial pressure (mmHg), *SIRS* systemic inflammatory response syndrome

sis. Both lack sensitivity and specificity in an obstetric population. In a retrospective study of intrapartum patients with chorioamnionitis, both SIRS and MEWS failed to accurately identify women who were admitted to the ICU, developed sepsis, or died [21]. At score thresholds deemed appropriate for clinical assessment, the MEWS criteria was found to have a positive predictive value of 0.05%, meaning only 0.05% of women meeting these criteria will have sepsis [21].

The lack of specificity of SIRS and MEWS criteria may be attributed to the physiologic differences between the obstetric population and the general medical/surgical population [21, 22]. Pregnant women have lower blood pressure compared to nonpregnant patients, a higher heart rate at the time of delivery (intermittent tachycardia often occurs during active labor), and an increase in respiratory rate related to hormonal changes [21]. However, additional confounders may also contribute to the lack of specificity. For example, fevers associated with neuraxial anesthesia or with treatment with prostaglandins (e.g., Misoprostol) may lead to overdiagnosis of sepsis. All of these factors contribute to the overall lack of specificity of standard scores in the obstetric population [23].

These challenges have inspired the creation of physiology-based surveillance scoring systems targeted specifically for use in obstetric patients. The Modified Obstetric Early Warning System (MOEWS) is routinely used for monitoring pregnant women in the UK National Health System. This score uses physiologic criteria tailored to pregnant women [24]. However, several studies have suggested that even the MOEWS has poor

sensitivity and specificity in pregnant women [24, 25], and it remains unclear whether implementation of MEOWS criteria improves clinical outcomes. Similarly, the obstetric-focused Sepsis in Obstetrics Score (SOS) offers superior validity over SIRS and MEWS for ICU admission, but still lacks specificity for predicting severe outcomes [26].

In addition to the value of an ideal scoring system for determining the need for critical care admission, it should also predict adverse outcomes such as severe maternal morbidity and mortality. Scoring systems which rely on physiologic parameters to predict mortality in ICU patients have also been shown to lack specificity in the obstetric population. The Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system analyzes 13 physiologic variables within 24 h of ICU admission [27]. A recent study analyzing the usefulness of the APACHE II scores in pregnancy showed that 7 of the 13 physiologic parameters are altered in baseline obstetric physiology, leading to overestimation of mortality risk [27].

When compared to organ-based screening tools such as the MODS (Multiple Organ Dysfunction Score) and SOFA scores, physiological-based screening tools such as SOS (Sepsis in Obstetrics) and APACHE II scores showed inferiority as predictors for sepsis-related mortality in obstetric patients [28]. These newer sepsis detection scores (SOFA/MODS) are based on organ failure rather than on the severity of inflammatory response and seem more promising for prediction of mortality in critically ill septic obstetric patients. However, the data suggesting this are still limited [29, 30].

2.4 Beyond Infection

Most of the evidence regarding the utility of screening tools in the obstetric population is limited to the realm of infection. With the evolving complexity of the modern parturient, the ideal screening tool should also have a high sensitivity and specificity for other sources of critical illness and adverse outcomes. Furthermore, these screening tools should also suggest the first step within a pathway to treat those at risk for morbidity and curb its development [14, 31]. The Maternal Early Warning Tool (MEWT) is one such tool that integrates physiologic screening for morbidity with management guidelines to address cases of clinical concern. The MEWT is comprised of a screening tool coupled with clinical pathways which address four common causes of maternal mortality: cardiovascular dysfunction, infection, hemorrhage, and hypertensive disorders of pregnancy (preeclampsia) [12]. A prospective study of this screening tool in six US hospitals has shown that implementing it led to reductions in severe maternal morbidity and composite morbidity. Furthermore, only 1 in 50 women triggered an alert when this tool was used. As noted above, the MEWT also incorporates clinical recommendations regarding treatment of prevailing causes of maternal morbidity. Inclusion of these recommendations has been shown to lead to high adherence rate to the protocols provided among treating physicians (83.1%) [12]. Drawbacks of MEWT include imperfect positive predictive values. The positive predictive value for all patients requiring ICU admission was 12% with a PPV of 7% for patients with suspected sepsis [12]. These limitations suggest that improvements in maternal screening are still required if women at risk of clinical deterioration are to be identified in a timely manner. It is also unclear whether the observed reduction in morbidity was due to use of the trigger tool or to better adherence to protocols in high-risk patients. Despite the limitation of a low positive predictive value, data from this study suggest that obstetric-specific tools such as this may potentially lower severe maternal morbidity through early recognition coupled with protocolized management.

2.5 The Identification and Management of High-Risk Pregnant and Postpartum Women

Identification of pregnant and postpartum women at risk of clinical deterioration requires use of a diverse set of strategies. Despite the inherent challenges in the available scoring systems, con-

sensus guidelines consistently underscore two key principles in identifying the high-risk parturient. First, obstetric units should implement and consistently utilize a screening system for the critically ill mother at risk of severe morbidity, however imperfect. Secondly, obstetric hospitals should have the protocols or pathways to mobilize available resources when a mother at risk for critical illness is identified [14, 31].

The importance of provider education and reinforcement in the use of screening tools cannot be overstated. Barriers to successful implementation of the MEOWS screening criteria in the UK National Health System included poor compliance with guidelines and difficulties in eliciting a response from physicians [24]. Such inconsistent use of screening tools or failure to respond can lead to delays in diagnosis that may predispose patients to severe morbidity and mortality. Studies show that up to 40% of maternal deaths are preventable; these deaths have largely been attributed to delays in diagnosis and in involvement of critical care [11, 32, 33]. Conversely, systemic implementation of screening tools alongside leadership efforts, management, and continual supervision by qualified practitioners has a demonstrated impact on the staff's perceived usefulness of screening tools when identifying high-risk parturients [24]. Therefore, maternal screening tools must be used in conjunction with other strategies to identify high-risk pregnant and peripartum women.

Once the high-risk women have been identified, clinician attention should switch quickly to management. National guidelines set forth evidence-based clinical pathways for common obstetric conditions such as postpartum hemorrhage, maternal infection, venous thromboembolism, and hypertensive disorders of pregnancies in a variety of clinical settings [1, 14, 31, 34]. The rising prevalence of chronic disease in pregnancy and a concomitant increase in patient complexity has underscored the importance of multidisciplinary management and maternal critical care in combating maternal mortality [7, 35].

Establishing maternal critical care as a formal discipline is a central strategy for preventing maternal deaths. The UK Intensive Care National Audit and Research Centre (ICNARC) recommends education in critical care scenarios pertinent to obstetric patients for staff at all levels of management (identification of sepsis for staff at all levels of training and appropriate anesthetic considerations for critically ill obstetric patients for anesthesia providers), appropriate staffing with multidisciplinary personnel trained in maternal critical care, and appropriate triaging of critically ill patients for transfer to centers with adequate resources [11]. Still, in some centers, dependent on the clinical setting, identification of an obstetric patient with critical illness may indicate transfer to an intensive care unit while in others it may not. Sometimes identification of the high-risk parturient may trigger involvement of consulting physicians to provide a multidisciplinary approach to patient management and ongoing assessment. Certain critical care skills, such as rapid assessment with transthoracic echocardiography hold promise for reproducible and rapid assessment of cardiac function and fluid status in pregnancy [36, 37]. Timely assessment of complex medical conditions will require healthcare professionals comfortable with obstetric physiology and critical care skills. Providing these critical care services, independent of location, for at risk mothers is central in reducing maternal mortality.

2.6 Accounting for Comorbidities in Screening for the High-Risk Parturient

Though rates of maternal morbidity are increasing, the relatively low absolute rate of critical illness in the obstetric patient population remains a significant challenge for achieving validity with any scoring system. The positive predictive value of any screening tool depends on the prevalence of the disease in the population of interest. A low prevalence of critical illness in an unselected patient population will preclude any attempt to increase the positive predictive value of physiology-based screening tools. Clinical covariates are important components of many disease-specific risk assessment tools. Screening tools incorporating specific comorbidities successfully

predict morbidity and mortality in non-obstetric patients [38, 39]. Incorporating such clinical comorbidities into risk assessment tools for the pregnant and critically ill population, therefore, offers exciting possibility for improving identification of those at risk of critical illness.

The Obstetric Comorbidity Index (OCI) (Table 2.3) is a clinical calculator that uses the underlying comorbidities of pregnant women to predict their need for ICU admission and the likelihood of severe maternal morbidity at delivery. The OCI considers 20 weighted maternal comorbid conditions in addition to maternal age to produce a patient-specific comorbidity index score predictive of maternal ICU admission [40]. This scoring index has been validated in independent populations and has demonstrated superiority compared to comorbidity indices derived for non-obstetric populations [41].

Table 2.3 Obstetric comorbidity index

Maternal comorbidity	Odds ratio (95% CI)	Weight
Preeclampsia with severe features or eclampsia	5.10 (4.63–5.60)	5
Chronic congestive heart failure	3.93 (1.35–11.47)	5
Congenital heart disease	3.81 (3.37–4.32)	4
Pulmonary hypertension	3.24 (2.31–4.56)	4
Chronic ischemic heart disease	2.72 (2.13–3.46)	3
Sickle cell disease	2.14 (1.63–2.81)	3
Multiple gestation	2.09 (1.86–2.35)	2
Cardiac valvular disease	1.95 (1.67–2.27)	2
Systemic lupus erythematosus	1.77 (1.24–2.52)	2
HIV	1.76 (1.37–2.27)	2
Mild or unspecified preeclampsia	1.95 (1.67–2.27)	2
Drug abuse	1.63 (1.48–1.79)	2
Placenta previa	1.61 (1.45–1.80)	2
Chronic renal disease	1.54 (1.32–1.80)	1
Previous cesarean delivery	1.45 (1.37–1.54)	1
Gestational hypertension	1.32 (1.14–1.54)	1
Alcohol abuse	1.31 (1.11–1.56)	1
Asthma	1.28 (1.19–1.39)	1
Preexisting diabetes mellitus	1.21 (1.1–1.33)	1
Maternal age (years)		
Older than 44	2.25 (1.28–3.95)	3
40–44	1.72 (1.47–2.02)	2
35–39	1.52 (1.39–1.66)	1

Bateman BT MJ, Hernandez-Diaz S, Huybrechts KF, Fischer MA, Creanga AA, Callaghan WM, Gagne JJ. Development of a comorbidity index for use in obstetric patients. *Obstet Gynecol.* 2013;122 (5):957–965

2.7 Antenatal and Early Pregnancy Screening

The role of early identification of high-risk pregnant women and appropriate referral has been underscored in the recent consensus guidelines published by the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) [35]. In response to increasingly complex patient population and rising maternal mortality, the guidelines encourage referral of women with specific comorbidities, such as those with abnormal placentation, severe preeclampsia and maternal cardiac disease, to appropriate facilities. The guidelines also offer a classification for facility level of maternal care based on the availability of potentially required resources. Among the resources outlined are nursing leadership and expertise, specialist availability, and critical care resources for the highest risk women [35]. In addition to listing the components of the hospital infrastructure recommended for these high-risk cases, the guidelines identify the availability of subspecialists and critical care unit capabilities as key features of higher-level centers.

The role of early and appropriate referral has already been recognized for certain high-risk conditions. Though all obstetric hospitals are encouraged to recognize and manage obstetric hemorrhage, facility-based criteria have been outlined for specific high-risk conditions such as abnormal placentation [42, 43]. Women with placenta accreta will benefit from antenatal referral to hospitals with adequate resources, such as a blood bank capable of massive transfusion and the availability of subspecialty services such as interventional radiology, obstetric anesthesiology, and critical care. However, older women and those with hypertension, placenta previa, and prior cesarean delivery may not be as readily

identified even though in some cases their risk of severe morbidity may be similar.

An increasingly complex obstetric population in a background, low rate of severe maternal morbidity and mortality, presents many challenges for early and reliable identification of the high-risk parturient. Screening women for high-risk conditions as a routine part of antenatal care will, therefore, likely play an increasingly important role in identifying women at risk for critical illness. Universal clinical comorbidity screening may offer an objective way to screen women for severe morbidity prior to the development of critical illness. The majority of the aforementioned screening tools and downstream pathways focus on assessment and management at the time of potential illness. However, the OCI, which has shown promise in identifying high-risk parturients, can be used in the antepartum period. This comorbidity index can identify high-risk women in the antenatal setting, allowing them to be directed to specialized centers equipped with adequate resources and personnel. Theoretically, such referral allows care coordination and provides time to plan a delivery strategy [40].

Multidisciplinary collaboration constitutes the optimal model for coordinating care and delivery planning in high-risk pregnant women [11, 35, 44, 45]. Early multidisciplinary consultation represents a valuable strategy in the care of parturients with multiple comorbidities who may benefit from coordination of care [35]. However, it remains uncertain whether maternal screening tools affect consultation practices and/or lead to timely intervention of specialists. Such scores continue to be underutilized for identifying high-risk women. In one study, only 25% of women eligible for an antepartum high-risk consultation received this resource [46]. Multidisciplinary management has been proclaimed as a vital strategy in the prevention of severe morbidity [47]; the impact that maternal screening tools may have with timely intervention of consultants represents potential areas of interest for improving clinical outcomes.

Antenatal screening for obstetric comorbidities coupled with physiology-based *intrapartum* risk assessment is a key complementary strategy for identifying mothers at risk for critical illness. Once identified, appropriate management pathways take priority. Prompt management and ongoing risk assessment according to evidence-based pathways should also follow early recognition of women with intrapartum derangements in physiology. An important potential confounding factor in studies attempting to identify high-risk women in the peripartum period may be the heterogeneity in delivery volume across hospitals. In the United States, one-third of hospitals have delivery volumes less than 500 per year and 39% of hospital births occurred in these low-volume hospitals. Given the prevalence of deliveries occurring at smaller hospitals, intrapartum access to risk-appropriate care for high-risk women cannot be assumed [48, 49]. Obstetric complications are more likely to occur in hospitals with lower delivery volumes, possibly reflecting associated experience by healthcare providers [35, 50].

2.8 Maternal Screening Tools: A Valuable Tool Looking Forward

Identification of high-risk pregnant and peripartum women represents a central strategy for an increasingly comorbid patient population. This requires a multifaceted approach which includes proper "maternal" screening tools and timely multidisciplinary management, with the goal of minimizing delays of care. Although maternal screening tools do have their limitations, implementing them has shown promise in reducing morbidity in the clinical setting. Moving forward, screening criteria should be optimized. Improving the sensitivity and specificity of the existing tools and achieving higher predictive values for identifying women at risk of clinical deterioration remain essential. Creation of maternal screening criteria which incorporate individual patient comorbidities represents an important area of potential research as this may improve the value of physiologic-based screening tools. Stratification of women based on their comorbidity indices in the antepartum setting may provide clinicians the time to assemble resources and

multidisciplinary input and enable timely transfer of women at risk to centers capabilities and resources that are adequate for their specific clinical needs.

References

1. Banayan JM, Scavone BM. National Partnership for maternal safety—maternal safety bundles. APSF Newslett. 2016;31(2). www.apsf.org/article/national-partnership-for-maternal-safety-maternal-safety-bundles/. Last Accessed 21 Oct 2018.
2. Kassebaum NJ, Bertozzi-Villa A, Coggeshall MS, et al. Global, regional, and national levels and causes of maternal mortality during 1990–2013: a systematic analysis for the global burden of disease study 2013. Lancet. 2014;384(9947):980–1004.
3. Mocumbi AO, Sliwa K, Soma-Pillay P. Medical disease as a cause of maternal mortality: the preimminence of cardiovascular pathology. Cardiovasc J Afr. 2016;27(2):84–8.
4. Mhyre JM, D'Oria R, Hameed AB, et al. The maternal early warning criteria: a proposal from the national partnership for maternal safety. J Obstet Gynecol Neonatal Nurs. 2014;43(6):771–9.
5. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA. 2016;315(8):801–10.
6. Callaghan WM, Creanga AA, Kuklina EV. Severe maternal morbidity among delivery and postpartum hospitalizations in the United States. Obstet Gynecol. 2012;120(5):1029–36.
7. Wheatly S. Maternal critical care: what's in a name? Int J Obstet Anesth. 2010;19(4):353–5.
8. Einav S, Bromiker R, Sela HY. Maternal critical illness. Curr Anesthesiol Rep. 2017;7:55–66.
9. Peña-Rosas JP, De-Regil LM, Garcia-Casal MN, Dowswell T. Daily oral iron supplementation during pregnancy. Cochrane Database Syst Rev. 2015;(7):CD004736.
10. O'Malley EG, Popivanov P, Fergus A, Tan T, Byrne B. Maternal near miss: what lies beneath? Eur J Obstet Gynecol Reprod Biol. 2016;199:116–20.
11. Knight M, Kenyon S, Brocklehurst P, Neilson J, Shakespeare J, Kurinczuk JJ, editors. on behalf of MBRRACE-UK. Saving lives, improving mothers' care—lessons learned to inform future maternity care from the UK and Ireland confidential enquiries into maternal deaths and morbidity 2009–12. Oxford: National Perinatal Epidemiology Unit, University of Oxford; 2014. www.npeu.ox.ac.uk/downloads/files/mbrrace-uk/reports/Saving%20Lives%20Improving%20Mothers%20Care%20report%202014%20Full.pdf. Last Accessed 21 Oct 2018.
12. Shields LE, Wiesner S, Klein C, Pelletreau B, Hedriana HL. Use of maternal early warning trigger tool reduces maternal morbidity. Am J Obstet Gynecol. 2016;214(4):527.e1–6.
13. Singh S, McGlennan A, England A, Simons R. A validation study of the CEMACH recommended modified early obstetric warning system (MEOWS). Anaesthesia. 2012;67(1):12–8.
14. D'Alton ME, Friedman AM, Smiley RM, et al. National partnership for maternal safety: consensus bundle on venous thromboembolism. Anesth Analg. 2016;123(4):942–9.
15. Goldhill DR, White SA, Sumner A. Physiological values and procedures in the 24 h before ICU admission from the ward. Anaesthesia. 1999;54(6):529–34.
16. Rhee C, Gohil S, Klompas M. Regulatory mandates for sepsis care--reasons for caution. N Engl J Med. 2014;370(18):1673–6.
17. Jerison HJ, Pickett RM. Vigilance: the importance of the elicited observing rate. Science. 1964;143(3609):970–1.
18. Bauer ME, Bauer ST, Rajala B, et al. Maternal physiologic parameters in relationship to systemic inflammatory response syndrome criteria: a systematic review and meta-analysis. Obstet Gynecol. 2014;124(3):535–41.
19. Bateman BT, Schmidt U, Berman MF, Bittner EA. Temporal trends in the epidemiology of severe postoperative sepsis after elective surgery: a large, nationwide sample. Anesthesiology. 2010;112(4):917–25.
20. Gauer RL. Early recognition and management of sepsis in adults: the first six hours. Am Fam Physician. 2013;88(1):44–53.
21. Lappen JR, Keene M, Lore M, Grobman WA, Gossett DR. Existing models fail to predict sepsis in an obstetric population with intrauterine infection. Am J Obstet Gynecol. 2010;203(6):573.e1–5.
22. Clark SL, Cotton DB, Lee W, et al. Central hemodynamic assessment of normal term pregnancy. Am J Obstet Gynecol. 1989;161(6 Pt 1):1439–42.
23. Segal S. Labor, epidural analgesia and maternal fever. Anesth Analg. 2010;111(6):1467–75.
24. Mackintosh N, Watson K, Rance S, Sandall J. Value of a modified early obstetric warning system (MEOWS) in managing maternal complications in the peripartum period: an ethnographic study. BMJ Qual Saf. 2014;23(1):26–34.
25. Dudley M, Wright A, Simons R, et al. Meows—time to review the trigger threshold? Arch Dis Child Fetal Neonatal Ed. 2010;95:Fa40.
26. Albright CM, Ali TN, Lopes V, Rouse DJ, Anderson BL. The sepsis in obstetrics score: a model to identify risk of morbidity from sepsis in pregnancy. Am J Obstet Gynecol. 2014;211(1):39.e31–8.
27. Ryan HM, Sharma S, Magee LA, et al. The usefulness of the APACHE II score in obstetric critical care: a structured review. J Obstet Gynaecol Can. 2016;38(10):909–18.
28. Aarvold AB, Ryan HM, Magee LA, von Dadelszen P, Fjell C, Walley KR. Multiple organ dysfunction score is superior to the obstetric-specific Sepsis in obstet-

rics score in predicting mortality in septic obstetric patients. Crit Care Med. 2017;45(1):e49–57.
29. Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. Lancet. 2006;367(9516):1066–74.
30. Cantwell R, Clutton-Brock T, Cooper G, et al. Saving mothers' lives: reviewing maternal deaths to make motherhood safer: 2006–2008. The eighth report of the confidential enquiries into maternal deaths in the United Kingdom. BJOG. 2011;118(Suppl 1):1–203.
31. Main EK, Goffman D, Scavone BM, et al. National partnership for maternal safety: consensus bundle on obstetric hemorrhage. Obstet Gynecol. 2015;126(1):155–62.
32. Berg CJ, Harper MA, Atkinson SM, et al. Preventability of pregnancy-related deaths: results of a state-wide review. Obstet Gynecol. 2005;106(6):1228–34.
33. Amaral E, Souza JP, Surita F, et al. A population-based surveillance study on severe acute maternal morbidity (near-miss) and adverse perinatal outcomes in Campinas, Brazil: the Vigimoma Project. BMC Pregnancy Childbirth. 2011;11:9.
34. Banayan JM, Scavone BM. National partnership for maternal safety: maternal safety bundles. Curr Anesthesiol Rep. 2017;7(1):67–75.
35. Moaveni DM, Cohn J, Zahid ZD, Ranasinghe S. Obstetric anesthesiologists as perioperative physicians: improving peripartum care and patient safety. Curr Anesthesiol Rep. 2015;5(1):65–73.
36. Dennis AT. Transthoracic echocardiography in obstetric anaesthesia and obstetric critical illness. Int J Obstet Anesth. 2011;20(2):160–8.
37. Cornette J, Laker S, Jeffery B, et al. Validation of maternal cardiac output assessed by transthoracic echocardiography against pulmonary artery catheterization in severely ill pregnant women: prospective comparative study and systematic review. Ultrasound Obstet Gynecol. 2017;49(1):25–31.
38. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83.
39. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care. 1998;36(1):8–27.
40. Bateman BT, Mhyre JM, Hernandez-Diaz S, et al. Development of a comorbidity index for use in obstetric patients. Obstet Gynecol. 2013;122(5):957–65.
41. Metcalfe A, Lix LM, Johnson JA, et al. Validation of an obstetric comorbidity index in an external population. BJOG. 2015;122(13):1748–55.
42. Silver RM, Fox KA, Barton JR, et al. Center of excellence for placenta accreta. Am J Obstet Gynecol. 2015;212(5):561–8.
43. Awan N, Bennett MJ, Walters WA. Emergency peripartum hysterectomy: a 10-year review at the Royal Hospital for women, Sydney. Aust N Z J Obstet Gynaecol. 2011;51(3):210–5.
44. Epstein NE. Multidisciplinary in-hospital teams improve patient outcomes: a review. Surg Neurol Int. 2014;5(Suppl 7):S295–303.
45. Zwart JJ, Dupuis JR, Richters A, Ory F, van Roosmalen J. Obstetric intensive care unit admission: a 2-year nationwide population-based cohort study. Intensive Care Med. 2010;36(2):256–63.
46. Bharwani F, Macarthur A. Review of a high-risk obstetric anesthesia antepartum consult clinic. Can J Anaesth. 2014;61(3):282–3.
47. Sachs A, Aaronson J, Smiley R. The role of the anesthesiologist in the care of the parturient with cardiac disease. Semin Perinatol. 2014;38(5):252–9.
48. Bucklin BA, Hawkins JL, Anderson JR, Ullrich FA. Obstetric anesthesia workforce survey: twenty-year update. Anesthesiology. 2005;103(3):645–53.
49. American Hospital Association. AHA guide to the health care field, 2015 ed. Chicago, IL: AHA; 2014.
50. Kyser KL, Lu X, Santillan DA, et al. The association between hospital obstetrical volume and maternal postpartum complications. Am J Obstet Gynecol. 2012;207(1):42.e41–17.

Maternal Near Miss

3

D. N. Lucas and K. J. Murray

Bullet Points

- Maternal mortality represents the tip of the iceberg, with maternal morbidity also placing a huge burden on women and their families.
- The relationship between maternal morbidity and mortality has been described as a 'continuum of adverse pregnancy events'.
- Near miss events occur significantly more frequently than maternal death.
- The prevalence of maternal near miss varies widely depending on screening criteria and geographical location.
- Study of near miss events enables more rapid review and reporting of the features of a clinical case, thus having a quicker impact on clinical practice.
- It is potentially easier for clinical staff to engage in the analysis of near miss events, as examination of the events around the near miss may be perceived as less threatening since the woman did not die.
- World Health Organization defines maternal near miss as 'a woman who nearly died but survived a complication that occurred during pregnancy, childbirth or within 42 days of termination of pregnancy'.
- Near miss can be defined by clinical criteria, intervention-based criteria and organ-based criteria.
- Worldwide, obstetric haemorrhage, hypertensive diseases of pregnancy, sepsis and obstructed labour have been identified as the major causes of maternal near miss.

3.1 Maternal Mortality and Maternal Morbidity

Worldwide childbirth is becoming safer, with rates of maternal mortality reduced by 44% between 1990 and 2015 [1, 2]. A significant contribution to this progress has been made by programmes of systematic surveillance and investigation of maternal deaths. The UK Confidential Enquiries into Maternal Deaths organized under various mantels over the last 60 years, currently by MBBRACE-UK (Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the

D. N. Lucas (✉) · K. J. Murray
London North West University, Healthcare NHS Trust, London, UK
e-mail: nuala@tuesday5.co.uk

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_3

UK) [3], The South African National Committee for Confidential Enquiry into Maternal Deaths [4] and the French National Experts Committee on Maternal Mortality [5] are examples of such programmes. These programmes have not only contributed to the reduction in maternal deaths but have also led to major improvements in the overall quality of maternity care.

In the developed world, maternal deaths are now rare events and even in low- to middle-income countries with more limited resources, absolute numbers of maternal deaths may be small in individual healthcare settings. As maternal care has improved and maternal mortality has fallen, the amount of data that may inform further improvements has fallen. However, it is widely recognized that maternal mortality only represents the tip of the iceberg, with maternal morbidity also placing a huge burden on women and their families. The relationship between maternal morbidity and mortality has been elegantly described as a 'continuum of adverse pregnancy events' [6]. Figure 3.1 in many cases, maternal death does not occur as an unexpected sudden event but is the endpoint of a clinical trajectory encompassing increasingly severe maternal morbidity. Assessment of this trajectory in individual cases can highlight features that can complement the findings of maternal death enquiries, thereby increasing the opportunities for learning and improving care.

3.2 The Advantages of Studying Maternal Near Miss Events

The advantages of studying maternal morbidity 'near miss events' in addition to mortality are numerous. Near miss events occur significantly more frequently than maternal death. For example, in the UK it has been estimated that around 1% of births are complicated by a near miss event [7], therefore this presents an opportunity for examination of approximately 8000 cases per year compared to around 80 maternal deaths in the same period. This increased sample size allows much greater power in identifying factors contributing to maternal morbidity and mortality and therefore more robust generalizable conclusions to be drawn. Studying near miss events also potentially enables more rapid review and reporting of the features of a clinical case, thus having a quicker impact on clinical practice. Near miss events share many of the features of maternal deaths, so comparison between near miss events and maternal deaths enables mapping of the progression from severe disease and morbidity to death [8]. This also provides valuable insights into how clinical care may have failed and how to avoid or overcome potential obstacles in the management of acute complications of pregnancy. In low- to middle-income countries with limited resources, where maternal mortality and morbidity are at their highest, near miss events can be used to the identify women who would benefit most from the scarce resources available so these can be used to the greatest benefit [9].

It is potentially easier for clinical staff to engage in the analysis of near miss events, because as the women have survived, examination of the events around the near miss may be perceived as less threatening. Although near miss events do not result in death, they can result in long-term mental and physical sequelae for women and their partners [10, 11], and studying these events can identify factors associated with the development of longer-term morbidity.

Examination of near miss events enables the study of rare conditions of pregnancy [12]. This has been a major area of research over the last 15 years with many previously neglected conditions now being objectively studied and evaluated.

Maternal near miss events are also associated with neonatal morbidity, particularly preterm

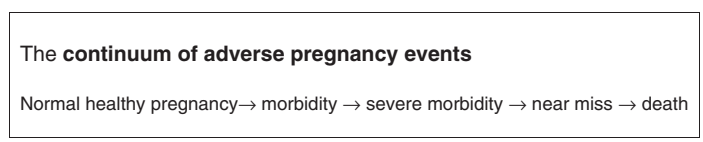


Fig. 3.1 The continuum of maternal morbidity and mortality [6]

delivery [13], and therefore also provide the opportunity to reduce the impact of maternal morbidity on the neonate.

3.3 Definition and Terminology

The term 'near miss' is borrowed from the airline industry [14]. Outside of medicine it is used to describe an unplanned or unforeseen event that has the potential to cause harm but has not actually resulted in harm or injury.

Various definitions of a near miss in obstetrics have been proposed. These have included a severe life-threatening obstetric complication necessitating an urgent medical intervention in order to prevent likely death of the mother; [15] any pregnant or recently delivered woman, in whom immediate survival is threatened and who survives by chance or because of the hospital care she received; [16] and a very ill woman who would have died had it not been that luck and good care was on her side [17].

In 2009 the World Health Organization published a paper which provided a now widely accepted definition for a maternal near miss as 'a woman who nearly died but survived a complication that occurred during pregnancy, childbirth or within 42 days of termination of pregnancy' [18]. In the past, the term near miss was used interchangeably with the term severe acute maternal morbidity. It is now recommended by the WHO that near miss should be used preferentially as it more accurately reflects the clinical scenario of a woman almost dying but surviving.

3.4 Identification of Maternal Near Miss

A number of methods have been suggested and used for the identification of near miss events. The various approaches can be broadly classified into three major groups, each having its own relative merits and disadvantages. The three methods are summarized in Table 3.1.

Table 3.1 Advantages and disadvantages of three approaches to identify maternal near miss events

	Advantages	Disadvantages
Clinical criteria related to a specific disease entity	Straightforward to interpret Data can be obtained retrospectively from case notes The quality of care of a particular disease can be assessed Complication rates for a particular disease can be calculated	Common causes of maternal mortality may be omitted The criteria used to define morbidity often have too low a threshold of morbidity to be called maternal near miss Retrospectively collected information might be unreliable due to poor documentation
Intervention-based criteria	Simple to identify the cases usually on the basis of retrospective analysis of a register in the hospital	Allows the identification of only a proportion of all severe morbidity cases, because of variation in the availability of different types of intervention such as intensive care *or* eligibility criteria for an intervention, e.g. intensive care or caesarean hysterectomy
Organ system dysfunction-based criteria	Mimics the confidential enquiries into maternal death systems, thus the same system could be used to complement maternal death enquiries Allows for identification of critically ill women thereby establishing the pattern of diseases causing morbidity and their relative importance Allows for the identification of new and emerging disease priorities, e.g. influenza Keeps focus on severe diseases that should not cause death with appropriate care Serious events are now routinely examined in many hospitals improving the opportunities for case identification	Dependent on the existence of a minimum level of care including functioning laboratory services and basic critical care monitoring Retrospective identification of cases might be difficult because of the inability to identify cases from registers

Adapted from Say L et Souza JP, Pattison RC. WHO working group on Maternal Mortality and Morbidity Classifications. Maternal near miss–towards a standard tool for monitor- ing quality of maternal healthcare. Best Practice & Research Clinical Obstetrics & Gynaecology, 2009,23:287–296

The clinical criteria based on a specific disease entity were utilized by Waterstone in a UK-based regional study of severe acute obstetric morbidity [7]. The conditions that formed inclusion criteria were severe pre-eclampsia, eclampsia, HELLP syndrome (haemolysis, elevated liver enzymes and low platelets), severe haemorrhage, severe sepsis and uterine rupture. Despite being a significant cause of maternal mortality and morbidity, pulmonary embolus was excluded because of the difficulty of accurate diagnosis of pulmonary embolus without pathological evidence. Additionally, early pregnancy conditions such as ectopic pregnancy were also excluded. Waterstone used definitions selected from a Medline search, that were clinically based and routinely measurable and that did not include management processes. When there was no definition available for the specific condition (e.g. sepsis), a modified definition was used, taking into account the physiological changes of pregnancy. In this study most events were related to obstetric haemorrhage and severe pre-eclampsia; disease-specific morbidities per 1000 deliveries were 6.7 (6.0–7.5) for severe haemorrhage, 3.9 (3.3–4.5) for severe pre-eclampsia. The authors found that caesarean delivery quadrupled the risk of morbidity.

The use of intervention-based criteria, such as admission to a critical care unit, is another relatively straightforward approach to identify near miss events. However, it relies on a range of variables that can vary widely even in the developed world. For example, critical care services may not be immediately available to stand alone maternity units. Furthermore, an intervention-based approach may lead to the omission of some near miss cases. A prospective observational study of severe maternal morbidity related to obstetric haemorrhage, found that only one 20% of women who developed haemorrhage-related morbidity were admitted to critical care. Most probably many of the women who suffered postpartum haemorrhage were cared for on labour wards rather than being transferred to critical care [19]. Other interventions, such as the use of hysterectomy to manage postpartum haemorrhage, have also been suggested as a straightforward binary endpoint [20, 21]. However, this again depends on the availability of local resources, equipment and personnel and is also vulnerable to subjective factors such as the decision-making process in postpartum haemorrhage.

Organ system dysfunction-based criteria for maternal near miss events, recognizes the trajectory of disease from normal healthy pregnancy, to pathological insult, to organ dysfunction and failure that can culminate in maternal death; to have ‘nearly missed’ death, a pregnant woman must have experienced organ dysfunction or failure without dying. This approach was proposed by Mantel et al. who defined markers of dysfunction for each organ system. The authors proposed that specific management options be used as markers of potential organ failure, that may have occurred if the treatment had not been applied promptly [17].

3.5 Development of the Near Miss Concept: The WHO Approach

In 2008 the WHO established a working group intended to develop a maternal death classification system and establish a consensus on how to define maternal near miss events [22]. The group was made up of obstetricians, midwives, epidemiologists and public health professionals from developing and developed countries. The same process that was used to develop a maternal death classification system was used to reach a consensus on maternal near miss to ensure the same principles applied to both in practice. Key principles guiding the development of both indicators were that the classification of maternal mortality and maternal near miss should facilitate comparison between healthcare facilities and also be practical for use in both high and low- to middle-income countries. It was recognized that there should be a high threshold for case ascertainment

so that any surveillance programme is not overwhelmed by a large number of cases.

The WHO recommended the use of organ system dysfunction-based criteria to identify near miss cases [18, 23]. However significant organ dysfunction is frequently diagnosed in the critical care setting. It was also recognized that there is a need to use markers of organ dysfunction that do not depend on the availability of specific facilities, such as critical care, that may be lacking in a low-resource setting. The clinical criteria therefore include such markers and are based largely on the Sequential Organ Failure Assessment (SOFA) score (see Chap. 19), a tool widely used to assess and classify critically ill patients and validated in the obstetric population [24, 25]. Management criteria are also included to facilitate case identification. Of note, the WHO working group also recommended that although these are technically not a 'near miss', maternal deaths should be included in near miss analyses.

In addition to the criteria for identification and classification of maternal near misses the WHO have described a standardized method, 'a conceptual framework', for implementing the use of near miss analyses into audit and quality improvement practices [26]. This framework aims to assist individual units and healthcare providers in utilizing the analysis of near miss events for the purpose of quality improvement. The standardized nature of the analysis enables comparison of data between different units regionally and internationally.

The framework encompasses a continuous cycle of baseline assessment (or reassessment) and situation analysis followed by implementation of interventions to improve the quality of healthcare. The main emphasis of this guide is on ensuring that all eligible women are identified at the baseline assessment, that the results inform policy decisions to improve the quality of maternal care and that findings are made public to allow the wider community to benefit from the lessons learned. This approach should also enable organizations such as the WHO to get a better large-scale picture of maternal health on a national or global scale.

The baseline assessment should consist of both near miss criterion-based audit [27] and also information from healthcare consumers (women who have suffered a maternal near miss event), providers and managers views via methods such as surveys or interviews. It is crucial that to ensure that identification of women who have suffered a near miss event is as complete as possible. Therefore in addition to spontaneous reporting, other strategies such as checklists included in medical records, regular group discussions and regular visits to areas where pregnant women are cared for must be employed. Once appropriate patients have been identified, data should be extracted from the case notes. Although technically a near miss can only be identified retrospectively as the woman, by definition, must survive the event, contemporaneous data collection has the advantage that any uncertainties in the case notes can be clarified by contact with the treating staff during retrospective data collection. The data collected should include details of the demographics, severe complications and outcomes of the women identified. It should also include the use of any critical interventions and the details of the woman's condition on arrival and delivery.

Situation analysis involves determining the prevalence of maternal near miss and mortality within the population evaluated and identifying barriers and opportunities for improving care. To assess the quality of care delivered in the treatment of individual life-threatening conditions, process indicators should be used. These can be determined from evidence-based recommendations applied appropriately to the local population [28]. For example, in women who develop eclampsia, the use of magnesium sulphate could be assessed with the process indicator being the number of women who received magnesium sulphate as treatment for eclampsia divided by the total number of eclamptic patients.

Interventions to improve care should be undertaken at a local level and include the use of education, evidence-based protocols, checklists and visual aids for some critical situations [29, 30].

3.6 Causes and Incidence of Near Miss Events

The prevalence of maternal near miss varies widely depending on screening criteria and geographical location. A major WHO systematic review of maternal near miss was published in 2004 [23] and a further review published in 2012 based on studies conducted between 2004 and 2010 [31].

The review published in 2004 predates the WHO recognized classification of maternal near miss and uses the nomenclature 'severe acute maternal morbidity'. The authors identified a total of 30 reports of severe acute maternal morbidity for inclusion in the systematic review. The definition of severe acute maternal morbidity used for the review fell broadly into two categories: one describing what the authors meant by a near miss (14 studies); and the other describing a response to an event such as hysterectomy (nine studies) or admission to intensive care unit (seven studies). The authors highlighted that in the included studies there was an 'intuitive agreement' on what a near miss means—a woman who almost died but survived. The prevalence of severe acute maternal morbidity varied between 0.80 and 8.23% in studies that used disease-specific criteria, 0.38–1.09% in the group that used organ system-based criteria and 0.01–2.99% in studies using management-based criteria.

The 2012 review included 82 studies, a dramatic increase on the 2004 review demonstrating the growing interest in this area. The prevalence rates of maternal near miss varied between 0.6 and 14.98% for disease-specific criteria, 0.14–0.92% for organ-based dysfunction (based on Mantel criteria) and 0.04–4.54% for management-based criteria.

Both reviews highlighted the disparities between high-income and low- and middle-income countries. In low- and middle-income countries: approximately 1% of the women experienced a near miss event before, during or after delivery when using a definition of organ dysfunction criteria, compared to 0.25% in high-income countries. Using mixed criteria combining different markers, the rate ranges between 2.10 and 4.43% in low-income and middle-income countries and 0.09 and 1.38% in higher-income countries.

Worldwide, obstetric haemorrhage, hypertensive diseases of pregnancy, sepsis and obstructed labour have been identified as the major causes of maternal near miss [32, 33]. Obstetric haemorrhage is the leading cause of maternal mortality worldwide accounting for two-thirds of all deaths. It is also a major cause of near miss events in developed and low- to middle-income countries. A systematic review of maternal near miss and mortality due to postpartum haemorrhage examined publications from 1995 to 2014 and included 26 studies and more than 500,000 deliveries [34]. The near miss ratio (defined as maternal near miss cases per 1000 live births) for postpartum haemorrhage was 6 for low-income and lower middle-income countries and 2 for high and higher middle-income countries.

3.7 Risk Factors

Risk factors for near miss events can vary depending on the specific cause of the event. Studies have consistently identified obesity [8], smoking during pregnancy [35] and advanced maternal age [36, 37] as risk factors for a range of near miss events. Pre-existing maternal medical conditions such as asthma, hypertension, malignant disease, cardiac disease and renal disease and diabetes mellitus are also associated with an increased risk for maternal near miss events and mortality [38–41]. Most countries today are multi-ethnic societies, and women from ethnic minority backgrounds have consistently been found to be at increased risk of near miss events, regardless of the country examined [42–46]. However considerable differences between ethnic minority groups in specific populations have been noted. In a nationwide population-based study in the Netherlands, non-Western immigrants showed a 1.3-fold increased risk of maternal morbidity. Within this group, large differences were observed among different ethnic minority groups; women from Morocco and Turkey had a risk equivalent to that seen in the general population, whereas women from sub-Saharan Africa had a 3.5-fold increased risk [44]. In a 10-year

nationwide study in Sweden, immigrant women from low-income countries had an increased risk of near miss events, whereas women from middle- and high-income countries showed no increased risk of near miss [45].

The role of antenatal care in identifying pregnant women with risk factors, thus enabling risk modification, has been established for several factors including anaemia, diabetes and hypertension. However, the role of antenatal care in preventing or contributing to the prevention of maternal mortality and serious morbidity remains subject to scrutiny, particularly for conditions that arise acutely around the time of delivery [46]. Underlying the uncertainty about the role of antenatal care, is a lack of information about the causes and pathophysiology of some of the more common complications of pregnancy (e.g. pregnancy-induced hypertension). Nevertheless inadequate utilization of antenatal care, particularly in women from ethnic minority backgrounds, has been identified as an additional risk factor for maternal morbidity [43, 47].

3.8 Healthcare Organizational Factors Contributing to Maternal Mortality

The majority of maternal near miss events occur around labour, delivery and the 24 h postpartum. Even in a patient without risk factors, a near miss event can develop precipitously and without warning. Studies have demonstrated that in the developing world, a significant number of maternal near miss cases have already occurred before the women's arrival at a healthcare facility. For example, in Ethiopia and Bolivia, 69 and 74% of the women with near miss were critically ill on arrival in hospital [48, 49]. Access to and the provision of emergency obstetric care has been described as the 'keystone in the arch of safe motherhood' [50]. The 'three delays model' has been described to characterize the different factors, divided into three 'phases', that can affect a woman's ability to access effective medical interventions in the event of an obstetric emergency [51, 52]. These phases are in turn affected by socioeconomic and cultural factors, accessibility of facilities and quality of care once a woman has reached a healthcare facility (Fig. 3.2).

Near miss cases that develop when a woman has reached or is in hospital can help to measure the quality of obstetric care provided within the healthcare facilities. A systematic review examined the facility-level barriers (the third delay) associated with maternal mortality in developing countries. This analysis identified 32 barriers to the receipt of timely and appropriate obstetric care once a patient had arrived in hospital [53]. These were categorized into five themes detailed in Table 3.2. Within these themes the most commonly cited barriers were inadequate training/skills mix (86%); drug procurement/logistics

Fig. 3.2 The Three Delays Model [51, 52]

The Three Delays Framework to describe delays in women accessing emergency obstetric care		
Delay in decision to seek care due to:	Delay in reaching care due to:	Delay in receiving adequate health care due to:
Poor understanding of complications and risk factors in pregnancy	*Distance to health care facilities and hospitals*	*Poor facilities and lack of medical supplies*
Poor understanding when to seek medical help	*Availability of and cost of transportation*	*Inadequately trained and poorly motivated medical staff*
Previous poor experience of health care	*Poor roads and infrastructure*	*Inadequate referral systems*
Acceptance of maternal death	*Geography e.g. mountainous terrain, rivers*	
Financial implications		

Table 3.2 Barriers to timely care

Drugs and equipment
Policy and guidelines
Human resources
Facility infrastructure
Patient and referral related

problems (65%); staff shortages (60%); lack of equipment (51%); and low staff motivation (44%). Although this study evaluated the effect on maternal mortality, it is a reasonable assumption that the themes identified would also be relevant with regard to prevention of near miss events. These themes are not unique to low- to middle-income countries with limited resources; they have been highlighted in many studies of maternal mortality and morbidity in the developed world also [3, 5].

3.9 Conclusions

Despite the relative success of the United Nation Millennium Development Goal for Maternal Health with the reduction of the number of maternal deaths worldwide, there remains much to be achieved. The maternal mortality ratio in low- to middle-income countries developing regions is still 14 times higher than in developed regions. If the Millennium Sustainable Goal [54] of reducing the global maternal mortality ratio to less than 70/100,000, live births by 2030 is to be reached, continuous and rigorous assessment of maternal mortality and morbidity must be undertaken. Evaluation of maternal near miss events must be an essential part of this process.

References

1. Trends in maternal mortality: 1990 to 2015. Estimates by WHO, UNICEF, UNFPA, The World Bank and the United Nations Population Division. http://www.afro.who.int/sites/default/files/2017-05/trends-in-maternal-mortality-1990-to-2015.pdf. Accessed Nov 2017.
2. Alkema L, Chou D, Hogan D, et al. Global, regional, and national levels and trends in maternal mortality between 1990 and 2015, with scenario-based projections to 2030: a systematic analysis by the UN Maternal Mortality Estimation Inter-Agency Group. Lancet. 2016;387(10017):462–74.
3. Knight M, Tuffnell D, Kenyon S, Shakespeare J, Gray R, Kurinczuk JJ, editors. On behalf of MBRRACE-UK. Saving lives, improving mothers' care—surveillance of maternal deaths in the UK 2011–13 and lessons learned to inform maternity care from the UK and Ireland confidential enquiries into maternal deaths and morbidity 2009–13. Oxford: National Perinatal Epidemiology Unit, University of Oxford; 2015.
4. National Committee for Confidential Enquiry into Maternal Deaths. Saving mothers 2011–2013: sixth report on confidential enquiries into maternal deaths in South Africa. Province of KwaZulu Natal: Department of Health. http://www.kznhealth.gov.za/mcwh/Maternal/Saving-Mothers-2011-2013-short-report.pdf. Accessed Nov 2017.
5. Saucedo M, Deneux-Tharaux C, Bouvier-Colle MH, French National Experts Committee on Maternal Mortality. Ten years of confidential inquiries into maternal deaths in France, 1998-2007. Obstet Gynecol. 2013;122:752–60.
6. Geller SE, Rosenberg D, Cox SM, Brown ML, Simonson L, Driscoll CA, Kilpatrick SJ. The continuum of maternal morbidity and mortality: factors associated with severity. Am J Obstet Gynecol. 2004;191:939–44.
7. Waterstone M, Bewley S, Wolfe C. Incidence and predictors of severe obstetric morbidity: case-control study. BMJ. 2001;322:1089–93.
8. Kayem G, Kurinczuk J, Lewis G, Golightly S, Brocklehurst P, Knight M. Risk factors for progression from severe maternal morbidity to death: a National Cohort Study. PLoS One. 2011;6:e29077.
9. van den Akker T, van Rhenen J, Mwagomba B, Lommerse K, Vinkhumbo S, van Roosmalen J. Reduction of severe acute maternal morbidity and maternal mortality in Thyolo District, Malawi: the impact of obstetric audit. PLoS One. 2011;6:e20776.
10. Furuta M, Sandall J, Bick D. Women's perceptions and experiences of severe maternal morbidity—a synthesis of qualitative studies using a meta-ethnographic approach. Midwifery. 2014;30:158–69.
11. Hinton L, Locock L, Knight M. Experiences of the quality of care of women with near-miss maternal morbidities in the UK. BJOG. 2014;121(Suppl 4):20–3.
12. Knight M. The UK obstetric surveillance system. Obstet Gynaecol Reprod Med. 2008;18:199–20.
13. Kilpatrick SJ, Abreo A, Gould J, Greene N, Main EK. Confirmed severe maternal morbidity is associated with high rate of preterm delivery. Am J Obstet Gynecol. 2016;215:233.e1–7.
14. Nashef SAM. What is a near miss? Lancet. 2003;361:180–1.
15. Filippi V, Ronsmans C, Gandaho T, Graham W, Alihonou E, Santos P. Women's reports of severe (near miss) obstetric complications in Benin. Stud Fam Plan. 2000;31:309–24.

16. Prual A, Bouvier-Colle M-H, de Bernis L, Breat G. Severe maternal morbidity from direct obstetric causes in West Africa: incidence and case fatality rates. Bull World Health Organ. 2000;78:593–602.
17. Mantel GD, Buchmann E, Rees H, Pattinson RC. Severe acute maternal morbidity: a pilot study of a definition for a near-miss. Br J Obstet Gynaecol. 1998;105:985–90.
18. Say L, Souza JP, Pattison RC, WHO working group on Maternal Mortality and Morbidity Classifications. Maternal near miss–towards a standard tool for monitoring quality of maternal health care. Best Pract Res Clin Obstet Gynaecol. 2009;23:287–96.
19. Brace V, Kernaghan D, Penney G. Learning from adverse clinical outcomes: major obstetric haemorrhage in Scotland, 2003–05. BJOG. 2007;114:1388–96.
20. Nasrat HA, Youssef MH, Marzoogi A, Talab F. Near miss obstetric morbidity in an inner city hospital in Saudi Arabia. East Mediterr Health J. 1999;5:717–26.
21. Knight M. Peripartum hysterectomy in the UK: management and outcomes of the associated haemorrhage. BJOG. 2007;114:1380–7.
22. Report on the World Health Organization working group on the classification of maternal deaths and severe maternal morbidities. Geneva: World Health Organization; 2009.
23. Say L, Pattinson RC, Gülmezoglu AM. WHO systematic review of maternal morbidity and mortality: the prevalence of severe acute maternal morbidity (near miss). Reprod Health. 2004;1:3.
24. Vincent JL, de Mendonça A, Cantraine F, Moreno R, Takala J, Suter PM, Sprung CL, Colardyn F, Blecher S. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med. 1998;26:1793–800.
25. Moreno R, Vincent JL, Matos R, Mendonça A, Cantraine F, Thijs L, Takala J, Sprung C, Antonelli M, Bruining H, Willatts S. The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care. Results of a prospective, multicentre study. Working Group on Sepsis related Problems of the ESICM. Intensive Care Med. 1999;25:686–96.
26. Evaluating the quality of care for severe pregnancy complications The WHO near-miss approach for maternal health. http://apps.who.int/iris/bitstream/10665/44692/1/9789241502221_eng.pdf. Accessed Nov 2017.
27. Graham WJ. Criterion-based clinical audit in obstetrics: bridging the quality gap? Best Pract Res Clin Obstet Gynaecol. 2009;23:375–88.
28. Wagaarachchi PT, Graham WJ, Penney GC, McCaw-Binns A, Yeboah Antwi K, Hall MH. Holding up a mirror: changing obstetric practice through criterion-based clinical audit in developing countries. BJOG. 2001;74:119–30.
29. Bernstein PS, Combs CA, Shields LE, Clark SL, Eppes CS, Society for Maternal-Fetal Medicine Patient Safety and Quality Committee. The development and implementation of checklists in obstetrics. Am J Obstet Gynecol. 2017;217:B2–6.
30. Wittenberg MD, Vaughan DJA, Lucas DN. A novel airway checklist for obstetric general anaesthesia. Int J Obstet Anesth. 2013;22:264–5.
31. Tunçalp Ö, Hindin M, Souza J, Chou D, Say L. The prevalence of maternal near miss: a systematic review. BJOG. 2012;119:653–61.
32. Murphy CM, Murad K, Deane R, Byrne B, Geary MP, McAuliffe FM. Severe maternal morbidity for 2004–2005 in the three Dublin maternity hospitals. Eur J Obstet Gynecol Reprod Biol. 2009;143:34–7.
33. Ghazal-Aswad S, Badrinath P, Sidky I, Safi TH, Gargash H, Abdul-Razak Y, et al. Severe acute maternal morbidity in a high-income developing multiethnic country. Matern Child Health J. 2013;17:399–404.
34. Maswime S, Buchmann E. A systematic review of maternal near miss and mortality due to postpartum hemorrhage. Int J Gynecol Obstet. 2017;137:1–7.
35. Roelands J, Jamison MG, Lyerly AD, James AH. Consequences of smoking during pregnancy on maternal health. J Womens Health. 2009;18:867–72.
36. McCall SJ, Nair M, Knight M. Factors associated with maternal mortality at advanced maternal age: a population-based case–control study. BJOG. 2017;124:1225–33.
37. Oliveira FC Jr, Surita FG, Pinto e Silva JL, Cecatti JG, Parpinelli MA, Haddad SM, Costa ML, Pacagnella RC, Sousa MH, Souza JP. Severe maternal morbidity and maternal near miss in the extremes of reproductive age: results from a national cross- sectional multicenter study. BMC Pregnancy Childbirth. 2014;14:77.
38. Mhyre JM, Bateman BT, Leffert LR. Influence of patient comorbidities on the risk of near-miss maternal morbidity or mortality. Anesthesiology. 2011;115:963–72.
39. Lindquist AC, Kurinczuk JJ, Wallace EM, et al. Risk factors for maternal morbidity in Victoria, Australia: a population-based study. BMJ Open. 2015;5:e007903.
40. Adeoye IA, Onayade AA, Fatusi AO. Incidence, determinants and perinatal outcomes of near miss maternal morbidity in Ile-Ife Nigeria: a prospective case control study. BMC Pregnancy Childbirth. 2013;13:93.
41. Gray KE, Wallace ER, Nelson KR, Reed SD, Schiffa MA. Population-based study of risk factors for severe maternal morbidity. Paediatr Perinat Epidemiol. 2012;26:506–14.
42. Knight M, Kurinczuk JJ, Spark P, Brocklehurst P. Inequalities in maternal health: national cohort study of ethnic variation in severe maternal morbidities. BMJ. 2009;338:b542.
43. Nair M, Kurinczuk JJ, Knight M. Ethnic variations in severe maternal morbidity in the UK—a case control study. PLoS One. 2014;9:e95086.
44. Zwart JJ, Jonkers MD, Richters A, Ory F, Bloemenkamp KW, Duvekot JJ, van Roosmalen

J. Ethnic disparity in severe acute maternal morbidity: a nationwide cohort study in the Netherlands. Eur J Pub Health. 2011;21:229–34.
45. Wahlberg Å, Rööst M, Haglund B, Högberg U, Essén B. Increased risk of severe maternal morbidity (near-miss) among immigrant women in Sweden: a population register-based study. BJOG. 2013;120:1605–12.
46. Carroli G, Rooney C, Villar J. How effective is antenatal care in preventing maternal mortality and serious morbidity? An overview of the evidence. Paediatr Perinat Epidemiol. 2001;15:1.
47. Pacheco AJC, Katz L, Souza ASR, de Amorim MMR. Factors associated with severe maternal morbidity and near miss in the São Francisco Valley, Brazil: a retrospective, cohort study. BMC Pregnancy Childbirth. 2014;14:91.
48. Liyew EF, Yalew AW, Afework MF, Essén B. Incidence and causes of maternal near-miss in selected hospitals of Addis Ababa, Ethiopia. PLoS One. 2017;12(6):e0179013.
49. Rööst M, Altamirano VC, Liljestrand J, Essén B. Priorities in emergency obstetric care in Bolivia—maternal mortality and near-miss morbidity in metropolitan La Paz. BJOG. 2009;116:1210–7.
50. Fortney J. Emergency obstetric care: the keystone in the arch of safe motherhood. IJOG. 2001;74:95–7.
51. Thaddeus S, Maine D. Too far to walk: maternal mortality in context. Soc Sci Med. 1994;38:1091–110.
52. https://www.maternityworldwide.org/what-we-do/three-delays-model/. Accessed Nov 2017.
53. Knight HE, Self A, Kennedy SH. Why are women dying when they reach hospital on time? A systematic review of the 'third delay'. PLoS One. 2013;8:e63846.
54. http://www.un.org/sustainabledevelopment/sustainable-development-goals/. Accessed Nov 2017.

The Epidemiology of Maternal Intensive Care Unit Admissions

4

Andreea A. Creanga

Bullet Points

- Obstetric patients represent a small proportion of patients in intensive care units.
- Threshold levels for obstetric ICU admission vary widely.
- The majority of pregnancy-associated ICU admissions occur during the delivery admission and <24 h after delivery.
- Postpartum hemorrhage, preeclampsia/eclampsia, and sepsis account for the majority (75–80%) of obstetric ICU admissions across the world.
- Indirect causes of obstetric ICU admission show geographic variation.
- Most obstetric patients spend <24–48 h in the ICU due to rapid reversal of many obstetric conditions after delivery.
- Maternal ICU patients tend to have better outcomes than other ICU patients, but the case fatality rate in these patients is a significant concern.

4.1 Maternal Mortality

Maternal mortality is a key indicator of the functioning of a country's health system and of the quality of care it provides [1]. The World Health Organization (WHO) defines a maternal death as "the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes." [2] While globally maternal mortality declined by 43% between 1990 and 2015, developing regions contribute 99% of the global burden; the lifetime risk of dying from pregnancy complications is 1 in 150 in developing regions compared to 1 in 4900 in developed regions [2].

4.2 Severe Maternal Morbidity and Maternal Near Miss Definitions

Because maternal deaths are rare events [1], especially in high-resource countries, context-specific clinical policies to prevent similar future deaths are limited. Hence, there is growing global interest in reviewing "severe maternal morbidity" (SMM) or "maternal near miss" (MNM) events, which are recognized as complex entities with a wide range of clinical presentations and severity

A. A. Creanga (✉)
Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Department of Gynecology and Obstetrics, Johns Hopkins School of Medicine, Baltimore, MD, USA
e-mail: acreanga@jhu.edu

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_4

within a continuum from healthy pregnancy to maternal death. Such reviews of SMM or MNM offer learning opportunities to improve their recognition and management and prevent related long-term disability and death, Chap. 3 [3, 4].

In 2009, in order to enable systematic data collection on MNM (which is defined as "a woman who nearly died but survived a pregnancy complication"), the WHO published criteria based on markers of management and of clinical and organ dysfunction [5]. These criteria require detailed information on MNM cases, thus limiting their practical use. Subsequently, in 2016, the WHO's Maternal Morbidity Working Group defined maternal morbidity as "any health condition attributed to and/or complicating pregnancy and childbirth that has a negative impact on the woman's wellbeing and/or functioning." [6] Proposed identification criteria for maternal morbidity include 58 symptoms, 29 signs, 44 investigations, and 35 management strategies and are supposed to serve as a framework for identifying maternal morbidity beyond maternal MNM [6].

In parallel with WHO efforts, in the United States (USA), the Centers for Disease Control and Prevention (CDC) developed an algorithm for identifying SMM using nationwide hospital administrative data and International Classification of Diseases (ICD) diagnosis and procedure codes for 20+ indicators of organ-system dysfunction, including maternal mortality [7, 8]. The CDC SMM identification algorithm has been validated and shown to perform well as a surveillance tool at the population level using administrative data [9]. For SMM surveillance at the facility level, the National Partnership for Maternal Safety (NPMS) proposed the use of the following two criteria: pregnant or postpartum women who have (1) been admitted to the intensive care unit (ICU), or (2) received ≥4 units of packed red blood cells for management of hemorrhage [10]. A SMM review form was also developed to allow standardization of these reviews, and use or adaptation for use by hospitals in the USA [11].

In Europe, the EURO-PERISTAT project reviewed potential maternal morbidity indicators aiming to propose a SMM definition and assess the availability of data to construct morbidity indicators from hospital systems in participating countries [12]. The initial SMM definition adopted included four indicators: (1) eclampsia, (2) hysterectomy, (3) blood transfusion, and (4) ICU admission, to which (5) embolization was subsequently added as a fifth indicator [12].

Given all these efforts, maternal morbidity has become the focus of several research projects in Europe, the USA, and elsewhere. An international network, the International Network of Obstetric Survey Systems (INOSS), now links obstetric surveillance data from over 12 countries and aims to advance knowledge and contribute to the evidence base on serious, rare disorders in pregnancy including SMM and MNM events through international cooperation and collaborative working [13].

4.3 Prevalence of Critical Maternal Events

Most pregnancies and births are uneventful, yet it has been estimated that 15% of all pregnant women develop potentially life-threatening complications with some in need of major obstetrical intervention to survive [14]. For each maternal death, it has been suggested that 20–30 women suffer from morbidity [6]; however, this figure is not based on standardized, well-documented methodologies [6].

A 2010 systematic literature review that aimed to assess the prevalence of SMM worldwide included 82 studies from 46 countries [15]. Among these studies, by and large, authors used three major approaches to identify SMM: (1) disease-specific (e.g., preeclampsia, peripartum hemorrhage), (2) management-based (e.g., ICU admission, emergency hysterectomy, blood transfusion), and (3) organ-system dysfunction (e.g., shock, respiratory distress). Prevalence rates of SMM varied widely, ranging between 0.60 and 14.98% for disease-specific criteria, 0.04 and 4.54% for management-based criteria, and 0.14 and 0.92% for organ-based dysfunction [15].

In the USA, SMM is currently estimated to occur in up to 1.4% of pregnancies and to affect

over 60,000 women every year [7, 8]. Based on national hospital discharge data reported by the CDC, the overall SMM rate almost tripled over the last two decades, driven by an increase in blood transfusions, a proxy for hemorrhage [7]. If blood transfusions are excluded, the SMM rate increased by about 40% over the last two decades to 34.3 SMM cases per 10,000 delivery hospitalizations in 2013–2014 [7].

In 2016, testing of new gold standard clinical guidelines to define SMM cases showed that while 2% of deliveries screened positive for SMM, only 0.9% were true SMM cases [9]. Women with true SMM were significantly older than women without SMM, 12.7% of them had multiple gestation, and about 87% were overweight or obese [16]. Preterm delivery was significantly more common in women with than without SMM, with 32 and 10.7% of them delivering at <37 and <32 weeks, respectively [16]. The most common underlying causes of SMM were hemorrhage (71.3%) and preeclampsia/eclampsia (10.7%), and 78% of women with SMM were delivered by cesarean [16]. Notably, the opportunity for improvement in care was present in 44% of SMM cases [16].

Twenty-two countries or regions in Europe provided at least one maternal morbidity indicator for the EURO-PERISTAT project [12]. Eclampsia was the most widely recorded condition in these countries, with prevalence rates ranging from 0.1/1000 deliveries in Finland, Sweden, and Scotland to 0.9/1000 deliveries in Latvia and France [12]. Seventeen countries or regions provided data about hysterectomies, with corresponding prevalence rates ranging from ≤0.1/1000 deliveries in Wales and Sweden to 1.2 and 1.3/1000 deliveries in Latvia and Estonia, respectively [12, 13].

National level SMM or MNM studies are less readily available in developing countries. Rates of SMM or MNM from relatively small studies were considerably higher in Asian and African countries than the rest of the world [15, 17–19]. Of note, across the world, groups of economically disadvantaged women (e.g., minorities, including immigrants) are shown to have higher rates of SMM [20, 21]. Severe morbidity is many times accompanied by delivery complications, preterm birth, stillbirth, and neonatal morbidity and mortality and can also have long-term health consequences [22–26]. For example, gestational diabetes confers a seven-fold higher risk for type 2 diabetes, and preeclampsia confers a 3.4-fold risk increase for hypertension later in life [23, 24].

Levels and trends in SMM rates are expected to influence utilization of critical care by obstetric patients over time. Trends in SMM appear to be increasing in developed countries, with disturbing reports from several countries of increasing incidence of peripartum hemorrhage, one of the key contributors to ICU admission in postpartum women [1, 4, 7].

4.4 Maternal Intensive Care Admission

4.4.1 General Considerations

Obstetric patients, including pregnant and postpartum women, may need intensive care to treat and/or support failing organs for obstetric or medical disorders or after trauma. Multiple organ failure may occur in both medical and obstetric disorders that occur during preganacy [27, 28]. However, the physiological changes occurring during pregnancy may cause medical disorders to present differently during pregnancy and in the immediate postpartum period. Thus, a key problem in identifying critical illness in obstetric patients is the close similarity of manifestations of medical and obstetric conditions. Specific treatment is available for medical conditions, while prompt delivery may be lifesaving in some obstetric disorders.

The vast majority of studies examining critical care admissions for obstetric patients are single center and are mostly conducted in tertiary care centers, thus limiting their external validity. Population-based studies are mainly available from high-resource countries [29–33]. These studies demonstrate marked differences between North American and Western European countries in obstetric ICU admission [34]. No guidelines

are available for triaging obstetric patients to intensive care anywhere in the world [29, 35, 36]. Therefore, there remains wide variability in ICU admission thresholds for obstetric patients between and within countries and regions. Across settings, reasons for this variability include ICU bed availability, patient case mix, healthcare system organization, and practice patterns. Decisions regarding admission of obstetric patients to ICU may also be confounded by physiologic changes in pregnancy; predisposition to certain conditions seen in the nonpregnant population; occurrence of epidemics and pandemics that may raise levels of illness severity and clinical suspicion of such; and, importantly, the accessibility and availability of such care, which is especially problematic in developing regions.

4.5 Levels, Patterns, and Trends

There is relatively wide geographical variation in the proportion of obstetric ICU admissions among all ICU cases (Table 4.1). Most of the current data has been derived from retrospective data. In order to fully capture obstetric ICU admissions during retrospective review, the case identification strategy should include antepartum and postpartum admissions that are distinct from the delivery admission [37]. Differences in reported obstetric ICU admission rates among all deliveries relate both to geographical location and available resources and also to careful case identification. One study used a strategy to identify all obstetric ICU admissions not just during the delivery admission; there, the overall rate of ICU utilization was 419.1/100,000 deliveries, among which 162.5, 202.6, and 54.0/100,000 deliveries were antepartum, during delivery, and postpartum, respectively [29].

Some larger obstetric units throughout the world have developed "high level" obstetric care. These are non-ICU units, usually located in or next to the labor and delivery units. They are staffed by medical personnel with training in critical care medicine. Such units can provide invasive cardiovascular monitoring, but they often lack specialized ventilation services or advanced life support

Table 4.1 Key characteristics of osbtetric ICU admissions (NR-not reported)

Country	Author	Number of obstetric ICU admissions	Incidence of ICU admissions (per deliveries) (%)	Obstetric patients among all ICU admissions (%)
UK	Harrison	1902	NR	0.9
Morocco	Mjahed	364	0.6	16
Argentina	Rios	242	0.8	3.9
UK	Hazelgrove	210	0.2	1.8
Spain	Vasquez	161	0.7	10
UK	Wheatley	144	0.8	12
Netherlands	Keizer	142	0.8	0.7
Turkey	Demirkiran	125	0.9	2.2
Saudi Arabia	Anwari	99	0.2	1.6
Kingdom of Bahrain	Rajab	83	0.2	3.0
South Africa	Plateau	80	NR	8.7
Saudi Arabia	Al-Jabari	65	NR	0.5
UAE	Mirghani	60	0.3	2.4
Israel	Lewinsohn	58	NR	0.4
Australia	Sriram	56	NR	0.4
Hong Kong	Leung	50	0.1	0.7
China	Tang	49	0.1	0.6
Israel	Cohen	46	2.4	0.2
Singapore	Cheng	43	0.3	1.1
Singapore	Ng	37	0.2	3.0
England	Selo-Oieme	33	0.1	0.8
Pakistan	Bibi	30	1.35	1.3
Nigeria	Okafor	18	0.3	2.2
Lebanon	Richa	15	0.2	0.4

techniques such as ECMO that are available in general ICUs [38]. Such units have been coined "obstetric intensive care," "obstetric intermediate care," and "obstetric high-dependency units." Between 0.9 and 1.7% of all obstetric patients in three studies conducted in the late 1980s and early 1990s were reported to receive "high level" care, and only 5–11% of the women were transferred to a general ICU [39–41].

Admission to a general ICU occurs with varied frequency [39–41] among obstetric patients [28, 42]. A recent report of ICU admissions among obstetric patients (2001–2010 statewide data from Texas) documented the highest incidence of ICU utilization in obstetric patients in the USA to date; 1 in 25 pregnancy-associated hospitalizations and 1 in 30 pregnancies involved an ICU admission [28]. This translates to an overall incidence of ICU admission of 39.0/1000 pregnancy-associated hospitalizations-years, ranging between 32.1/1000 delivery hospitalizations-years and 144.8/1000 postpartum hospitalizations-years [28]. Approximately 1% of women who deliver are readmitted within 6 weeks [42]. The majority of pregnancy-associated ICU admissions occur during the delivery admission; however, proportionately, more obstetric-related admissions occur among those admitted postpartum [43]. This is not surprising given obstetric providers' reluctance to transfer mothers until the infant is delivered. Postpartum ICU admission in the Texas series was accompanied by 14-times higher rates of SMM and 32-times higher rates of hospital mortality than women admitted for delivery [28]. Pregnancy-associated ICU admission rates were highly variable by pregnancy outcome, ranging between 0.6/1000 abortions-years and 85.9/1000 stillbirths-years [28]. During the study period, the rates of postpartum admission with severe complications more than doubled, and the overall mortality of women admitted postpartum to the ICU increased by 66% [28].

Previously reported US state-level incidence of ICU admission were considerably lower; 1.5/1000 deliveries during 1984–1997 [31], 4.2/1000 deliveries during 1998–2008 in Maryland [29], and 15.4/1000 deliveries during 1997–2005 in New Jersey [32]. Between 2009 and 2012, the rate of ICU admission was 2.9/1000 maternities in the UK [43]. The much lower availability of surgical and medical ICUs in the developing regions of the world limits the relevance of ICU admission frequencies between developed and developing regions [14, 15].

The rate of emergency cesarean delivery is one of the criteria used by the WHO for assessing the quality of obstetric care [14]. Cesarean delivery rates are high among ICU-admitted pregnant and postpartum women, ranging between 50.0 and 87.4% with an average of about 65% in a recent literature review [38]. Of note, however, in most cases, cesarean delivery was not the primary cause of ICU admission but was performed because of SMM and the clinical condition of the woman [38].

Early identification and management of SMM is expected to reduce the number of women who need ICU care and to restrict its use to the most severe cases and those with unexpected complications among women with low-risk pregnancies. However, given increases in maternal age and the higher burden of chronic medical conditions that women carry into pregnancy, current levels of need for ICU admission may persist.

4.6 Key Characteristics of Women Admitted to ICUs During Pregnancy and/or Peripartum

Several cohort and case-control studies identified key characteristics and risk factors for ICU admission in obstetric patients. In the 1984–1997 Maryland study [31], age >35 years, non-white race, treatment in small teaching hospitals, and transfer to a higher-level hospital were predictors of pregnancy-associated ICU admission. In a French cohort [44], higher order parity, multiple pregnancy, non-European nationality, and having a consultation (which is mandatory at 36 weeks in France) at a hospital other than the one where the woman delivered were key predictors of ICU admission in pregnant women. The odds ratio of requiring ICU care was 2.5 (95% CI 0.3–4.6) in

the study from France [44], and 3.3 (95% CI 1.5–7.0) in a tertiary hospital in Canada among women with multiple pregnancies compared to those with singleton pregnancies [45].

More women in developed countries are increasingly delaying childbearing. As a result, more are expected to enter pregnancy with a burden of chronic medical conditions and other risk factors. These women are more likely to require not only heightened clinical vigilance, but also complex care, including cesarean delivery. For example, almost 15% of the pregnant women admitted to an ICU in the Texas series were over 35 years of age, 9.7% of them had a chronic medical condition, and 6.2% had organ dysfunction [28].

4.7 Causes of ICU Admission

Conditions that may result in ICU admission during pregnancy and the postpartum period can be categorized as: (1) pregnancy-related, (2) pre-existing comorbidities that may worsen during pregnancy (e.g., epilepsy, myasthenia gravis, valvular disease, congenital heart disease, primary pulmonary hypertension, diabetes mellitus, chronic kidney disease), (3) diseases for which the woman has an increased risk during pregnancy (e.g., infection/sepsis, pulmonary embolism, deep venous thrombosis, acute kidney injury, renal failure), and (4) acute diagnoses that may be coincidental to pregnancy (e.g., trauma, ruptured intracranial aneurysm, appendicitis, cholecystitis).

Direct, pregnancy-related conditions that most often lead to ICU admission include obstetric complications such as postpartum hemorrhage, hypertensive disorders of pregnancy, amniotic fluid embolism, and complications of cesarean delivery. Postpartum hemorrhage, preeclampsia/eclampsia, and sepsis account for the vast majority (75–80%) of ICU admissions in pregnant women across the world [17, 29, 31, 39, 40, 43, 46–55]. Preeclampsia/eclampsia and postpartum hemorrhage were, indeed, the most common causes of pregnancy-associated ICU admission in the recent Texas series [28]. Yet, only a minority of women diagnosed with each of these conditions (12.0% and 8.9%, respectively) were admitted to the ICU. Conversely, two-thirds of those with status epilepticus received care in the ICU [28]. Indirect causes of morbidity leading to maternal ICU admission show more of a geographic variation [38], with conditions like asthma, pneumonia, pulmonary thromboembolism, collagen vascular disorders, and injuries (e.g., motor vehicle accidents, drug overdoses) being common in the developed world, while viral and parasitic infections being more prevalent in developing regions [56–59]. For example, a study from one center in New Jersey noted that 80% of antepartum ICU admissions were for medical conditions, whereas 77% of postpartum admission were for obstetric conditions [60]. By comparison, a study in India found that 45% of antepartum admissions and 19% of postpartum admissions were for medical disorders [57]. Community-acquired infections are the most common conditions requiring ICU admission in the antepartum period, especially in developing countries [17].

Obstetric disorders appear to be more common causes for pregnancy-associated ICU admission in western European and some Asian countries than they are in the USA [17, 61, 62]. A lower incidence of serious respiratory infections and fewer women requiring mechanical ventilation were reported in Spain, for example, than in the USA [62]. Studies from Asia also contrast with those from Europe and the USA in that no ICU-admitted obstetric patients had deep venous thrombosis [63, 64]. Also of note, massive postpartum hemorrhage was responsible for 73% of pregnancy-associated ICU admissions in a study in Finland, yet all of the 22 obstetric ICU admissions were women with low risk [65]. This is likely the result of early identification and management of complications in women with high-risk pregnancies in many developed countries. Thus, there appear to be differences in causes of ICU admission both within and between countries, as well as differences dependent on the time of admission in relation to pregnancy in different reports. Such differences may stem from different threshold for admitting a

pregnant or postpartum woman to an ICU or the different phases of obstetric transition in various countries.

Of note, anesthesia complications were responsible for maternal ICU admissions in up to 26% of cases reported in studies throughout the 1980s and 1990s [31, 54, 66–70], but their contribution to this subpopulation has declined in recent times, in parallel with a documented decline in their contribution to maternal mortality in developed regions [71].

Finally, studies conducted in the early 2000s suggest that about 65% of pregnant and postpartum women admitted to the ICU experience failure of one or more organ systems [17, 43, 61]. The respiratory and hematological systems are most commonly affected [17, 28, 57, 61]—the former especially so in antepartum patients admitted to an ICU—while the latter is most common in postpartum cases [50, 57]. As of the time of this writing, more contemporary data are lacking.

4.8 Severity of Cases Admitted to ICU

Obstetric patients tend to have better outcomes than other intensive care patients [17], with 2% versus 11% ICU mortality rates respectively reported in the UK in 2007 [72]. Studies have shown that many obstetric patients spend less than 24–48 h in the ICU, likely due to the rapid reversal of many obstetric conditions after delivery [73, 74]. While some argue that many obstetric patients could be managed in a high-dependency unit (HDU) rather than an intensive care unit [74, 75], these HDUs generally have capabilities that in other centers are only available in ICUs. That a certain proportion of patients admitted to intensive care may be managed successfully outside the ICU is probably true for any group of patients, since a certain margin of safely is desirable if resources permit. The threshold for ICU admission has not been delineated for most patient populations, and obstetric patients are no different in this sense. The relative prevalence of "high level" units for obstetric patients compared to other patient groups may suggest a reluctance to refer or admit pregnant or peripartum women to intensive care units. Considerations potentially leading to such reluctance include the high likelihood of rapid maternal recuperation and a desire to encourage maternal-neonatal bonding.

Severity of illness is usually ascertained by using physiological information to derive severity scores [51]. Commonly used prognostic systems (e.g., APACHE II) have not been accurate in predicting outcomes of ICU-admitted obstetric patients [51]. This is likely because most scoring systems do not include adjustments for normal obstetric physiologic changes, such as decreased blood pressure and increased respiratory rate. As a result, high scores may be given to normal score parameter values for pregnant women that are outside the normal range in nonpregnant individuals.

Case severity potentially meeting indications for ICU admission can be defined by the number of organ dysfunctions or the All Patients Refined Diagnosis-Related Groups (APR-DRG) codes routinely reported in administrative data [38]. ICU admissions can be categorized into minor, moderate, high, and extreme case severity by integrating patients' demographics, principal and secondary diagnoses, and procedure codes [28]. Using APR-DRG categorization, more than one-quarter (26.5%) of ICU-admitted pregnancy-associated cases in the Texas series, for example, was classified as "highly severe" and 3.6% as "extremely severe." [28] Severity of illness measured by mean APR-DRG scored showed an annual decrease of 1.1% per year in the same report [28].

The case fatality rate, defined as the number of ICU-admitted pregnant or postpartum women who died in hospital divided by the total number of pregnancy-associated ICU admissions, is not negligible. Over 400 pregnant or postpartum women died in an ICU as reported in the Texas series (2001–2010), yielding a 0.3% case fatality rate, which did not change significantly over time [28]. Case fatality rates for obstetric cases admitted to an ICU are significantly higher in developing countries than they are in developed countries [55, 58]. This can be explained by case severity at

the time of hospital and ICU admission which likely reflects the poor functionality of health systems in developing regions of the world.

Another measure of case severity reported in the literature is the death to ICU transfer ratio, which in a recent literature review ranged widely between 1:5 and 1:126 [38]. For example, a majority (58.6%) of maternal deaths in the earlier Maryland report occurred without ICU admission, potentially suggesting ICU underutilization in this state [29]. By comparison, in Texas, only 26% of deaths in pregnancy-associated hospitalizations did not involve ICU admission [28]. The distribution of antepartum, intrapartum, and postpartum ICU admissions closely matches the timing of maternal deaths with about 25% occurring antepartum, 28% intrapartum/immediately postpartum, and 36% subacute/delayed postpartum [76]. Over time, a decrease occurred mainly in intrapartum maternal deaths worldwide [76].

4.9 Surveillance and Future Research Considerations

SMM and MNM are promising indicators for monitoring the quality of obstetric care throughout the world. Reductions in adverse maternal outcomes should translate into improvements in these indicators. For surveillance purposes, routine administrative hospital data can provide valuable information about SMM and ICU admissions, yet efforts should be made to validate the data and improve their quality. ICU admission has long been considered a proxy for SMM; this is now considered one of two criteria recommended for facility-level SMM surveillance in the USA, for example [5, 10]. Notably, audits of SMM have shown that about two-thirds of cases will be missed if ICU admission is the only indicator of SMM [77]. Moreover, the 2017 Texas series documented the highest incidence of ICU admission in obstetric patients in a high-resource country to date [28], demonstrating a relatively low threshold for admitting pregnant and postpartum women to an ICU and raising questions regarding the use of ICU admission as a proxy or marker for SMM. The USA has one of the highest population-indexed number of adult ICU beds in high-resources settings [33], and the increasing number of ICU beds may be a driver for rising ICU utilization in the general population [78]. Yet, when looking at settings with similar levels of ICU bed availability, the incidence of general obstetric ICU admission is considerably higher in the USA [33]. Thus, international comparisons of SMM, MNM, or just maternal ICU admission are even more difficult to make than country-level comparisons.

Is there a model in SMM or MNM surveillance? The UK Obstetric Surveillance System (UKOSS) is a national system for research into MNM. The conditions studied through UKOSS change over time, according to the key questions and challenges identified from within UK maternity services. The recent addition of a program for MNM case reviews, called the Confidential Enquiries into Maternal Morbidity (CEMM), permits a complete examination of the incidence, risk factors, care, and outcomes of the most severe complications in pregnancy [79]. A different near miss condition is chosen each year for the CEMM on the basis of an open call for topic proposals. Of note, however, no attempt has been made in the UK to define SMM as an entity and conduct surveillance for a list of SMM indicators. The topic-based approach to study MNM conditions allows for new studies to be introduced when there are specific clinical questions to be addressed and minimizes the data collection burden and fatigue [79, 80].

Studies are needed to assess the avoidable variability in ICU utilization by pregnant and postpartum women in order to inform planning and resource allocation as well as to assess ICU utilization as a proxy measure for SMM at state, regional and national levels, and for international comparisons.

Future studies reporting data on pregnancy-associated ICU admissions should use specific denominators (i.e., deliveries or postpartum hospitalizations) for deriving ICU admission incidence to facilitate comparisons between studies. When examining antepartum or postpartum hospitalizations separately, using delivery hos-

pitalizations as the denominator underestimates the demand for ICU services. More specific data on utilization of ICU services by women with specific maternal morbidities can inform the development of triage and management guidelines for pregnant and postpartum women who need critical care. Since the association between ICU admission and preventable maternal death or long-term disability cannot be examined through a randomized experimental approach, there is need for observational studies that include sufficient detailed clinical and temporal information to help develop prognostic markers of maternal death or long-term disability, which in turn provide a sufficient window for clinical intervention.

References

1. Creanga AA. Maternal mortality in the developed world: a review of surveillance methods, levels and causes of maternal deaths during 2006-2010. Minerva Ginecol. 2017;69:608–17.
2. WHO, UNICEF, UNFPA, The World Bank and the United Nations Population Division. Trends in maternal mortality: 1990 to 2015. http://www.who.int/reproductivehealth/publications/monitoring/maternal-mortality-2015/en/ Accessed 25 Jun 2018.
3. American College of Obstetricians and Gynecologists and the Society for Maternal–Fetal Medicine, Kilpatrick SK, Ecker JL. Severe maternal morbidity: screening and review. Am J Obstet Gynecol. 2016;215(3):B17–22.
4. Kilpatrick SJ, Berg C, Bernstein P, Bingham D, Delgado A, Callaghan WM, Harris K, Lanni S, Mahoney J, Main E, Nacht A, Schellpfeffer M, Westover T, Harper M. Standardized severe maternal morbidity review: rationale and process. Obstet Gynecol. 2014;124(2 Pt 1):361–6.
5. Say L, Souza JP, Pattinson RC, WHO Working Group on Maternal Mortality and Morbidity Classifications. Maternal near miss--towards a standard tool for monitoring quality of maternal health care. Best Pract Res Clin Obstet Gynaecol. 2009;23(3):287–96.
6. Chou D, Tunçalp Ö, Firoz T, Barreix M, Filippi V, von Dadelszen P, van den Broek N, Cecatti JG, Say L, Maternal Morbidity Working Group. Constructing maternal morbidity—towards a standard tool to measure and monitor maternal health beyond mortality. BMC Pregnancy Childbirth. 2016;16:45.
7. Callaghan WM, Creanga AA, Kuklina EV. Severe maternal morbidity among delivery and postpartum hospitalizations in the United States. Obstet Gynecol. 2012;120(5):1029–36.
8. Centers for Disease Control and Prevention. Severe maternal morbidity. http://www.cdc.gov/reproductivehealth/maternalinfanthealth/severematernalmorbidity.html. Accessed 25 Jun 2018.
9. Main EK, Abreo A, McNulty J, Gilbert W, McNally C, Poeltler D, Lanner-Cusin K, Fenton D, Gipps T, Melsop K, Greene N, Gould JB, Kilpatrick S. Measuring severe maternal morbidity: validation of potential measures. Am J Obstet Gynecol. 2016;214(5):643.e1–643.e10.
10. Callaghan WM, Grobman WA, Kilpatrick SJ, Main EK, D'Alton M. Facility-based identification of women with severe maternal morbidity: it is time to start. Obstet Gynecol. 2014;123:978–81.
11. Council on Patient Safety in Women's Health. Severe maternal morbidity review form. http://safehealthcareforeverywoman.org/patient-safety-tools/severe-maternal-morbidity-review/. Accessed 25 June 2018.
12. 2010 European Perinatal Health Report. 2013. http://www.europeristat.com/images/doc/EPHR2010_w_disclaimer.pdf. Accessed 25 Jun 2018.
13. Knight M, INOSS. The international network of obstetric survey systems (INOSS): benefits of multi-country studies of severe and uncommon maternal morbidities. Acta Obstet Gynecol Scand. 2014;93(2):127–31.
14. World Health Organization, UNFPA, UNICEF and Mailman School of Public Health. Averting Maternal Death and Disability. Monitoring emergency obstetric care. A Handbook. 2009. http://apps.who.int/iris/bitstream/10665/44121/1/9789241547734_eng.pdf. Accessed 25 Jun 2018.
15. Tunçalp O, Hindin MJ, Souza JP, Chou D, Say L. The prevalence of maternal near miss: a systematic review. BJOG. 2012;119(6):653–61.
16. Ozimek JA, Eddins RM, Greene N, Karagyozyan D, Pak S, Wong M, Zakowski M, Kilpatrick SJ. Opportunities for improvement in care among women with severe maternal morbidity. Am J Obstet Gynecol. 2016;215(4):509.e1–6.
17. Karnad DR, Guntupalli KK. Critical illness and pregnancy: review of a global problem. Crit Care Clin. 2004;20(4):555–76.
18. Naylor DF Jr, Olson MM. Critical care obstetrics and gynecology. Crit Care Clin. 2003;19(1):127–49.
19. Ryan M, Hamilton V, Bowen M, McKenna P. The role of a high-dependency unit in a regional obstetric hospital. Anaesthesia. 2000;55(12):1155–8.
20. Creanga AA, Berg CJ, Syverson C, Seed K, Bruce FC, Callaghan WM. Race, ethnicity, and nativity differentials in pregnancy-related mortality in the United States: 1993–2006. Obstet Gynecol. 2012;120(2 Pt 1):261–8.
21. Urquia ML, Glazier RH, Mortensen L, Nybo-Andersen AM, Small R, Davey MA, Rööst M, Essén B, ROAM (Reproductive Outcomes and Migration. An International Collaboration). Severe maternal morbidity associated with maternal birthplace in three high-immigration settings. Eur J Pub Health. 2015;25(4):620–5.

22. Gongora MC, Wenger NK. Cardiovascular complications of pregnancy. Int J Mol Sci. 2015;16(10):23905–28.
23. Nerenberg K, Daskalopoulou SS, Dasgupta K. Gestational diabetes and hypertensive disorders of pregnancy as vascular risk signals: an overview and grading of the evidence. Can J Cardiol. 2014;30(7):765–73.
24. Magnussen EB, Vatten LJ, Smith GD, Romundstad PR. Hypertensive disorders in pregnancy and subsequently measured cardiovascular risk factors. Obstet Gynecol. 2009;114:961–70.
25. Garovic VD, Bailey KR, Boerwinkle E, Hunt SC, Weder AB, Curb D, Mosley TH Jr, Wiste HJ, Turner ST. Hypertension in pregnancy as a risk factor for cardiovascular disease later in life. J Hypertens. 2010;28:826–33.
26. Irgens HU, Reisaeter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. BMJ. 2001;323(7323):1213–7.
27. American College of Obstetricians and Gynecologists. Practice bulletin no. 170: critical care in pregnancy. Obstet Gynecol. 2016;128(4):e147–54.
28. Oud L. Epidemiology of pregnancy-associated ICU utilization in Texas: 2001–2010. J Clin Med Res. 2017;9(2):143–53.
29. Wanderer JP, Leffert LR, Mhyre JM, Kuklina EV, Callaghan WM, Bateman BT. Epidemiology of obstetric-related ICU admissions in Maryland: 1999-2008*. Crit Care Med. 2013;41(8):1844–52.
30. Chantry AA, Deneux-Tharaux C, Bonnet MP, Bouvier-Colle MH. Pregnancy-related ICU admissions in France: trends in rate and severity, 2006–2009. Crit Care Med. 2015;43(1):78–86.
31. Panchal S, Arria AM, Harris AP. Intensive care utilization during hospital admission for delivery: prevalence, risk factors, and outcomes in a statewide population. Anesthesiology. 2000;92(6):1537–44.
32. Madan I, Puri I, Jain NJ, Grotegut C, Nelson D, Dandolu V. Characteristics of obstetric intensive care unit admissions in New Jersey. J Matern Fetal Neonatal Med. 2009;22(9):785–90.
33. Wunsch H, Angus DC, Harrison DA, Collange O, Fowler R, Hoste EA, de Keizer NF, et al. Variation in critical care services across North America and Western Europe. Crit Care Med. 2008;36(10):2787–93.
34. Van Parys AS, Verstraelen H, Roelens K, Temmerman M. Maternal intensive care': a systematic literature review. Facts Views Vis Obgyn. 2010;2(3):161–7.
35. Gaffney A. Critical care in pregnancy - is it different? Semin Perinatol. 2014;38(6):329–40.
36. Collop NA, Sahn SA. Critical illness in pregnancy. An analysis of 20 patients admitted to a medical intensive care unit. Chest. 1993;103(5):1548–52.
37. James AH, Bushnell CD, Jamison MG, Myers ER. Incidence and risk factors for stroke in pregnancy and the puerperium. Obstet Gynecol. 2005;106(3):509–16.
38. Baskett TF. Epidemiology of obstetric critical care. Best Pract Res Clin Obstet Gynaecol. 2008;22(5):763–74.
39. Zeeman GG, Wendel GD Jr, Cunningham FG. A blueprint for obstetric critical care. Am J Obstet Gynecol. 2003;188(2):532–6.
40. Mabie WC, Sibai BM. Treatment in an obstetric intensive care unit. Am J Obstet Gynecol. 1990;162(1):1–4.
41. Johanson R, Anthony J, Dommisse J. Obstetric intensive care at Groote Schuur Hospital, Cape Town. J Obstet Gynaecol. 2009;15(3):174–7.
42. Belfort MA, Clark SL, Saade GR, Kleja K, Dildy GA 3rd, Van Veen TR, Akhigbe E, Frye DR, Meyers JA, Kofford S. Hospital readmission after delivery: evidence for an increased incidence of nonurogenital infection in the immediate postpartum period. Am J Obstet Gynecol. 2010;202:35.e1–7.
43. ICNARC. Report from the Intensive Care National Audit & Research Centre: Female admissions (aged 16–50 years) to adult, general critical care units in England, Wales and Northern Ireland reported as 'currently pregnant' or 'recently pregnant': 1 January 2009 to 31 December 2012. 2013. https://www.oaa-anaes.ac.uk/assets/_managed/cms/files/Obstetric%20admissions%20to%20critical%20care%202009-2012%20-%20FINAL.pdf. Accessed 3 Mar 2019.
44. Bouvier-Colle MH, Varnoux N, Salanave B, Ancel PY, Bréart G. Case-control study of risk factors for obstetric patients' admission to intensive care units. Eur J Obstet Gynecol Reprod Biol. 1997;74:173–7.
45. Baskett TF, O'Connell CM. Maternal critical care in obstetrics. J Obstet Gynaecol Can. 2009;31(3):218–21.
46. Zwart JJ, Dupuis JR, Richters A, Ory F, van Roosmalen J. Obstetric intensive care unit admission: a 2-year nationwide population-based cohort study. Intensive Care Med. 2010;36:256–63.
47. Vasquez DN, Estenssoro E, Canales HS, et al. Clinical characteristics and outcomes of obstetric patients requiring ICU admission. Chest. 2007;131:718–24.
48. Leung NY, Lau AC, Chan KK, Yan WW. Clinical characteristics and outcomes of obstetric patients admitted to the intensive care unit: a 10-year retrospective review. Hong Kong Med J. 2010;16(1):18–25.
49. Neligan PJ, Laffey JG. Clinical review: special populations—critical illness and pregnancy. Crit Care. 2011;15(4):227.
50. Kilpatrick SJ, Matthay MA. Obstetric patients requiring critical care. A five-year review. Chest. 1992;101(5):1407–12.
51. Lapinsky SE, Kruczynski K, Seaward GR, Farine D, Grossman RF. Critical care management of the obstetric patient. Can J Anaesth. 1997;44(3):325–9.
52. Loverro G, Pansini V, Greco P, Vimercati A, Parisi AM, Selvaggi L. Indications and outcome for intensive care unit admission during puerperium. Arch Gynecol Obstet. 2001;265(4):195–8.
53. Rizk NW, Kalassian KG, Gilligan T, Druzin MI, Daniel DL. Obstetric complications in pulmonary and critical care medicine. Chest. 1996;110:791–809.

54. Bouvier-Colle MH, Salanave B, Ancel PY, Varnoux N, Fernandez H, Papiernik E, Bréart G, Benhamou D, Boutroy P, Caillier I, Dumoulin M, Fournet P, Elhassani M, Puech F, Poutot C. Obstetric patients treated in intensive care units and maternal mortality. Eur J Obstet Gynecol Reprod Biol. 1996;65:121–5.
55. Pollock W, Rose L, Dennis CL. Pregnant and postpartum admissions to the intensive care unit: a systematic review. Intensive Care Med. 2010;36(9):1465–74.
56. Guntupalli KK, Hall N, Karnad DR, Bandi V, Belfort M. Critical illness in pregnancy: part I: an approach to a pregnant patient in the ICU and common obstetric disorders. Chest. 2015;148(4):1093–104.
57. Karnad DR, Lapsia V, Krishnan A, Salvi VS. Prognostic factors in obstetric patients admitted to an Indian intensive care unit. Crit Care Med. 2004;32:1294–9.
58. Munnur U, Karnad DR, Bandi VDP, Lapsia V, Suresh MS, Ramshesh P, Gardner MA, Longmire S, Guntupalli KK. Critically ill obstetric patients in an American and an Indian public hospital: comparison of case-mix, organ dysfunction, intensive care requirements, and outcomes. Intensive Care Med. 2005;31:1087–94.
59. Platteau P, Engelhardt T, Moodley J, Muckart DJJ. Obstetric and gynaecological patients in an intensive care unit: a 1 year review. Trop Dr. 1997;27(4):202–6.
60. Gilbert TT, Smulian JC, Martin AA, Ananth CV, Scorza W, Scardella AT, Critical Care Obstetric Team. Obstetric admissions to the intensive care unit: outcomes and severity of illness. Obstet Gynecol. 2003;102(5 Pt 1):897–903.
61. Afessa B, Green B, Delke I, Koch K. Systemic inflammatory response syndrome, organ failure, and outcome in critically ill obstetric patients treated in an ICU. Chest. 2001;120(4):1271–7.
62. Olara J, Longarela AM, Suarez L, Palacio FJ. Critically ill obstetric patients treated in an ICU. Chest. 2002;121:2077.
63. Cheng C, Raman S. Intensive care use by critically ill obstetric patients: a five year review. Int J Obstet Anesth. 2003;12:89–92.
64. Tang LC, Kwok AC, Wong AY, Lee YY, Sun KO, So AP. Critical care in obstetrical patients: an eight-year review. Chin Med J. 1997;110:936–41.
65. Heinonen S, Tyrväinen E, Saarikoski S, Ruokonen E. Need for maternal critical care in obstetrics: a population-based analysis. Int J Obstet Anesth. 2002;11:260–4.
66. Tripathi R, Rathore AM, Saran S. Intensive care for critically ill obstetric patients. Int J Gynecol Obstet. 2000;68:257–8.
67. Lewinsohn G, Herman A, Leonov Y, Klinowski E. Critically ill obstetrical patients: outcomes and predictability. Crit Care Med. 1994;22:1412–4.
68. Ng TI, Lim E, Tweed WA, Arulkumaran S. Obstetric admissions to the intensive care unit—a retrospective study. Ann Acad Med Singap. 1992;21:804–6.
69. Stephens ID. ICU admissions from an obstetrical hospital. Can J Anaesth. 1991;38:677–81.
70. Graham SG, Luxton MC. The requirement for intensive care support for the pregnant population. Anaesthesia. 1989;44:581–4.
71. Creanga AA, Syverson C, Seed K, Callaghan WM. Pregnancy-related mortality in the United States, 2011–2013. Obstet Gynecol. 2017;130(2):366–73.
72. ICNARC. Report from the Intensive Care National Audit & Research Centre: Female admissions (aged 16–50 years) to adult, general critical care units in England, Wales and Northern Ireland reported as 'currently pregnant' or 'recently pregnant': 1 January 2007 to 31 December 2007. 2009. https://www.oaa-anaes.ac.uk/assets/_managed/editor/File/Reports/ICNARC_obs_report_Oct2009.pdf. Accessed 12 Mar 2019.
73. Cartin-Ceba R, Gajic O, Iyer VN, Vlahakis NE. Fetal outcomes of critically ill pregnant women admitted to the intensive care unit for nonobstetric causes. Crit Care Med. 2008;36(10):2746–51.
74. Hazelgrove JF, Price C, Pappachan VJ, Smith GB. Multicenter study of obstetric admissions to 14 intensive care units in southern England. Crit Care Med. 2001;29:770–5.
75. Wheatley E, Farkas A, Watson D. Obstetric admissions to an intensive therapy unit. Int J Obstet Anesth. 1996;5:221–4.
76. Kassebaum NJ, Bertozzi-Villa A, Coggeshall MS, et al. Global, regional, and national levels and causes of maternal mortality during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384(9947):980–1004.
77. Mantel GD, Buchmann E, Rees H, Pattinson RC. Severe acute maternal morbidity: a pilot study of a definition for a near-miss. Br J Obstet Gynaecol. 1998;105(9):985–90.
78. Gooch RA, Kahn JM. ICU bed supply, utilization, and health care spending: an example of demand elasticity. JAMA. 2014;311(6):567–8.
79. Knight M, Lewis G, Acosta CD, Kurinczuk JJ. Maternal near-miss case reviews: the UK approach. BJOG. 2014;121(Suppl 4):112–6.
80. Knight M, Nair M, Tuffnell D, Kenyon S, Shakespeare J, Brocklehurst P, Kurinczuk JJ (Eds.). On behalf of MBRRACE-UK. Saving lives, improving mothers' care—surveillance of maternal deaths in the UK 2012–14 and lessons learned to inform maternity care from the UK and Ireland confidential enquiries into maternal deaths and morbidity 2009–14. Oxford: National Perinatal Epidemiology Unit, University of Oxford 2016.

Part II

The Coagulation System

5 Physiology and Pathology of Coagulation in Pregnancy

Samir N. Patel and Aryeh Shander

Bullet Points

- About 7.6% of healthy pregnant women have platelet counts less than 150,000/mm^3.
- Fibrinogen (factor I) levels increase steadily from 28 weeks' gestation and are doubled by the time of delivery.
- Lupus anticoagulant has no in vivo anticoagulation effect; a laboratory artifact affects phospholipid binding assays, including aPTT, without effect on prothrombin time.
- Antiphospholipid syndrome in pregnancy is highly associated with thrombosis, including cerebral infarction, deep vein thrombosis, myocardial infarction, and pulmonary embolism.
- Without anticoagulation therapy, pregnant and postpartum women with protein C deficiency will suffer thrombosis 25% of the time; most events will occur postpartum.
- Pregnant women with factor V Leiden mutation should be treated with low molecular weight heparin (LMWH) from the first trimester of pregnancy.
- DIC may be caused by massive hemorrhage, preeclampsia, sepsis, retained dead fetus, placental abruption, and amniotic fluid embolus.
- If warfarin is administered during pregnancy, it is usually discontinued in favor of heparin 1–4 weeks prior to the estimated delivery date/critical care admission.
- Prophylactic treatment during labor is recommended for pregnant women with factor VIII levels below 25%.
- Thrombocytopenic purpura (TTP) is challenging to distinguish from hemolytic uremic syndrome (HUS), DIC, sepsis, transient ischemic attack, and even some types of gastroenteritis.
- Contrary to HUS, TTP is accompanied by a severe deficiency of a von Willebrand factor (vWF) cleaving protease called ADAMTS 13 which cleaves vWF multimers.

S. N. Patel
Englewood Health, Englewood, NJ, USA

A. Shander (✉)
Department of Anesthesiology, Critical Care Medicine, Hyperbaric Medicine and Pain Management, Englewood, NJ, USA

Team Health Research Institute, Englewood, NJ, USA

Department of Anesthesiology, Medicine and Surgery at Icahn School of Medicine, Mount Sinai, New York, NY, USA

Department of Anesthesiology at Rutgers New Jersey Medical School, Newark, NJ, USA
e-mail: Aryeh.Shander@EHMCHEALTH.org

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_5

5.1 Normal Physiology of Coagulation in Pregnancy

Clot formation occurs through the endothelial wall (extrinsic) and platelet surface (intrinsic) pathways with intricate feedback systems interconnecting both [1]. Complicating matters is the change in blood volume occurring during pregnancy. Total blood volume steadily increases to 45% above nonpregnant levels by term. Plasma volume begins to expand at 6 weeks gestation and steadily rises until it peaks to a total increase approximating 50% at 34 weeks of gestation. Red blood cell volume decreases during the first 8 weeks of gestation, rises to prepregnancy levels by 16 weeks of gestation, and finally increases to 30% above prepregnancy levels by term. The relative dilution of clotting factors caused by these changes determines the delicate balance between bleeding and clotting as pregnancy progresses (see Fig. 5.1) [2, 3].

Platelet turnover is enhanced during pregnancy. Increases in platelet factor 4 and beta-thromboglobulin signal, elevated platelet activation, and an increase in platelet distribution lead to increased platelet consumption during pregnancy. However, platelet levels tend to either remain normal or slightly decrease (~20%) during pregnancy, suggesting a parallel compensatory increase in platelet production. About 7.6% of healthy pregnant women have platelet counts less than 150,000/mm^3, and another 0.9% have platelet counts less than 100,000/mm^3, which is termed gestational thrombocytopenia. Gestational thrombocytopenia is generally not associated with increased risk of bleeding [4, 5].

The blood levels of many coagulation factors increase in pregnancy. Factor II may increase by up to 1000%, and factors I, VIII, IX, X, and XII and von Willebrand factor all increase by more than 100% [6]. Factors VII, VIII, IX, and X all steadily increase during pregnancy. Factor XII remains stable at a slightly higher than normal level throughout pregnancy [7]. Previously, factor XI was thought to decrease during pregnancy. However, recent studies show that this is only found in women with a preexisting factor XI deficiency. For women with normal prepregnancy factor XI levels, the levels stay stable throughout gestation. Conversely, the concentrations of factors II, V, X, and XI remain unchanged, and factor XIII and protein S may decrease by 50% (see Table 5.1). Prothrombin time (PT) and partial thromboplastin time (PTT) are shortened by approximately 20%.

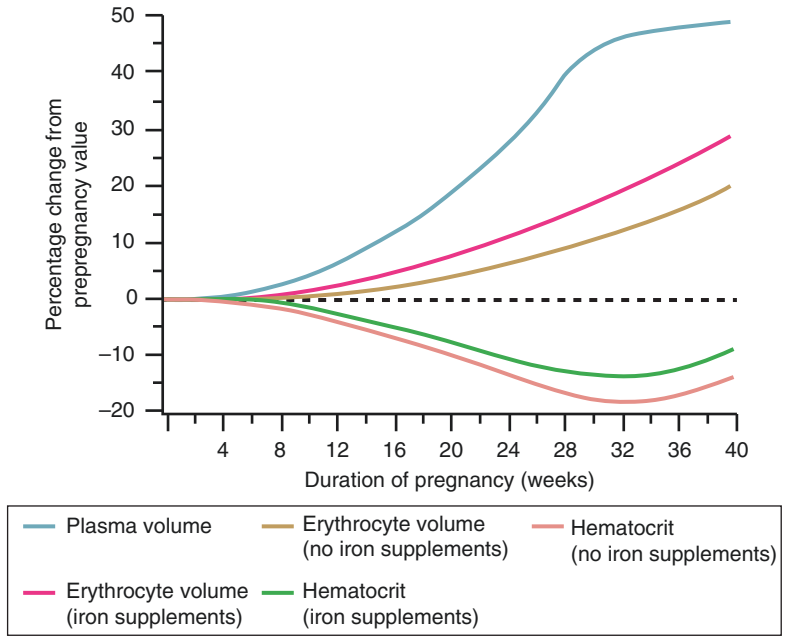


Fig. 5.1 Changes in blood volume during pregnancy. Changes in plasma volume, RBC volume, and hematocrit during pregnancy. The increase in plasma volume is greater than the increase in RBC volume, causing the "physiological anemia of pregnancy," which can be partially corrected with iron supplements. (*With permission from Bonow, R. O., Mann, D. L., Zipes, D. P., & Libby, P. (2011). Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 9th edition. Philadelphia: Elsevier Science*)

Table 5.1 Changes in coagulation elements in pregnancy at term gestation

Coagulation element	Change at term gestation
Factor 1 (fibrinogen)	Increased
Factor II (prothrombin)	Unchanged
Factor V	Unchanged
Factor VII	Increased
Factor VIII	Increased
Factor IX	Increased
Factor X	Increased
Factor XI	Decreased or unchanged
Factor XII	Increased
Factor XIII	Decreased
Protein C	Unchanged
Protein S	Decreased
Antithrombin III	Unchanged
Plasminogen	Increased
D-dimer	Increased

Fibrinogen (factor I) levels stay close to prepregnancy values until 28 weeks' gestation, at which point levels begin to increase steadily to double the prepregnancy values by the time of delivery. D-dimer levels equal or exceed 0.5 mg/L (cutoff for thromboembolism) in 25% of parturients by weeks 13–20 gestation. By 36–42 weeks of gestation, almost all pregnant women have D-dimer levels above 0.5 mg/L.

At delivery and during postpartum day 1, platelet counts decline rapidly, while fibrinogen, factor VIII, plasminogen, and antifibrinolytic activity increase. The levels of both fibrinogen and D-dimer start to decrease by the second postpartum day. At postpartum days 3–5, fibrinogen concentration and platelet count increase coinciding with a higher incidence of thrombotic complications during this period. Coagulation dynamics return to the nonpregnant state approximately 2 weeks postpartum.

5.2 Hypercoagulable Conditions and Pregnancy

5.2.1 Antiphospholipid Syndrome

Hughes' syndrome, which was first recognized in the early 1980s, is a prothrombotic disorder characterized by the presence of two autoantibodies, lupus anticoagulant and anticardiolipin antibody. Hughes' syndrome was initially considered rare, but this perception has changed with recent diagnostic advances. Although these two autoantibodies are also prevalent in systemic lupus erythematosus (SLE), antiphospholipid syndrome is distinct from SLE (Chap. 15). Only 8% of patients with antiphospholipid syndrome also have concomitant SLE [8], and the two are quite distinct in their clinical manifestations. Women with Hughes' syndrome may suffer both arterial and venous thrombosis. The two antiphospholipid antibodies bind to beta-2-glycoprotein-1, which in turn binds to glycoprotein-1ba on platelets and causes platelet adhesion and complement activation. Conversely, lupus anticoagulant has no in vivo anticoagulation effect. Its anticoagulant effect is a result of a laboratory artifact that affects phospholipid binding assays, including aPTT. aPTT is prolonged in the presence of lupus anticoagulant even when repeated with a 1:1 mixture of the patient's plasma and control. However, it has little to no effect on prothrombin time. In this sense the terminology "anticoagulant" is a misnomer.

Diagnosis of Hughes' syndrome is made by clinical evidence of recurrent venous and/or arterial thrombosis and/or pregnancy loss along with laboratory evidence of anticardiolipin antibody and lupus anticoagulant. Laboratory evidence includes (a) elevated aPTT, (b) evidence that abnormal aPTT is caused by inhibitor rather than factor deficiency based on results of mixing studies (elevated aPTT with 1:1 mix of patient plasma and control), and (c) proof that inhibitor is directed specifically against phospholipid factors. For example, the antiphospholipid antibodies present in syphilis (diagnosed using the VDRL and Wasserman tests) may be falsely positive in patients with antiphospholipid syndrome [9, 10].

As noted above, pregnant women with antiphospholipid syndrome may suffer from arterial and/or venous thrombosis, including cerebral infarction, deep vein thrombosis, myocardial infarction, and pulmonary embolism. Silver et al. studied 130 women with antiphospholipid syndrome for a median period of approximately 3 years. Forty eight percent of these women expe-

rienced one or more transient ischemic attacks, peripheral thrombosis, stroke, amaurosis fugax, and other clinically significant findings/events. Among these women, 24% had experienced these events during pregnancy [11]. Catastrophic antiphospholipid syndrome is a rare syndrome causing multisystem organ thrombosis and failure and is also linked to pregnancy in 4% of cases [12].

Antiphospholipid antibodies also endanger the fetus. Death often occurs in utero due to placental infarction, mostly at mid- to late pregnancy. Fetal mortality is high in antiphospholipid pregnancies and seems to relate to the antibody profile. In one study of 750 pregnancies of women with positive antiphospholipid profiles, it was shown that 7% had only lupus anticoagulant, 61% had only anticardiolipin, and 17% had only anti-beta-2-glycoprotein-1; additionally, 12% of women had two positive antibodies and 3% had all 3 antibodies. Live birth rates were related to the specific antiphospholipid antibodies: 80% for lupus anticoagulant, 56% for anticardiolipin, 48% for anti-beta-2-glycoprotein-1, 43% for double positive women, and 30% for triple positive women [13]. A reduction in maternal thrombotic events and improved fetal survival has been evaluated with use of combined treatment with acetylsalicylic acid and heparin [14].

The American College of Obstetrics and Gynecologists recommends that women with recurrent unexplained pregnancy loss (including fetal loss after 10 weeks' gestation or 3 or more unexplained embryonic losses) or vascular thrombosis undergo investigation. Diagnosis is confirmed if lupus anticoagulant, anticardiolipin, anti-beta-2-glycoprotein-1 antibodies are positive on two occasions 12 weeks apart. Women with antiphospholipid syndrome and no history of thrombosis should receive prophylactic doses of heparin and low-dose acetylsalicylic acid throughout pregnancy and 6–8 weeks postpartum. Women with antiphospholipid syndrome and a previous history of thrombosis should receive full anticoagulation throughout the same period. The risk-benefit ratio of treatment with prednisone, with or without intravenous immunoglobulin, remains unclear. These are therefore not recommended as primary therapy [9].

5.2.2 Protein C Deficiency

Protein C is a vitamin K-dependent protein (anticoagulant) produced in the liver. It normally acts by inhibiting activated factors V and VIII. In pregnancy, protein C levels increase gradually by 35%. This increase is lessened in women with protein C deficiency. The incidence of protein C deficiency is about 1:15,000. Without anticoagulation therapy (i.e., heparin, warfarin), pregnant and postpartum women with protein C deficiency will suffer thrombosis 25% of the time with 66% of these thrombotic events occurring in postpartum [15]. Heparin is usually administered in the first trimester, and either heparin or warfarin is administered from the second trimester to the postpartum period. Since protein C is a vitamin K-dependent anticoagulant with a very short half-life (~7 h), heparin anticoagulation must be administered prior to warfarin since protein C levels would otherwise drop faster than levels of factors II, VII, IX, and X. This could potentially result in thrombosis. Direct oral anticoagulants, such as factor Xa inhibitors (e.g., apixaban, edoxaban, and rivaroxaban) and direct thrombin inhibitors (dabigatran), are not used routinely in pregnant women due to concerns regarding teratogenicity, although these concerns are based only on limited animal and human studies [16].

5.2.3 Protein S Deficiency

Protein S is an anticoagulant produced by the liver and depends on vitamin K for synthesis. Protein S acts as a cofactor for protein C. Protein S deficiency has an autosomal dominant inheritance and is therefore relatively rare with a population-based disease prevalence ranging from 1 in 500–3000 [13]. The treatment for protein S deficiency is identical to that of protein C deficiency.

5.2.4 Factor V Leiden Mutation

The mutation of factor V Leiden is displacement of a single amino acid. This mutation results in a

factor V variant that persists in the plasma longer than usual due to decreased degradation by activated protein C. This effective increase in plasma levels of factor V leads to a propensity for hypercoagulability. The prevalence of heterozygous factor V Leiden mutation is about 5–8%. Pregnant and postpartum women with the heterozygous mutation have the double the risk of thrombosis compared to those without the mutation. The prevalence of a homozygous mutation is 1:6000. This mutation may increase the risk of thrombosis by as much as 80-fold in the obstetric population.

Pregnant women with factor V Leiden mutation should be treated with low molecular weight heparin (LMWH) from the first trimester of pregnancy. Treatment should be continued until approximately 2 weeks before the estimated date of delivery. At this point, LMWH treatment should be transitioned to unfractionated heparin. Following delivery, LMWH is restarted and continued for an additional 6 weeks [14].

5.2.5 Antithrombin III Deficiency

Antithrombin III (ATIII) is a non-vitamin K-dependent protease that is produced in the liver and endothelial cells. It inhibits coagulation by inactivating the enzymatic activity of thrombin via factors IXa, Xa, and XIIa. Heparin increases the binding of ATIII to these factors, thereby potentiating its effect. For this reason, heparin is less effective in patients with ATIII deficiency. ATIII has an overall prevalence approximating 1:5000 in the general population. The congenital form of ATIII is rarely seen in adults. The acquired form, which is most commonly seen in adult women, has both quantitative (type I) and qualitative (type II) variants. Type 1 deficiency is caused by a decrease in antithrombin activity and antigen levels, while type 2 deficiency results from production of a variant antithrombin protein with decreased function [17].

Increased consumption is the form of ATIII most likely to be encountered by clinicians treating pregnant and postpartum women in the acute care setting, as it occurs during abnormal coagulation system activation. Conditions that typically induce ATIII deficiency include massive hemorrhage with disseminated intravascular coagulation (DIC), microangiopathic-hemolytic and veno-occlusive diseases, as well as nephrotic syndrome. However, use of heparin has also been associated with antithrombin III deficiency, which is important in the context of prolonged acute critical illness. Treatment is discussed below (see DIC).

Contrary to other coagulopathies which may often be diagnosed by the presence of a specific antigen, diagnosing the specific type of ATIII deficiency requires both functional and immunologic assays. In other words, during acute hemorrhage a definite diagnosis is not possible.

The risk of thrombosis during pregnancy in women with untreated ATIII deficiency is 55–68% (compared to 0.1% in pregnant women without this condition) [18]. LMWH heparin (40–60 mg QD-BID) is the anticoagulant of choice for the first and third trimester. In the second trimester and postpartum, women may be treated with LMWH or warfarin. LMWH dosing may need to be increased substantially or administered concomitantly with antithrombin III concentrate (20–40 mg/kg) [19].

5.3 Acquired Hypocoagulable Conditions and Pregnancy

A hypocoagulated state may be aquired during pregnancy for several reasons. Disseminated intravascular coagulation is a common complication of several conditions that arise in pregnancy. Treatment administered for hypercoagulable conditions may also cause hypocoagulation. Medications commonly used in pregnancy can cause drug-related coagulopathy. These are hereby discussed.

5.3.1 Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is an acquired, diffuse, intravascular, pathological form of activation of the coagulation cascade. DIC is characterized on the one hand by formation of large amounts of thrombin and consumption of coagulation factors and on the other hand

by activation of the fibrinolytic system. In the process of activation, microvascular thromboses are created that obstruct the microvasculature, eventually producing end organ dysfunction and failure.

In pregnant women, DIC may be caused by massive hemorrhage, preeclampsia, sepsis, retained dead fetus, placental abruption, and amniotic fluid embolus [20]. In the setting of DIC, laboratory tests reveal a rapid decrease in platelet count, fibrinogen, and ATIII concentrations. Concomitantly, there are varying increases in PT, PTT, D-dimer, fibrin monomer, and fibrin degradation products.

Management of the pregnant or peripartum woman with DIC is multifaceted. The underlying cause must be removed and/or treated rapidly. In addition, coagulation factors must be replaced (see Table 5.2). Hemodynamic resuscitation with fluids and vasopressors may also be indicated. Finally, ongoing fibrinolysis should be halted.

The use of antifibrinolytic agents in the setting of DIC remains controversial. Inhibition of fibrinolysis may cause widespread fibrin formation and deposition leading to small and midsize blood vessel thromboses.

Heparin has been used by some physicians for patients with DIC who do not have severe hemorrhage but have evidence of peripheral deposition of fibrin and resulting multiorgan failure. If a decision is made that administration of unfractionated heparin is justified, it may be administered either intravenously or subcutaneously at a dose of 300–700 units/h. Alternatively, low molecular weight heparin (LMWH) can be given at a dose of 75 UN/kg/day [20, 21]. Heparin is only effective if ATIII levels are not low; thus concomitant administration of fresh frozen plasma (which contains ATIII) or ATIII concentrate may also be required. Some evidence also exists for improved organ function and patient outcomes with the use of ATIII concentrate alone in the presence of DIC [22]. Since use of both antifibrinolytic agents and heparin in DIC remains controversial, it is of paramount importance to determine treatment case by case after multidisciplinary consultation.

Table 5.2 Plasma half-life of coagulation factors and minimum plasma concentration needed for hemostasis

Factor	Plasma half-life	Minimum plasma concentration needed for hemostasis (mg/dL)
Fibrinogen (factor I)	2–4 days	50–75
Prothrombin (factor II)	3–4 days	25–30
Factor V	36 h	15–20
Factor VII	4–6 h	15–20
Factor VIII	10–12 h	15–20
Factor IX	18–24 h	15–20
Factor X	40–60 h	15–20
Factor XI	40–70 h	15–20
Factor XIII	11–14 days	2–5

5.3.2 Therapeutic Anticoagulation

The anticoagulant most commonly used in pregnant women who require long-term anticoagulation is heparin, either as unfractionated or LMWH.

Unfractionated heparin is a short-acting drug with a half-life of 1.5 h if given subcutaneously and 30 min if given intravenously [23]. When administered either intravenously or subcutaneously, normalization of hemostasis will occur 4–6 h after discontinuation [24]. Therapeutic dosing via the subcutaneous route requires administration 2–3 times daily. The degree of anticoagulation with heparin is monitored by following the aPTT or activated coagulation time (ACT).

Low molecular weight heparins (e.g., enoxaparin) are longer-acting drugs with a half-life of 3–4 h if administered subcutaneously or intravenously [25]. In women treated with either unfractionated or low molecular weight heparin, if immediate reversal is required, protamine (50 mg) may be given intravenously. However, there is considerable variance in the response to protamine in terms of reversal effectiveness. Therefore, this treatment is not recommended unless ACT may be followed after dosing.

If warfarin has been administered during pregnancy, it is usually discontinued in favor of heparin 1–4 weeks prior to the estimated delivery date

or at the time of critical care admission. Women who go into labor or require surgery while on warfarin will require reversal of anticoagulation. Options for reversal include prothrombin complex concentrate (PCC) dosed at 25–50 units/kg intravenously (rapid and complete correction, within 10–15 min, although controversial due to concerns over thrombogenicity and DIC), FFP at 10–20 mL/kg (fast but partial correction), and 10 mg intravenous/intramuscular vitamin K (quick correction, within 4–6 h depending on starting INR; effect can last 1–2 weeks; may be repeated every 6–8 h) [26].

5.3.3 Drug-Related Coagulopathy

Many medications that are commonly used in obstetric populations can cause platelet dysfunction. Low-dose aspirin is often used as prophylactic therapy for conditions such as preeclampsia and antiphospholipid syndrome. Aspirin irreversibly inactivates cyclooxygenase and may prolong bleeding time by a factor of 1.5–2 for 1–4 days, while in vitro platelet function tests may remain abnormal for up to 7 days [27]. Although there is concern for both maternal and neonatal hemorrhage in pregnant women treated with aspirin, studies have shown that prolonged bleeding time from aspirin ingestion does not necessarily correlate to prolonged bleeding [28]. In the absence of other preexisting coagulopathy, treatment with low-dose aspirin does not clinically correlate to an increased risk of fetal or maternal bleeding complications during/after pregnancy [29].

Nonsteroidal anti-inflammatory drugs (NSAIDS) reversibly inhibit cyclooxygenase (COX) and are either selective (COX-2 only) or nonselective (COX-1 and COX-2). COX-1 is expressed in platelets and leads to production of thromboxane A_2, which is responsible for platelet aggregation. Therefore, selective COX-2 inhibitors (e.g., celecoxib and rofecoxib) do not affect platelet aggregation. In addition, nonselective NSAIDS depress platelet thromboxane formation transiently and unpredictably; platelet function is impaired for an unpredictable part of their dosing interval [30]. These medications should be used cautiously in patients at high risk for bleeding complications.

Increases in cyclic adenosine monophosphate (cAMP) cause a decrease in platelet function. This can happen with drugs that cause an increase in cAMP by stimulation of adenylyl cyclase (e.g., prostaglandin E_1) or through phosphodiesterase inhibitors that prevent destruction of cAMP (e.g., theophylline, aminophylline, caffeine).

Hydroxyethyl starch solutions and dextran are taken up by platelet membranes and may impede platelet aggregation [31]. Dextran-40 at doses as low as 100 mL enhances fibrinolysis, reduces platelet binding to von Willebrand factor (vWF), and prevents platelet activation by thrombin [32].

5.4 Non-acquired Hypocoagulable Conditions and Pregnancy

5.4.1 von Willebrand's Disease (vWD)

The vWF is produced by megakaryocytes and endothelial cells lining blood vessels. The vWF has two important functions in the coagulation cascade: it forms a complex with factor VIII, thereby stabilizing it and preventing its removal, and it facilitates platelet adhesion by binding to collagen through a reaction that is boosted by ristocetin [33].

The inheritance of vWD is autosomal dominant. The milder (heterozygous) form of this disease has a prevalence of 1:100–2500, while the more severe (homozygous) form has a prevalence of 1:200,000–2,000,000 [34]. Variability in the levels of both vWF and factor VIII in those with vWD explains why some patients remain asymptomatic. Patients with vWD usually have less than 50% of normal vWF in their plasma.

Severe vWD disease can present like hemophilia A with muscle and joint hemorrhages. However, unlike classic hemophilia, platelet function is affected, and bleeding time is prolonged in severe vWD. In patients with hemophilia, infusing small amounts of normal serum has a negligible effect on factor VIII levels,

whereas in a patient with vWD, factor VIII levels are greatly increased after infusing a small amount of normal plasma. A platelet aggregation assay will show an abnormal response to ristocetin (ristocetin cofactor test) with normal responses to the other agonists used [35].

von Willebrand's disease is divided into three types: type 1, type 2, and type 3. Type 1 accounts for 60–80% of all cases and is typically a mild quantitative defect which is heterozygous for the defective gene. Patients with type 1 vWD have vWF levels ranging from 20 to 50% of normal and are often asymptomatic.

Type 2 (20–30% of cases) is a qualitative defect and is further divided into four subtypes (see Table 5.3).

Type 3 is the most rare form of the disease (5–10% of cases). In this form of vWD, the patient is homozygous for the defective gene, and the clinical manifestations of the disease are severe. As vWF is completely absent, leading also to a low factor VIII level, the clinical presentation is identical to severe hemophilia A [36].

In pregnant women, prophylactic treatment is used for patients with factor VIII levels below 25%. For type 1 and type 2a vWD, 0.3 μg/kg of 1-deamino-8-*D*-arginine vasopressin (DDAVP) should be administered as labor begins and given every subsequent 12 h [37]. DDAVP stimulates the release of vWF from endothelial cells and increases plasma levels of vWF, factor VIII, and tissue plasminogen activator (t-PA) [38]. For patients with no response to DDAVP, or when DDAVP is contraindicated/ineffective (type 2b and type 3 vWD), fresh frozen plasma or cryoprecipitate should be given. Factor VIII concentrates may also be used, but care must be taken to use formulations that contain vWF as well [39].

Table 5.3 Subtypes of type 2 von Willebrand's disease

1.	*Type 2A*: Quantitatively normal (low normal to normal) vWF levels but qualitatively defective since the ability of abnormal vWFs to form large multimers needed for platelet aggregation is impaired
2.	*Type 2B*: Qualitatively defective vWF that has abnormally enhanced binding to glycoprotein-1b receptor on platelets, leading to increased clearance of platelets bound to vWF multimers which may lead to thrombocytopenia. DDAVP cannot be used as treatment in this subtype because it can lead to unwanted platelet aggregation and aggravation of thrombocytopenia
3.	*Type 2M*: Qualitative defect in vWF characterized by a decreased ability to bind to glycoprotein-1b receptor on platelets with a normal capacity for forming vWF multimers
4.	*Type 2N*: Deficiency in binding of vWF to factor VIII leading to a quantitative decrease in factor VIII levels with normal vWF levels

5.4.2 Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (TTP) is a rare syndrome, defined by the presence of blood clots in small vessels throughout the body due to widespread platelet aggregation. Signs and symptoms are often nonspecific and include nausea, vomiting, abdominal pain, and malaise. The syndrome includes six findings that may be present alone or in combination. These include thrombocytopenia, hemolytic anemia, petechiae and purpura, fever, neurologic symptoms (including headache), and renal failure.

TTP may be inherited or acquired, and acquired TTP is more common. The triggers for developing TTP are not clear but have been described to include pregnancy, cancer, lupus, infections, chemotherapy, clopidogrel, hormone therapy, quinine, and oral contraceptives. The acute disease usually lasts days to weeks but can last for months, with relapses occurring in up to 50% of cases [40].

It is challenging to distinguish TTP from diseases with similar manifestations. Examples include hemolytic uremic syndrome, DIC, sepsis, transient ischemic attack, and even some types of gastroenteritis. Contrary to hemolytic uremic symdrome, TTP is accompanied by a severe deficiency of a vWF cleaving protease called ADAMTS 13 which cleaves vWF multimers. Lacking this protease, there is an increase in vWF multimers in the circulation which leads to increased platelet aggregation [41]. TTP is distinguishable from DIC by the presence of vWF and lack of fibrinogen in platelet aggregates. The exact opposite is true in DIC [42].

Scully et al. showed in a cohort of 47 pregnant women that careful monitoring and treatment of both acquired and congenital TTP results in positive pregnancy outcomes [43]. Treatment includes plasmapheresis with approximately 75% plasma exchange, high-dose plasma (25–30 mL/kg), intravenous immumoglobulin infusion (400 mg/kg/day), and oral prednisone [44, 45]. Platelet transfusion, in contrast, may cause more thrombosis and is controversial [46, 47]. Development of TTP in one pregnancy does not predict relapse during subsequent pregnancies [48].

5.4.3 Autoimmune Thrombocytopenic Purpura (ATP)

ATP, previously known as idiopathic thrombocytopenic purpura (ITP), is an autoimmune-mediated thrombocytopenia that is caused by the development of an IgG antiplatelet antibody following environmental exposure to an antigen. IgG antibodies directed toward platelets lead to clearance by the reticuloendothelial system (spleen). In addition, binding of IgG antibodies to megakaryocytes injures them, leading to decreased platelet formation [49].

Gingival bleeding, easy bruising, epistaxis, petechiae, and purpura are the most common initial clinical symptoms. Usually the diagnosis of ATP requires a platelet count lower than 100,000/mm^3 and a normal (or higher than normal) number of megakaryocytes shown in a parallel bone marrow aspirate. However, bone marrow biopsy is rarely conducted in obstetric practice. Therefore, in many cases, a presumptive diagnosis is often made based on response to treatment. Obstetric management of ATP is dictated by the platelet count as well as the stage of pregnancy. However, there is no absolute correlation between the platelet count and risk of perinatal hemorrhage [50, 51]. In fact, in ATP, the platelet function may be normal or enhanced despite having the low number of platelets [52].

Corticosteroids are used if the platelet count is less than 20,000/mm^3 before labor ensues or less than 50,000/mm^3 at time of delivery [53]. Prednisone is most commonly used at a dose of 0.5 mg/kg daily, and the platelet count should increase to greater than 50,000/mm^3 in responders within a few days. Intravenous immunoglobulin is used in cases that are refractory to corticosteroid therapy with 65–80% of patients responding to treatment. However, the increase in platelet count seen is often transient (10–14 days). The usual dosing regimen of intravenous immunoglobulin is 1 g/kg daily for 1–2 days. Chronic ATP that is refractory to corticosteroids or intravenous immunoglobulin may benefit from thrombopoietin mimetics, such as romiplostim and eltrombopag, which stimulate platelet production [54]. Splenectomy is often a last resort in patients who do not respond to any treatment modality.

5.5 Blood Management Strategies in Pregnant Women

Administration of blood components should be guided by laboratory testing including PT, PTT, complete blood count, fibrinogen, and point-of-care viscoelastic tests such as ROTEM® or TEG®. Fibrinogen testing is of special importance in the obstetric population since a low fibrinogen level (<2 g/dL) has been found to be an independent predictor of severe postpartum hemorrhage (PPH) [55]. This suggests that a decrease in plasma fibrinogen from prepartum to postpartum levels, even if within a normal range, may be the earliest laboratory indicator of potential PPH. Cryoprecipitate (which contains 15 g/dL of fibrinogen) and human fibrinogen concentrate can be used to correct hypofibrinogenemia concomitantly with antifibrinolytics, such as aminocaproic acid and tranexamic acid. ROTEM® can also be used to identify hypofibrinogenemia as well as hyperfibrinolysis in this setting.

Cell saver has been used successfully and safely in obstetric patients despite perceived fears of amniotic fluid embolism [56]. A common practice in many institutions is to have a double suction setup for patients at risk for post partum hemorrhage undergoing cesarean delivery; one

suction is used immediately after uterine incision for amniotic fluid (~250 mL volume), and the second suction is employed for cell saver use.

Massive transfusion protocols in obstetrics employ blood component ratios ranging between 1:1:1 to 2:1:1 of RBC/FFP/platelets, respectively. Cryoprecipitate is a key initial component that is unique to the protocol in this patient population due to the role of hypofibrinogenemia in post partum hemorrhage. Despite being a recommended practice, ratio-based transfusion has not been validated in the obstetric patient when laboratory-guided resuscitation is an option.

5.6 Conclusion

The physiological changes that occur in coagulation processes and the pathologies that may be encountered during pregnancy are complex and dynamic and may differ between individual women. Understanding the different pathways and presentations will help the clinician make cogent decisions when faced with coagulation abnormalities at the bedside.

References

1. De Lange NM, Lancé MD, de Groot R, Beckers EAM, Henskens YM, Scheepers HCJ. Obstetric hemorrhage and coagulation: an update. Thromboelastography, thromboelastometry, and conventional coagulation tests in the diagnosis and prediction of postpartum hemorrhage. Obstet Gynecol Surv. 2012;67:426–35.
2. Collis RE, Collins PW. Haemostatic management of obstetric haemorrhage. Anaesthesia. 2015;70 (Suppl. 1):78–86, e27–8.
3. Pritchard JA. Changes in blood volume during pregnancy and delivery. Anesthesiology. 1965;26:393–9.
4. Sill PR, Lind T, Walker W. Platelet values during normal pregnancy. Br J Obstet Gynaecol. 1985;92(5):480–3.
5. Fay RA, Hughes AO, Farron NT. Platelets in pregnancy: hyperdestruction in pregnancy. Obstet Gynecol. 1983;61:238–40.
6. Abbassi-Ghanavati M, Greer LG, Cunningham FG. Pregnancy and laboratory studies: a reference table for clinicians. Obstet Gynecol. 2009;114(6):1326–31.
7. Szecsi PB, Jørgensen M, Klajnbard A, Andersen MR, Colon NP, Stender S. Haemostatic reference intervals in pregnancy. Thromb Haemost. 2010;103:718–27.
8. Gomez-Puerta JA, Martin H, Amigo MC, et al. Long-term follow-up in 128 patients with primary antiphospholipid antibody syndrome: do they develop lupus? Medicine (Baltimore). 2005;84:225–30.
9. Committee on Practice Bulletins—Obstetrics, American College of Obstetricians and Gynecologists. Practice bulletin no. 132: antiphospholipid syndrome. Obstet Gynecol. 2012;120(6):1514–21.
10. Vermylen J, Carreras LO, Arnout J. Attempts to make sense of the antiphospholipid syndrome. J Thromb Haemost. 2007;5:1–4.
11. Silver RM, Draper ML, Scott JR, et al. Clinical consequences of antiphospholipid antibodies: a historic cohort study. Obstet Gynecol. 1994;83:372–7.
12. Asherson RA. The catastrophic antiphospholipid (Asherson's) syndrome. Autoimmun Rev. 2006;6:64–7.
13. Saccone G, Berghella V, Maruotti GM, et al. Antiphospholipid antibody profile based obstetric outcomes of primary antiphospholipid syndrome: the PREGNANTS study. Am J Obstet Gynecol. 2017;216(5):525.e1–525.e12.
14. Lu C, Liu Y, Jiang HL. Aspirin or heparin or both in the treatment of recurrent spontaneous abortion in women with antiphospholipid antibody syndrome: a meta-analysis of randomized controlled trials. J Matern Fetal Neonatal Med. 2019;32(8):1299–311.
15. Conrad J, Horellou MH, Van Dreden P, Samama M. Pregnancy and congenital deficiency in antithrombin III or protein C. Abstract in XIth International Congress on Thrombosis and Haemostasis, Brussels, Belgium, 6–10.7.1987. Thromb Haemost. 1987;58(1):039.
16. Bapat P, Kedar R, Lubetsky A, Matlow JN, Aleksa K, Berger H, Koren G. Transfer of dabigatran and dabigatran etexilate mesylate across the dually perfused human placenta. Obstet Gynecol. 2014;123(6):1256–61.
17. Khor B, Van Cott EM. Laboratory tests for antithrombin deficiency. Am J Hematol. 2010;85:947–50.
18. Hellgren M, Tengborn L, Abildgaard U. Pregnancy in women with congenital antithrombin III deficiency: experience of treatment with heparin and antithrombin. Gynecol Obstet Investig. 1982;14:127–41.
19. Conard J, Horellou MH, Samama M. Incidence of thromboembolism in association with congenital disorders in coagulation and fibrinolysis. Acta Chir Scand Suppl. 1988;543:15–25.
20. Brandjes DPW, Schenk BE, Büller HR, ten Cate JW. Management of disseminated intravascular coagulation in obstetrics. Eur J Obstet Gynecol Reprod Biol. 1991;42(Suppl):S87–9.
21. Risberg B, Andreasson S, Eriksson E. Disseminated intravascular coagulation. Acta Anesthesiol Scand Suppl. 1991;95:60–71.
22. Eisele B, Lamy M, Thijs LG, et al. Antithrombin III in patients with severe sepsis. A randomized, placebo-controlled, double-blind multicenter trial plus a meta-analysis on all randomized, placebo-controlled, double-blind trials with antithrombin III in severe sepsis. Intensive Care Med. 1998;24(7):663–72.

23. Blann AD, Landray MJ, Lip GY. ABC of antithrombotic therapy: an overview of antithrombotic therapy. BMJ. 2002;325(7367):762–5.
24. Horlocker TT. Regional anaesthesia in the patient receiving antithrombotic and antiplatelet therapy. Br J Anaesth. 2011;107(Suppl 1):i96–106.
25. Bara L, Samama M. Pharmacokinetics of low molecular weight heparins. Acta Chir Scand Suppl. 1988;543:65–72.
26. Hanley JP. Warfarin reversal. J Clin Pathol. 2004;57(11):1132–9.
27. Weiss HJ, Aledort LM, Kochwa S. The effect of salicylates on the hemostatic properties of platelets in man. J Clin Invest. 1968;47:2169–80.
28. O'Laughlin JC, Hoftiezer JW, Mahoney JP, Ivey KJ. Does aspirin prolong bleeding from gastric biopsies in man? Gastrointest Endosc. 1981;27:1–5.
29. Navaratnam K, Alfirevic A, Alfirevic Z. Low dose aspirin and pregnancy: how important is aspirin resistance? BJOG. 2016;123(9):1481–7.
30. Pedersen AK, Fitzgerald GA. Cyclooxygenase inhibition, platelet function, and metabolite formation during chronic sulfinpyrazone dosing. Clin Pharmacol Ther. 1985;37:36–42.
31. Boldt J, Knothe C, Zickmann B, et al. Influence of different intravascular volume therapies on platelet function in patients undergoing cardiopulmonary bypass. Anesth Analg. 1993;76:1185–90.
32. Jones CI, Payne DA, Hayes PD, et al. The antithrombotic effect of dextran-40 in man is due to enhanced fibrinolysis in vivo. J Vasc Surg. 2008;48(3):715–22.
33. Rodeghiero F, Castaman G, Dini E. Epidemiological investigation of the prevalence of von Willebrand's disease. Blood. 1987;69:454–9.
34. Berliner SA, Seligsohn U, Zivelin A, Zwang E, Sofferman G. A relatively high frequency of severe (type III) von Willebrand's disease in Israel. Br J Haematol. 1986;62:535–43.
35. Goodeve AC, Rosén S, Verbruggen B. Haemophilia A and von Willebrand's disease. Haemophilia. 2010;16(Suppl 5):79–84.
36. Bloom AL. The von Willebrand syndrome. Semin Hematol. 1980;17:215–27.
37. Roqué H, Funai E, Lockwood CJ. von Willebrand disease and pregnancy. J Matern Fetal Med. 2000;9:257–66.
38. Kaufmann JE, Vischer UM. Cellular mechanisms of the hemostatic effect of desmopressin (DDAVP). J Thromb Haemost. 2003;1(4):687–9.
39. Castaman G. Treatment of von Willebrand disease with FVIII/VWF concentrates. Blood Transfus. 2011;9(Suppl 2):s9–13.
40. George JN. Clinical practice. Thrombotic thrombocytopenic purpura. N Engl J Med. 2006;354(18):1927–35.
41. Lämmle B, Kremmer Hovinga JA, Alberio L. Thrombotic thrombocytopenic purpura. J Thromb Haemost. 2005;3:1663–75.
42. Asada Y, Sumiyoshi A, Hayashi T, Suzumiya J, Kaketani K. Immunohistochemistry of vascular lesion in thrombotic thrombocytopenic purpura, with special reference to factor VIII related antigen. Thromb Res. 1985;38(5):469–79.
43. Scully M, Thomas M, Underwood M, et al. Thrombotic thrombocytopenic purpura and pregnancy: presentation, management and subsequent pregnancy outcomes. Blood. 2014;124(2):211–9.
44. Coppo P, Bussel A, Charrier S, et al. High-dose plasma infusion versus plasma exchange as early treatment of thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome. Medicine (Baltimore). 2003;82(1):27–38.
45. Park SJ, Kim SJ, Seo HY, et al. High-dose immunoglobulin infusion for thrombotic thrombocytopenic purpura refractory to plasma exchange and steroid therapy. Korean J Intern Med. 2008;23(3):161–4.
46. Harkness DR, Byrnes JJ, Lian EC, Williams WD, Hensley GT. Hazard of platelet transfusion in thrombotic thrombocytopenic purpura. JAMA. 1981;246(17):1931–3.
47. Swisher KK, Terrell DR, Vesely SK, et al. Clinical outcomes after platelet transfusions in patients with thrombotic thrombocytopenic purpura. Transfusion. 2009;49:873–87.
48. Jiang Y, McIntosh JJ, Reese JA, et al. Pregnancy outcomes following recovery from acquired thrombotic thrombocytopenic purpura. Blood. 2014;123:1674–80.
49. Gernsheimer T, Stratton J, Ballem PJ, Slichter SJ. Mechanisms of response to treatment in autoimmune thrombocytopenic purpura. N Engl J Med. 1989;320:974–80.
50. O'Reilly RA, Taber BZ. Immunologic thrombocytopenic purpura and pregnancy. Six new cases. Obstet Gynecol. 1978;179:264–6.
51. Druzin ML, Stier E. Maternal platelet count at delivery in patients with idiopathic thrombocytopenic purpura, not related to perioperative complications. J Am Coll Surg. 1994;179:264–6.
52. Rand ML, Dean JA. Platelet function in autoimmune (idiopathic) thrombocytopenic purpura. Acta Paediatr Suppl. 1998;424:57–60.
53. Pillai M. Platelets and pregnancy. Br J Obstet Gynaecol. 1993;100:201–4.
54. Liebman HA, Pullarkat V. Diagnosis and management of immune thrombocytopenia in the era of thrombopoietin mimetics. Hematology Am Soc Hematol Educ Program. 2011;2011:384–90.
55. Butwick AJ. Postpartum hemorrhage and low fibrinogen levels: the past, present and future. Int J Obstet Anesth. 2013;22:87–91.
56. Goucher H, Wong CA, Patel SK, Toledo P. Cell salvage in obstetrics. Anesth Analg. 2015;121(2):465–8.

Peripartum Hemorrhage

6

Nicola M. Dobos, Tim M. Crozier, and Claire McLintock

Bullet Points

- Obstetric hemorrhage may be ante-, intra-, or postpartum.
- It is associated with significant maternal and fetal morbidity and mortality.
- Peripartum hemorrhage may be difficult to diagnose, with a high frequency of concealed bleeding.
- Optimal maternal management usually results in the best outcome for the fetus.
- Management requires a multidisciplinary approach.
- Antepartum hemorrhage requires rapid decision-making regarding the need for and timing of delivery.
- Resuscitate with fluid and blood products, including using a massive transfusion protocol as necessary.
- Correct coagulopathy and liaise with a hematologist and the blood bank.
- There should be rapid definitive treatment of the bleeding source.
- Tranexamic acid (TXA) has been shown to reduce maternal mortality in postpartum hemorrhage in the developing world.

6.1 Introduction

Hemorrhage associated with pregnancy and childbirth is a global issue associated with both maternal and fetal morbidity and mortality [1]. In healthcare settings with access to intensive care (ICU) services, obstetric hemorrhage and hypertensive disorders constitute the leading causes of maternal ICU admission, while in low-income countries, postpartum hemorrhage (PPH) is the leading cause of maternal mortality (Chaps. 1 and 4) [2, 3]. Globally, PPH is the primary cause of nearly one-quarter of all maternal deaths [1, 4–6].

For the critical care physician, obstetric hemorrhage and its complications are frequently the cause of ICU admission following identification by emergency or obstetric staff or as the result of a rapid response call (see also Chap. 4). However, pregnant women who are being cared for within

N. M. Dobos (✉)
Intensive Care Unit, Western Health, Melbourne, VIC, Australia
e-mail: nicky.dobos@wh.org.au

T. M. Crozier
Intensive Care Unit, Monash Medical Centre, Monash Health, Clayton, VIC, Australia
e-mail: timothy.crozier@monash.edu

C. McLintock
National Women's Health, Auckland City Hospital, Auckland, New Zealand
e-mail: doctorclaire@redhealth.org

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_6

Table 6.1 Causes of obstetric hemorrhage

Antepartum/intrapartum
• Placenta previa
• Placental abruption
• Placenta accreta, increta and percreta
• Vasa previa
• Uterine rupture
• Cervical incompetence
• Splenic artery rupture
• Lower genital tract trauma
• Cervical infection, inflammation, carcinoma
Post-partum
• Uterine atony
• Retained placenta
• Genital tract trauma
• Placenta accreta, increta, and percreta
• Uterine inversion
• Bleeding disorders
– Inherited, e.g., von Willebrand disease, coagulation factor deficiencies
– Acquired coagulopathy, e.g., placental abruption, amniotic fluid embolism, sepsis, anticoagulation therapy

the ICU for other reasons may also have their stay complicated by obstetric hemorrhage. This may be antepartum, intrapartum, or postpartum (Table 6.1). Obstetric hemorrhage constitutes an obstetric emergency, and recognition and correct management are vital to prevent adverse maternal and/or fetal outcomes [7, 8].

6.2 Diagnostic Considerations for Obstetric Hemorrhage

Pregnancy is associated with altered maternal physiology. There is the potential for hidden and high-volume hemorrhage which can be obscured by the body's compensatory mechanisms and lead to rapid clinical deterioration [9, 10]. Close monitoring of maternal vital signs (pulse, respiratory rate, temperature and blood pressure) and symptoms is critical in the early evaluation and ongoing assessment of the pregnant or postpartum woman with hemorrhage. Significant hemorrhage may have occurred even in the absence of overt hemodynamic compromise and may lead to rapid decline if appropriate management steps are delayed. Maternal well-being will have a direct impact on fetal well-being. Unless simultaneous assessment can be performed, always assess the mother first and evaluate the fetus promptly afterward.

Flowchart 6.1 summarizes the important considerations in the diagnosis of obstetric hemorrhage.

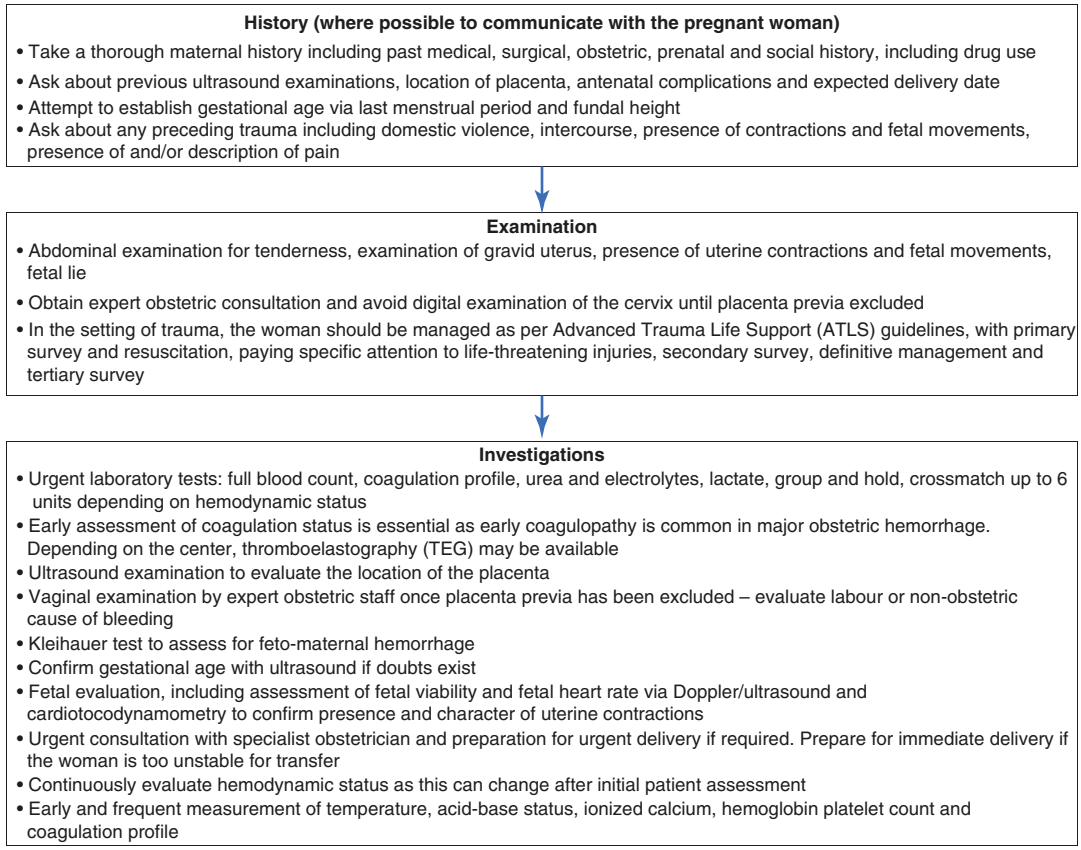
6.3 Management Considerations for Obstetric Hemorrhage

The pregnant or postpartum woman with hemorrhage requires immediate and coordinated assessment and management, including a focused history, physical examination and investigation, as well as prompt resuscitation with specific and supportive measures while giving immediate attention to potentially life-threatening features [10–12]. The first priority is maternal resuscitation, which may also result in improved fetal status. Depending on the cause and severity of obstetric hemorrhage, the possible management strategies will likely include immediate delivery, continued labor, or expectant management. Management strategies are based on the etiology of the bleeding, maternal hemodynamic stability, fetal well-being, and gestational age [13–15]. Early obstetric input is essential, especially in the antepartum setting, where the decision regarding the need for urgent delivery should be made as early as possible.

Flowchart 6.2 summarizes the important considerations in the management of obstetric hemorrhage.

6.3.1 Antepartum Hemorrhage (APH)

Several conditions with differing presentations may complicate the antepartum course. With a high index of suspicion in women with risk factors, many of these can be diagnosed early. Risk factors for obstetric hemorrhage in the antepartum period are presented in Table 6.2. Flowcharts 6.1 and 6.2 summarize the important consider-



Flowchart 6.1 Diagnosis of obstetric hemorrhage

ations for assessment and management of risk factors for PPH [14].

Placenta previa occurs when placental tissue extends over the internal cervical os, or is in proximity to it. Placenta previa may be complete, where the placenta completely covers the internal os; it may also be incomplete or low-lying. In these cases, the placental edge lies within 2 cm of the internal os but does not cover it. It may partially cover or approach the internal os. There is an increased risk of bleeding if the inferior margin of the placenta is less than 2 cm from the internal os. This bleeding is the result of marginal separation of the placenta from the lower uterine segment [16].

Clinical features: Placenta previa is often diagnosed in early pregnancy, however it should be suspected when a woman presents with sudden and painless vaginal bleeding after 20 weeks' gestation. The risk factors for placenta previa are presented in Table 6.2.

Diagnosis: Immediate sonographic examination can determine the location of the placenta in the lower uterine segment either partially or completely covering the internal cervical os. Avoid digital examination of the cervix if placenta previa is suspected, as it may precipitate severe hemorrhage.

Management considerations are determined in the acute phase by maternal stability, fetal well-being and gestational age (Flowchart 6.2). Angiography or hysterectomy may be indicated for massive uncontrollable hemorrhage [17].

Placenta accreta spectrum (PAS) refers to invasive placentation that may present as accreta/increta/percreta. This occurs when placental villi directly adhere to the myometrium rather than the decidua. In placenta increta, placental villi invade the myometrium. In placenta percreta, placental villi penetrate the full thickness of the myometrium into the uterine serosa and may involve peri-

Monitoring
- Escalate monitoring and lines in case of rapid deterioration
- Monitoring must include: ECG monitoring, respiratory monitoring, oxygen saturation monitoring, temperature probe and indwelling catheter
- Assess fetal viability via Doppler or ultrasound once mother is stabilized
- Fetal heart rate monitor may alert to maternal compromise

↓

Lines
- Insert 2 large bore intravenous cannulae (14G) and an intra-arterial line
- Consider additional invasive hemodynamic monitoring
- Consider rapid infuser systems and cell saver
- If vasoactive support is considered imminent or likely, insert a central line to help guide management

↓

Environment
- Manage the patient in a suitably equipped area, such as an emergency department resuscitation cubicle or the intensive care unit
- Consider transfer to a tertiary facility with neonatal intensive care services in cases of maternal stability and if time permits

↓

Multidisciplinary Team
- Early involvement of specialist obstetric staff
- Early involvement of senior anesthetic staff, operating room, interventional radiology and hematology/transfusion specialists
- If the fetus is viable, early pediatric/neonatal notification should take place., including preparation for potential fetal resuscitation

↓

Early recognition and control of hemorrhage
- Assess severity of hemorrhage. Blood loss may be underestimated and hemorrhage may be concealed
- Frequent monitoring of maternal vital signs to assess for signs of shock, including restlessness, anxiety, pallor, tachycardia, tachypnea, hypotension, cold and clammy skin, poor capillary refill, oliguria and altered mental state
- Interpret normal vital signs with caution
- Avoid vaginal examination until placenta previa excluded
- Use ultrasound to confirm location of placenta
- Control of hemorrhage may include local pressure, operative exploration, uterotonics or removal of retained placenta
- Consider the need for massive transfusion and activate protocol early. Ensure availability of appropriately cross-matched blood

↓

Maternal resuscitation and stabilization
- ABCDE approach, including securing of the airway and maintenance of adequate oxygenation and ventilation
- Trendelenburg position in the setting of hypotension. Position patient in left lateral tilt (30 –45 degrees) or perform manual displacement of the uterus if antepartum. Take care if suspecting a uterine rupture
- Urgent investigations as detailed in Flow chart 1
- Rapid and appropriate fluid replacement to correct hypovolemia
- Restore circulating (intravascular) volume with crystalloids (normal saline or Hartman's solution)
- Give blood early in massive obstetric hemorrhage – O negative blood in the event of catastrophic hemorrhage and/or if cross matched blood is unavailable
- Correct coagulopathy -Ensure adequate replacement of clotting factors and other blood products as guided by laboratory hematology specialist, including tranexamic acid
- Early and frequent measurement and correction of temperature, acid-base status, electrolytes, ionized calcium, hemoglobin, platelet count and coagulation profile. With successful treatment, values should trend towards normal
- Maintain urine output
- Consider vasopressors for persistent hypotension only in the setting of adequate fluid resuscitation
- Monitor for evidence of end-organ dysfunction, including oliguria, altered mentation and lactic acidosis

↓

Seek and treat cause of obstetric hemorrhage and prevent complications
- Prevent and treat late or delayed complications of shock and hypotension, including renal, hepatic, lung, and central nervous system injury
- Avoid iatrogenic volume overload
- Once stabilized, assess for presence and quantity of feto-maternal hemorrhage in the antepartum setting and consider Rh immune globulin for Rh-negative patients as per local guidelines
- Consider steroids for lung maturity if less than 34 weeks gestation and delivery can be delayed

↓

Ongoing ICU supportive care
- Including appropriate nutritional support, analgesia, antibiotics, stress ulcer prophylaxis, thromboprophylaxis, glycemic control, bowel management, psychological and social support, lactation support and mother baby contact where possible

Flowchart 6.2 Management of obstetric hemorrhage

Table 6.2 Risk factors for obstetric hemorrhage

Antepartum/intrapartum hemorrhage	Postpartum hemorrhage
Placenta previa • Previous placenta previa • Previous intrauterine surgical procedures (caesarean section, fibroid surgery, and dilatation and curettage) • Multiparity • Multiple gestation • Advanced maternal age • Smoking and drug use during pregnancy • Breech or transverse lying fetus	*Uterine etiology* (Atonic uterus, overdistended uterus, uterine inversion) • Induction of labor • Prolonged and/or precipitous labor • Vaginal birth after previous cesarean section • Instrumental birth • Episiotomy • Grand multiparity, multiple gestation, fetal macrosomia • Polyhydraminios • Chorioamnionitis
Placental abruption • Maternal hypertension • Blunt abdominal trauma • Motor vehicle accidents where there is rapid acceleration-deceleration and uterine decompression • Uterine abnormalities • Smoking and cocaine use	*Genital tract trauma* (Episiotomy, cervical/vaginal/perineal lacerations, uterine rupture) • Precipitous labor • Instrumental birth
Uterine rupture • Preexisting uterine scar (previous classical caesarean or lower uterine caesarean section, myomectomy, metroplasty, corneal resection) • Trauma (motor vehicle accidents, instrumental delivery) • Uterine overdistension (multiple gestation, polyhydramnios, macrosomia) • Uterine anomalies • Placental implantation abnormalities (placenta accreta, increta, percreta) • Choriocarcinoma	*Placental etiology* (Retained placenta/membranes, abnormal placentation, e.g., placenta previa or suspected morbidly adherent, placenta accreta) • Previous uterine surgery • Incomplete placenta at delivery • Succenturiate placenta
Placenta accreta/increta/percreta • Placenta previa • Prior uterine surgery (cesarean section, myomectomy, suction curettage, corneal resection, hysteroscopy) • Advanced maternal age • Multiparity • Ultrasound with suspicious features	*Coagulation etiology—Inherited and acquired* • Placental abruption • Amniotic fluid embolism • Severe preeclampsia, eclampsia • Sepsis • Dilutional coagulopathy secondary to massive transfusion • Anticoagulation therapy • Inherited bleeding disorders such as von Willebrand disease and other bleeding disorders
Vasa previa • Velamentous umbilical cord insertion • Accessory placental lobes (succenturiate or bilobate placenta) • Multiple gestation • IVF pregnancy	

toneal structures and adjacent organs. The risk factors for PAS are presented in Table 6.2.

Clinical features: Many pregnant women with PAS are asymptomatic. However, women with an associated placental previa may present with vaginal bleeding in, or prior to labor. Other presentation features include abdominal pain or hematuria.

Diagnosis: A high index of suspicion is important for the antenatal diagnosis of PAS, although some cases may not be diagnosed until hemorrhage occurs [18]. Pregnant women at risk should undergo a detailed assessment, including ultrasound examination looking for abnormal blood flow within the myometrium and magnetic resonance imaging (MRI).

Management considerations: Women should be transferred prior to labor to a tertiary setting with availability of a multidisciplinary team and blood management capabilities. The recommendation is to perform early cesarean delivery at 35–36 weeks to avoid APH [17]. Women with invasive placentation frequently require hysterectomy, although conservative management with uterine sparing may be performed [17, 18]. Women who undergo conservative management are at particular risk of delayed hemorrhage in the ICU or in the postpartum period. In some cases of invasive placentation, adjacent organs may require resection or repair (e.g., a full or partial cystectomy), which may increase the risk of bladder, ureteral, or bowel injury, as well as postoperative complications such as pelvic infection and abscess. Severe cases of invasive placental implantation may require preoperative pelvic artery embolization to minimize blood loss during hysterectomy [18]. Women should be monitored postpartum to identify re-bleeding; in these cases, laparotomy or angiography may be required [19].

Placental abruption (abruptio placentae) is defined as bleeding associated with the premature separation (complete or partial) of the placenta from the uterine wall after 20 weeks' gestation and prior to the delivery of the fetus. The severity of placental abruption depends on the amount of bleeding and on whether it is accompanied by uterine contractions and/or fetal compromise. The cause of placental abruption is unknown in most cases. The risk factors for placental abruption are presented in Table 6.2.

Clinical features: Placental abruption usually presents as painful vaginal bleeding associated with uterine contractions, uterine tenderness and a non-reassuring fetal heart rate pattern [20–23]. Placental abruption can present as overt (presenting as vaginal bleeding), concealed (abdominal pain only and no vaginal bleeding) or mixed (where the amount of vaginal bleeding does not accurately reflect the extent of abruption).

Diagnosis: Abruption is usually diagnosed clinically, as hemorrhage may be concealed and associated with disseminated intravascular coagulation (DIC), and ultrasound is usually only useful in large abruptions.

Management is largely expectant, with ongoing evaluation of fetal and maternal well-being. Treatment depends on the severity of the abruption and the presence of complications (Flowchart 6.2), such as severe hemorrhage, coagulopathy and shock. Abruption of more than 50% of the placenta is frequently associated with fetal death. All women with abruption should be admitted to the hospital and ICU/HDU admission must be considered. DIC is a concern for women with abruption, particularly when the fetal condition is poor or intrauterine fetal death (IUFD) occurs. Flowchart 6.2 summarizes important considerations in the management of placental abruption [24, 25].

Uterine rupture can be complete or incomplete. Complete uterine rupture involves the entire thickness of the uterine wall and results in communication between the uterine and peritoneal cavities. Incomplete uterine rupture refers to dehiscence of a previous uterine surgical scar where the uterine serosa remains intact [6, 25].

Clinical features: Uterine rupture can occur due to uterine wall weakness or raised intrauterine pressure. Uterine rupture usually occurs in labor at the site of a previous lower cervical scar. In the setting of previous classical cesarean scar, uterine rupture can also occur in the third trimester. Any pregnant patient with sudden onset of abdominal pain and tenderness, vaginal bleeding, uterine contraction abnormalities, hematuria, maternal hemodynamic instability, and FHR abnormalities either preceding or during labor may have uterine rupture. The clinical presentation is variable and depends on the extent of the uterine rupture. If the rupture in incomplete, it is possible for women to be totally asymptomatic. The risk factors for uterine rupture are presented in Table 6.2.

Diagnosis: Uterine rupture is usually diagnosed clinically. Obtaining sonographic confirmation increases the risk of delayed treatment. A high index of suspicion is required in women with risk factors for uterine rupture who present with suggestive signs and symptoms.

Management considerations: Uterine rupture is a life-threatening pregnancy complication for

both mother and fetus. Management involves urgent specialist obstetric and anesthesia consultation with emergency delivery of the fetus (Flowchart 6.2). Ongoing management depends on the extent of rupture and can range from simple surgical repair of the defect to subtotal or total hysterectomy, depending on the site of rupture and the patient's clinical stability. If the uterine artery is involved in the rupture, massive bleeding with shock may occur. Other adverse outcomes include amniotic fluid embolism due to exposure of compartments usually not exposed to amniotic fluid, bladder or ureter damage, DIC, postoperative infection, and neonatal morbidity and mortality due to hypoxic ischemic damage [6, 24].

Vasa previa can cause hemorrhage when fetal blood vessels in the fetal membranes cross the internal cervical os and present in advance of the fetus. The vessels may arise from a velamentous insertion of the umbilical cord into the placenta or from a smaller, accessory (succenturiate) lobe of the placenta [25].

Clinical features: Vasa previa presents as painless vaginal bleeding and sudden-onset fetal tachycardia in the setting of labor and ruptured placental membranes. The risk factors for vasa previa are presented in Table 6.2 [26].

Diagnosis: Transvaginal ultrasound combined with color Doppler can exclude fetal vessels close to or crossing the internal os. Pulsating fetal vessels may be occasionally be palpated overlying the presenting part via digital vaginal examination [27–29].

Management considerations: Vasa previa is a medical emergency that will rapidly result in an unstable patient and will usually require simultaneous maternal resuscitation and immediate delivery of the neonate (Flowchart 6.2) [27–30].

6.3.2 Postpartum Hemorrhage (PPH)

PPH is the leading cause of maternal mortality in low-income countries and contributes to almost one-quarter of maternal deaths around the world [1, 4–6, 31]. PPH contributes to significant maternal morbidity, including shock and multi-organ failure. The causes of PPH relate to the "4 Ts" (Table 6.3), with uterine atony being the most common cause [32–34].

Table 6.3 Management of PPH by etiology

Tone (uterine atony)
Mechanical
• Uterine massage or bimanual uterine compression
• Ensure empty bladder
Pharmacological
• First-line uterotonic: Oxytocin
• Secondary uterotonics: Methylergometrine, 15-methyl-prostaglandin F2α, misoprostol
• Uterotonic agents can be given in combination in the event of severe ongoing atonic bleeding
Trauma (lacerations)
• Thorough inspection of the entire genital tract, in either the labor ward or operating theater, with pressure applied to bleeding areas and repair of lacerations as required
• Cover the patient with broad-spectrum antibiotics
• Consider concealed source of bleeding in a clinically unstable patient with apparently small amount of vaginal bleeding
• Other sources: uterine inversion, intra-abdominal (uterine rupture), broad ligament hematoma, subscapular liver rupture, rupture of aneurysmal visceral artery, i.e., splenic artery
Tissue (retained placenta, abnormally adherent placenta)
• Inspect placenta for missing tissue
• Thoroughly inspect the vagina for retained placental tissue
• Return to the theater for examination under anesthetic and manual removal of the placenta
• Cover the patient with broad-spectrum antibiotics
Thrombin (inherited or acquired coagulation defects)
• Maternal coagulation disorders are a less common cause of PPH; however coagulopathies can develop in the setting of massive hemorrhage or other events, such as amniotic fluid embolism, placental abruption, or severe preeclampsia
• Check coagulation profiles and replace blood product components as necessary

Table 6.2 presents the risk factors for PPH by etiology. While many risk factors for PPH have been identified, most women who develop PPH have no identifiable risk factors [35–37]. This has important ramifications, as women may present suddenly. An institutional strategy must be in place to identify and rapidly resuscitate these women [38]. Most deaths resulting from PPH occur during the first 24 hours after birth, with 90% occurring in the first 4 hours [39, 40]. Most of the deaths associated with PPH could be avoided with appropriate antenatal care, treat-

ment of antenatal anemia, skilled attendance in labor and prophylactic use of uterotonics during the third stage of labor.

6.4 Definitions

There is no globally agreed definition of PPH [41]. Below are some recent classifications.

The World Health Organization (WHO), 2013, define PPH as a blood loss of 500 mL or greater within 24 hours of birth, independent of the mode of delivery [42].

The American College of Obstetricians and Gynecologists (ACOG), 2017, define PPH as cumulative blood loss of greater than or equal to 1000 mL, or blood loss accompanied by signs or symptoms of hypovolemia within 24 hours of birth (including intrapartum loss), regardless of the mode of delivery [39].

This differed to previous definitions of PPH, 2015: estimated blood loss ≥500 mL after vaginal birth or ≥1000 mL after cesarean delivery [43].

The Royal College of Obstetricians and Gynaecologists (RCOG), 2016, define PPH as minor (500–1000 mL) or major (>1000 mL), with further subdivisions of major hemorrhage as moderate (1001–2000 mL) or severe (>2000 mL) [44]. An international expert panel in obstetrics, gynecology, hematology, transfusion, and anesthesiology defined PPH at a meeting in November 2011 as "active bleeding >1000 mL within the 24 h following birth that continues despite the use of initial measures, including first-line uterotonic agents and uterine massage" [35].

Primary (or early) PPH occurs in the first 24 hours after delivery, and secondary (or late or delayed) PPH occurs 24 hours to 6 weeks after delivery [40].

6.5 Prevention

All women with risk factors for PPH must be assessed by a multidisciplinary team (including obstetric, anesthesia, and intensive care specialists) in the antenatal period, as well as recording of placental location prior to delivery. Women with significant risk factors for PPH should have anemia corrected in the antenatal period and should plan to deliver in an obstetric unit with rapid access to blood and blood products [45]. On the day of delivery, women at risk should have adequate large-bore IV access and have their blood typed and cross-matched. Active management of the third stage of labor is essential for PPH prevention and must include the administration of prophylactic uterotonics (oxytocin) after the baby is delivered, as well as uterine massage [39, 44, 46, 47]. There is minimal evidence that early cord clamping and cutting, or controlled umbilical cord traction has a significant effect on the incidence or volume of PPH [43, 48]. After delivery of the placenta, the genital tract should be examined for evidence of lacerations and repaired as necessary.

6.6 Identification

One of the key management strategies for PPH is early recognition. This enables early escalation to a coordinated multidisciplinary team (senior obstetric staff, anesthetic staff, operating room, hematology/transfusion specialists, interventional radiology, and ICU/HDU services). In the setting of abnormal maternal vital signs in the postpartum period, always consider and exclude PPH as a cause [40, 49]. When no obvious bleeding is seen, an intraperitoneal or retroperitoneal hemorrhage must be excluded. Visual estimation of blood loss is often unreliable and can lead to underestimation; however an attempt to quantify blood loss is still recommended [50–53]. Consider the patient's prior hemoglobin and total blood volume when assessing the severity of PPH, as well as any ongoing losses [54]. It is also important to note that vital signs can be both variable and misleading in relation to the volume of hemorrhage, and even slight tachycardia in young, otherwise healthy women may indicate blood losses of 1–2 L [55].

6.7 Management of PPH

All obstetric care facilities should have site-specific institutional guidelines for the management of PPH. Early recognition and control of

hemorrhage with blood or blood products, and, if available, the timely involvement of a multidisciplinary team of specialists is vital to avoid maternal morbidity and mortality [56, 57]. These guidelines must be familiar to the treating teams and must take into account the resources available [58]. Practice drills can ensure timely and efficient management and coordination in such events [46]. In rural hospitals or smaller centers with less resources, a comprehensive plan for the management of PPH, including guidelines for anticipating and initiating early transfer to a higher level facility, is essential [39, 59]. Resuscitative efforts should occur in tandem with escalation of monitoring and investigations, and targeted treatment [56, 59–64].

Flowchart 6.2 outlines the management of obstetric hemorrhage. Additional steps to promote uterine contraction may include bimanual uterine massage, intrauterine balloon tamponade (Bakri balloon), vaginal packing and uterine packing [11, 39, 46, 65–68].

For all causes, consider early transfer to the operating room for examination under anesthesia and potential advanced surgical management. For those too unstable for transfer, urgent surgical exploration may be required in the intensive care unit [69].

Surgical techniques include the following: evaluation under anesthetic looking for genital tract lacerations and placental fragments in the uterine cavity, laparotomy for persistent bleeding (including uterine artery ligation, internal iliac artery ligation and B-lynch brace suture), pelvic packing, aortic compression and hysterectomy (subtotal or total). Interventional radiology may be useful for selective arterial embolization [19, 32, 70–73].

6.8 Pharmacological Management

6.8.1 Uterotonics

Together with uterine massage and compression, uterotonics should be used as the first-line treatment for PPH caused by uterine atony [39, 41, 57]. The decision to use one uterotonic over another is at the discretion of the clinician, as none have been found to be more efficacious than another [39]. Rapid administration of uterotonics followed by ongoing assessment of their effect is critical in the management of PPH due to uterine atony. Often, multiple uterotonics are used and the priority is prompt initiation and assessment of effect, rather than the type and sequence, which may vary between institutions. Effect should be evident within 30 minutes of pharmacological administration. If there is delay to uterotonic administration or if therapy is ineffective or partially effective, management with balloon tamponade, interventional radiology, and/or surgery must all be expediently explored with the relevant expert teams [60].

Table 6.4 describes common uterotonics used in the setting of PPH due to uterine atony, including their doses, contraindications and adverse effects [34, 39, 47, 74].

6.9 Tranexamic Acid (TXA)

Previous evidence for the use of TXA in obstetric hemorrhage and PPH was scarce and most institutional guidelines did not advocate for its use [75–77]. In the recent World Maternal Antifibrinolytic (WOMAN) Trial, patients with PPH were administered TXA at an intravenous dose of 1 g over 10 minutes, with a second 1 g dose administered at 30 minutes if the bleeding persisted. Death due to bleeding was statistically significantly reduced in the TXA group compared to the placebo group (1.5% versus 1.9%). The trial reported that TXA reduced death due to bleeding in women with PPH by nearly one-third, with no evidence of adverse effects or complications if administered within 3 hours of birth [78]. There is a strong suggestion that when TXA is used as an adjunct to early resuscitation, administration of uterotonics, management of coagulopathy and other surgical management strategies for PPH, the most effective timing of TXA treatment is soon after the onset of PPH, whereas late treatment is unlikely to be beneficial. The trial suggests that further research is needed as to the

Table 6.4 Uterotonics for PPH due to uterine atony

Drug	Dose and route	Frequency	Contraindications/adverse effects
Oxytocin	40 units in 1 L normal saline as a continuous IV infusion 10 units IM	Maximum 3 L of IV fluids containing oxytocin	Hypotension and cardiovascular collapse can result from rapid IV bolus, which is not recommended
15-methyl-prostaglandin F2α	250 mcg IM or intramyometrial	Every 15–90 min as required (up to 8 doses, total 2 mg)	Contraindicated in asthma Adverse effects include nausea, vomiting, diarrhea, headache, chills, and bronchospasm
Methylergometrine	200 mcg IM or intramyometrial	Every 2–4 h (5 doses, maximum 1 mg)	Contraindicated in preeclampsia, hypertension, and coronary or cerebral artery disease Adverse effects include nausea, vomiting, and severe hypertension
Misoprostal	400 mcg–1 mg sublingual, oral, or rectal	Once	Adverse effects include nausea, vomiting, diarrhea, fever, and headache

IV intravenously, *IM* intramuscularly

dosing and time course of the changes in coagulation and fibrinolysis after childbirth. Given the mortality reduction findings, TXA (initially 1 g intravenously and repeated if required) should be considered in the setting of obstetric hemorrhage when initial medical therapy fails, while factoring in local institutional guidelines and expert obstetric and hematological advice [46].

6.10 Recombinant Factor VIIa (rFVIIa)

rFVIIa is not licensed for use in the management of major PPH. In the setting of catastrophic obstetric hemorrhage not controlled by other methods, recommendations for its use remain largely expert in nature and based on anecdotal evidence [34, 79, 80]. While rFVIIa has been reported to show significant hemostatic improvement in hemorrhaging obstetric patients, it also poses the risk of life-threatening thrombosis [81–83]. After consultation with a hematology/transfusion specialist, administration should be considered in women with life-threatening obstetric hemorrhage, where standard obstetric, surgical and transfusion approaches have failed. If administering rFVIIa, ensure it is given with strict attention to the control of bleeding, physiological and metabolic parameters, coagulation status and temperature maintenance. The effectiveness of rFVIIa is significantly reduced by hypothermia, acidosis and low platelets, so directed resuscitation towards normal physiology is imperative prior to its use. There is no agreed recommended dose of rFVIIA in obstetric hemorrhage, but generally doses of 60–90 mcg/kg have been given in published cohorts [34, 83]. When effective, an improvement in bleeding should be seen within 10–15 minutes of rFVIIa administration [83]. If ineffective, a second dose may be given, but further doses are not recommended [84, 85].

6.11 Blood Component Therapy

Initial fluid management and workup: In the setting of obstetric hemorrhage, inadequate early resuscitation and hypoperfusion may lead to lactic acidosis and multi-organ failure. Rapid fluid resuscitation with crystalloids up to 30 mL/kg may be initiated while awaiting blood. Simultaneously, blood should be sent for urgent full blood count, coagulation profile and crossmatch, and the cause of hemorrhage should be sought and treated (Table 6.3). In order to avoid dilutional coagulopathy, continuous resuscitation with crystalloid or another volume expander should be avoided, and replacement with blood

and blood products should be prioritized [86–89]. There is evidence from the hemorrhaging trauma population that crystalloid resuscitation at a ratio of greater than 1.5:1 per unit of RBC transfused is associated with higher rates of multiple organ failure [88–90].

Red blood cell transfusion: The aim of transfusion in severe hemorrhage is restoration of circulating blood volume to prevent hypoperfusion, lactic acidosis, multi-organ failure and coagulopathy. Early hemostatic resuscitation with type-specific or O Rh-negative blood is recommended [88, 91]. There are no firm criteria for initiating red blood cell (RBC) transfusion; however, in the setting of PPH, changes to hemoglobin and hematocrit are often a poor reflection of the extent of bleeding and maternal vital signs often remain normal until significant blood loss has occurred [92]. Hemodynamic compromise may not occur until blood loss of up 1.5–2 L has occurred. Packed RBCs should therefore be given in response to hemodynamic compromise, estimated blood loss and ongoing bleeding, rather than a hemoglobin trigger [54, 59, 93]. Timing and indications for initiation of a massive transfusion protocol should be part of institutional guidelines for the management of PPH [94–96].

Blood products: Blood products, including platelets, fresh frozen plasma (FFP), and cryoprecipitate or fibrinogen concentrate, are used to reverse or prevent coagulopathy. Provision of coagulation factors during massive hemorrhage should ideally be guided by protocol and consultation with a transfusion/hematology specialist, followed by point-of-care coagulation tests, such as thromboelastography (TEG®) or rotational thrombolestometry (ROTEM®) [64, 97–102].

Multicomponent therapy with a fixed ratio of transfusion of RBCs, FFP and platelets should be administered as guided by individual institutional protocols. The recommended initial transfusion ratio for packed RBCs/FFP/platelets is 1:1:1 [40]. While fixed ratio transfusion approaches exist in the trauma setting, it is currently uncertain if such approaches improve outcomes in the obstetric setting. Further research into optimal timing and ratios is required in this area [35, 89, 90, 103].

Administration of fibrinogen replacement with cryoprecipitate or fibrinogen concentrate should be considered in the setting of consumptive coagulopathy and/or low fibrinogen [94, 98, 104–106]. Fibrinogen levels are typically higher in pregnancy (normal range 4–6 g/L), so fibrinogen levels <2.0 g/L, or those rapidly falling in the context of obstetric hemorrhage, should prompt consideration of fibrinogen replacement.

Triggers of coagulopathy (hypothermia and acidosis) and electrolyte imbalances caused by transfusion (hypocalcemia, hyperkalemia) should be treated in parallel to blood component administration [107].

Values indicative of critical physiologic derangement include temperature <35 °C, pH < 7.2, base excess worse than −6, lactate >4 mmol/L, ionized calcium <1.1 mmol/L, platelet count $<50 \times 10^9$ mmol/L, PT 1.5 × normal, INR >1.5, APTT >1.5 × normal, and fibrinogen level <2.0 g/L [95].

It is worth noting that the PT and APTT may often remain normal despite massive obstetric hemorrhage [87, 103].

6.12 Pitfalls

- Bleeding that is concealed.
- Delay in diagnosis, with deterioration of vital signs prior to recognition of PPH.
- Underestimated blood loss—signs or symptoms of significant blood loss (e.g., tachycardia and hypotension) may be absent or only appear once blood loss is substantial [55].
- Delay in request for senior multidisciplinary team involvement.
- Inadequate resuscitation (fluid and blood).
- Delay in transfer to operating room.
- Inadequate correction of coagulopathy.
- Ongoing care - Once hemorrhage is controlled and the woman is stabilized, attention should be given to preempting and managing the potential complications of PPH and massive transfusion, including ongoing supportive intensive care.

6.13 Transfusion-Related Lung Injury and Transfusion-Associated Circulatory Overload

Massive transfusion in the setting of massive obstetric hemorrhage can be complicated by both transfusion-related lung injury (TRALI) and transfusion-associated circulatory overload (TACO). TRALI is an uncommon but potentially fatal complication following transfusion of blood products and is characterized by an acute onset (within 6 hours of transfusion) of non-cardiogenic pulmonary edema [108]. Other diagnostic criteria include hypoxemia, defined as a PaO_2/FiO_2 ratio of ≤300 or oxygen saturation of <90% on room air and bilateral pulmonary infiltrates seen on chest radiograph [108–111]. Hypotension may also occur. Treatment is supportive [108, 111].

TACO is a transfusion reaction characterized by respiratory distress and/or pulmonary edema due to volume overload in the setting of transfusion (within 6 hours) [112, 113]. TACO may be differentiated from TRALI by the existence of hypertension, but the distinction may be challenging [111]. Management includes supporting the airway, providing supplemental oxygen and/or ventilation and the use of diuretics to remove fluid [113].

Women receiving multiple transfusions should be monitored carefully. The diagnosis of TRALI or TACO should be considered in any woman showing symptoms of cardiovascular or respiratory compromise within 6 hours of transfusion, especially those with additional risk factors, such as underlying cardiac disease or a positive fluid balance [111].

6.14 Further Hemorrhage and Venous Thromboembolism

Monitor for evidence of further hemorrhage and correct abnormal coagulation parameters. Infection due to retained products of conception or postoperative surgical site infection may be a cause of delayed hemorrhage. Also consider recanalization of previously embolized arteries as a source of potential bleeding [19].

Women with major PPH are also at an increased risk of venous thromboembolism [114, 115]. Thromboprophylaxis with mechanical devices such as intermittent compression devices should be used until there are no clinical concerns with ongoing bleeding, at which point pharmacological thromboprophylaxis should be initiated.

6.15 Other Complications of Global Hypoperfusion/Post-circulatory Arrest

Massive obstetric hemorrhage may lead to circulatory collapse and cardiac arrest from hypovolemia. Even with prompt and successful resuscitation efforts, significant end-organ damage may occur resulting in multiple organ system failure. These may include pulmonary edema and acute respiratory distress syndrome (ARDS), acute myocardial infarction, acute (prerenal) kidney injury, ischemic hepatitis, hepatic infarction or hepatic failure, splanchnic ischemia accompanied by bowel sloughing, gastrointestinal hemorrhage, bacterial translocation and bowel infarction, ischemic pituitary necrosis (i.e., Sheehan's syndrome), global hypoxic ischemic encephalopathy resulting in varying degrees of ongoing neurological impairment, and even brain death [116]. Detailed discussion and management of the above conditions plus other related complications is described elsewhere in this book.

References

1. Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. Lancet. 2006;367(9516):1066–74.
2. Kelsey JJ. Obstetric emergencies in the ICU. In: PSAP-VII Critical and urgent care: Book 2. 17th. Lenexa, KS: American College of Clinical Pharmacy ACCP; 2010. p. 7–19.
3. Pollock W, Rose L, Dennis CL. Pregnant and postpartum admissions to the intensive care unit: a systematic review. Intensive Care Med. 2010;36(9):1465–74.

4. Baskett TF. Epidemiology of obstetric critical care. Best Pract Res Clin Obstet Gynaecol. 2008;22(5):763–74.
5. Driessen M, Bouvier-Colle MH, Dupont C, Khoshnood B, Rudigoz RC, Deneux-Tharaux C, Pithagore Group. Postpartum hemorrhage resulting from uterine atony after vaginal delivery: factors associated with severity. Obstet Gynecol. 2011;117(1):21–31.
6. Hofmeyr GJ, Say L, Gülmezoglu AM. Systematic review: WHO systematic review of maternal mortality and morbidity: the prevalence of uterine rupture. BJOG. 2005;112(9):1221–8.
7. Shapiro JM. Critical care of the obstetric patient. J Intensive Care Med. 2006;21(5):278–86.
8. Zeeman GG. Obstetric critical care: a blueprint for improved outcomes. Crit Care Med. 2006;34(9):S208–14.
9. Gaffney A. Critical care in pregnancy—is it different? Semin Perinatol. 2014;38(6):329–40.
10. Pearlman M, Tintinalli J, Dyne P, editors. Obstetric & gynecologic emergencies: diagnosis and management. Chicago: McGraw-Hill; 2004.
11. Munnur U, Bandi V, Guntupalli KK. Management principles of the critically ill obstetric patient. Clin Chest Med. 2011;32(1):53–60.
12. Paxton JL, Presneill J, Aitken L. Characteristics of obstetric patients referred to intensive care in an Australian tertiary hospital. Aust N Z J Obstet Gynaecol. 2014;54(5):445–9.
13. Price LC, Slack A, Nelson-Piercy C. Aims of obstetric critical care management. Best Pract Res Clin Obstet Gynaecol. 2008;22(5):775–99.
14. Qureshi H, Massey E, Kirwan D, Davies T, Robson S, White J, Jones J, Allard S. BCSH guideline for the use of anti-D immunoglobulin for the prevention of haemolytic disease of the fetus and newborn. Transfus Med. 2014;24(1):8–20.
15. Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Guidelines for the use of Rh(D) Immunoglobulin (Anti-D) in obstetrics in Australia. 2015. https://www.ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women's%20Health/Statement%20and%20guidelines/Clinical-Obstetrics/Guidelines-for-the-use-of-Rh(D)-Immunoglobulin-(Anti-D)-(C-Obs-6)-Review-November-2015.pdf?ext=.pdf. Accessed 15 Aug 2018.
16. Faiz AS, Ananth CV. Etiology and risk factors for placenta previa: an overview and meta-analysis of observational studies. J Matern Fetal Neonatal Med. 2003;13(3):175–90.
17. Allahdin S, Voigt S, Htwe TT. Management of placenta praevia and accreta. J Obstet Gynaecol. 2011;31(1):1–6.
18. Fitzpatrick KE, Sellers S, Spark P, Kurinczuk JJ, Brocklehurst P, Knight M. The management and outcomes of placenta accreta, increta, and percreta in the UK: a population-based descriptive study. Br J Obstet Gynaecol. 2014;121(1):62–70.
19. Choi W, Shin JH, Kim PH, Han K, Ohm JY, Kim JH, Kim JW. Clinical outcomes of 23 patients who had repeat pelvic arterial embolisation for uncontrolled post-partum haemorrhage at a single centre. Clin Radiol. 2018;73(7):665–71.
20. Ananth CV, Lavery JA, Vintzileos AM, Skupski DW, Varner M, Saade G, Biggio J, Williams MA, Wapner RJ, Wright JD. Severe placental abruption: clinical definition and associations with maternal complications. Am J Obstet Gynecol. 2016;214(2):272.e1–9.
21. Hladky K, Yankowitz J, Hansen WF. Placental abruption. Obstet Gynecol Surv. 2002;57(5):299–305.
22. Oyelese Y, Ananth CV. Placental abruption. Obstet Gynecol. 2006;108(4):1005–16.
23. Tikkanen M. Placental abruption: epidemiology, risk factors and consequences. Acta Obstet Gynecol Scand. 2011;90(2):140–9.
24. Ozdemir I, Yucel N, Yucel O. Rupture of the pregnant uterus: a 9-year review. Arch Gynecol Obstet. 2005;272(3):229–31.
25. Ruiter L, Kok N, Limpens J, Derks JB, Graaf IM, Mol BW, Pajkrt E. Incidence of and risk indicators for vasa praevia: a systematic review. Br J Obstet Gynaecol. 2016;123(8):1278–87.
26. Royal College of Obstetricians and Gynaecologists (RCOG). Placenta praevia, placenta accreta and vasa praevia: diagnosis and management—Green-top Guideline No. 27. https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_27.pdf. Accessed 22 Aug 2018.
27. Catanzarite V, Oyelese Y. Diagnosis and management of vasa previa. Am J Obstet Gynecol. 2016;214(6):764.
28. Sinkey RG, Odibo AO, Dashe JS. # 37: diagnosis and management of vasa previa. Am J Obstet Gynecol. 2015;213(5):615–9.
29. Swank ML, Garite TJ, Maurel K, Das A, Perlow JH, Combs CA, Fishman S, Vanderhoeven J, Nageotte M, Bush M, Lewis D. Vasa previa: diagnosis and management. Am J Obstet Gynecol. 2016;215(2):223.e1–6.
30. Gagnon R, Morin L, Bly S, Butt K, Cargill YM, Denis N, Hietala-Coyle MA, Lim KI, Ouellet A, Racicot MH, Salem S. Guidelines for the management of vasa previa. Int J Gynaecol Obstet. 2010;108(1):85–9.
31. Li XF, Fortney JA, Kotelchuck M, Glover LH. The postpartum period: the key to maternal mortality. Int J Gynaecol Obstet. 1996;54(1):1–10.
32. Breathnach F, Geary M. Uterine atony: definition, prevention, nonsurgical management, and uterine tamponade. Semin Perinatol. 2009;33(2):82–7.
33. Kramer MS, Berg C, Abenhaim H, Dahhou M, Rouleau J, Mehrabadi A, Joseph KS. Incidence, risk factors, and temporal trends in severe postpartum hemorrhage. Am J Obstet Gynecol. 2013;209(5):449.e1–7.
34. McLintock C, James AH. Obstetric hemorrhage. J Thromb Haemost. 2011;9(8):1441–51.

35. Abdul-Kadir R, McLintock C, Ducloy AS, El-Refaey H, England A, Federici AB, Grotegut CA, Halimeh S, Herman JH, Hofer S, James AH. Evaluation and management of postpartum hemorrhage: consensus from an international expert panel. Transfusion. 2014;54(7):1756–68.
36. Matsuzaki S, Endo M, Ueda Y, Mimura K, Kakigano A, Egawa-Takata T, Kumasawa K, Yoshino K, Kimura T. A case of acute Sheehan's syndrome and literature review: a rare but life-threatening complication of postpartum hemorrhage. BMC Pregnancy Childbirth. 2017;17(1):188.
37. Wetta LA, Szychowski JM, Seals S, Mancuso MS, Biggio JR, Tita AT. Risk factors for uterine atony/postpartum hemorrhage requiring treatment after vaginal delivery. Am J Obstet Gynecol. 2013;209(1):51.e1–6.
38. Bingham D, Lyndon A, Lagrew D, Main EK. A state-wide obstetric hemorrhage quality improvement initiative. MCN Am J Matern Child Nurs. 2011;36(5):297–304.
39. Committee on Practice Bulletins-Obstetrics. Practice bulletin no. 183: postpartum hemorrhage. Obstet Gynecol. 2017;130(4):e168–86.
40. Mousa HA, Blum J, Abou El Senoun G, Shakur H, Alfirevic Z. Treatment for primary postpartum haemorrhage. Cochrane Database Syst Rev. 2014;(2):CD003249.
41. Lier H, von Heymann C, Korte W, Schlembach D. Peripartum haemorrhage: haemostatic aspects of the new German PPH guideline. Transfus Med Hemother. 2018;45(2):127–35.
42. Tuncalp O, Souza JP, Gulmezoglu M. New WHO recommendations on prevention and treatment of postpartum hemorrhage. Int J Gynaecol Obstet. 2013;34(4):254–6.
43. Dahlke JD, Mendez-Figueroa H, Maggio L, Hauspurg AK, Sperling JD, Chauhan SP, Rouse DJ. Prevention and management of postpartum hemorrhage: a comparison of 4 national guidelines. Am J Obstet Gynecol. 2015;213(1):76.e1–76.e10.
44. Mavrides E, Allard S, Chandraharan E, Collins P, Green L, Hunt BJ, Riris S, Thomson AJ on behalf of the Royal College of Obstetricians and Gynaecologists. Prevention and management of postpartum haemorrhage. BJOG. 2016;124:e106–e149.
45. Peña-Rosas JP, De-Regil LM, Garcia-Casal MN, Dowswell T. Daily oral iron supplementation during pregnancy. Cochrane Database Syst Rev. 2015;(7):CD004736.
46. Arulkumaran S, Mavrides E, Penney GC. Prevention and management of postpartum haemorrhage. Royal College of Obstetricians and Gynaecologists RCOG Green-top Guideline 52. http://www.jsog.org/GuideLines/Prevention_and_management_of_postpartum_haemorrhage.pdf. Accessed 22 Aug 2018.
47. World Health Organization. WHO recommendations for the prevention and treatment of postpartum haemorrhage. http://apps.who.int/iris/bitstream/handle/10665/75411/9789241548502_eng.pdf;jsessionid=3C848394963ECC6E126AA982BDC5DE56?sequence=1. Accessed 22 Aug 2018.
48. Hofmeyr GJ, Mshweshwe NT, Gülmezoglu AM. Controlled cord traction for the third stage of labour. Cochrane Database Syst Rev. 2015;1:CD008020.
49. Martel MJ, MacKinnon KJ, Arsenault MY, Bartellas E, Klein MC, Lane CA, et al. Hemorrhagic shock. J Obstet Gynaecol Can. 2002;24(6):504.
50. Lertbunnaphong T, Lapthanapat N, Leetheeragul J, Hakularb P, Ownon A. Postpartum blood loss: visual estimation versus objective quantification with a novel birthing drape. Singap Med J. 2016;57(6):325–8.
51. Lilley G, Burkett-St-Laurent D, Precious E, Bruynseels D, Kaye A, Sanders J, et al. Measurement of blood loss during postpartum haemorrhage. Int J Obstet Anesth. 2015;24(1):8–14.
52. Prata N, Gerdts C. Measurement of postpartum blood loss. BMJ. 2010;340:c555.
53. Stafford I, Dildy GA, Clark SL, Belfort MA. Visually estimated and calculated blood loss in vaginal and cesarean delivery. Am J Obstet Gynecol. 2008;199(5):519.e1–7.
54. Alexander JM, Sarode R, McIntire DD, Burner JD, Leveno KJ. Whole blood in the management of hypovolemia due to obstetric hemorrhage. Obstet Gynecol. 2009;113(6):1320–6.
55. Pacagnella RC, Souza JP, Durocher J, Perel P, Blum J, Winikoff B, et al. A systematic review of the relationship between blood loss and clinical signs. PLoS One. 2013;8(3):e57594.
56. Austin DM, Sadler L, McLintock C, McArthur C, Masson V, Farquhar C, Rhodes S. Early detection of severe maternal morbidity: a retrospective assessment of the role of an early warning score system. Aust N Z J Obstet Gynaecol. 2014;54(2):152–5.
57. Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Management of post-partum haemorrhage. https://www.ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical-Obstetrics/Management-of-Postpartum-Haemorrhage-C-Obs-43-Amended-February-2016.pdf?ext=.pdf. Accessed 22 Aug 2018.
58. Kozek-Langenecker SA, Afshari A, Albaladejo P, Santullano CAA, De Robertis E, Filipescu DC, et al. Management of severe perioperative bleeding. Eur J Anaesthesiol. 2013;30(6):270–382.
59. Shields LE, Smalarz K, Reffigee L, Mugg S, Burdumy TJ, Propst M. Comprehensive maternal hemorrhage protocols improve patient safety and reduce utilization of blood products. Am J Obstet Gynecol. 2011;205(4):368.e1–8.
60. Bodner LJ, Nosher JL, Gribbin C, Siegel RL, Beale S, Scorza W. Balloon-assisted occlusion of the internal iliac arteries in patients with placenta accreta/percreta. Cardiovasc Intervent Radiol. 2006;29(3):354–61.

61. de Lloyd L, Bovington R, Kaye A, Collis RE, Rayment R, Sanders J, Rees A, Collins PW. Standard haemostatic tests following major obstetric haemorrhage. Int J Obstet Anesth. 2011;20(2):135–41.
62. Guise JM, Segel S. Teamwork in obstetric critical care. Best Pract Res Clin Obstet Gynaecol. 2008;22(5):937–51.
63. Rath W, Schneider M. Definitions and diagnosis of postpartum haemorrhage (PPH): underestimated problems! Geburtshilfe Frauenheilkd. 2010;70:36–40.
64. Solomon C, Collis RE, Collins PW. Haemostatic monitoring during postpartum haemorrhage and implications for management. Br J Anaesth. 2012;109(6):851–63.
65. Cameron C, Roberts CL, Olive EC, Ford JB, Fischer WE. Trends in postpartum haemorrhage. Aust N Z J Public Health. 2006;30(2):151–6.
66. Georgiou C. Balloon tamponade in the management of postpartum haemorrhage: a review. Br J Obstet Gynaecol. 2009;116(6):748–57.
67. Honiden S, Abdel-Razeq SS, Siegel MD. The management of the critically ill obstetric patient. J Intensive Care Med. 2013;28(2):93–106.
68. Knight M, Callaghan WM, Berg C, et al. Trends in postpartum hemorrhage in high resource countries: a review and recommendations from the International Postpartum Hemorrhage Collaborative Group. BMC Pregnancy Childbirth. 2009;9(1):55.
69. James AH, McLintock C, Lockhart E. Postpartum hemorrhage: when uterotonics and sutures fail. Am J Hematol. 2012;87(Suppl 1):S16–22.
70. Dilauro MD, Dason S, Athreya S. Prophylactic balloon occlusion of internal iliac arteries in women with placenta accreta: literature review and analysis. Clin Radiol. 2012;67(6):515–20.
71. Gonsalves M, Belli A. The role of interventional radiology in obstetric hemorrhage. Cardiovasc Intervent Radiol. 2010;33(5):887–95.
72. Niola R, Cavaliere C, Marcello L, Maglione F, de Ritis R, Di Pietto F, et al. Role of interventional radiology in treating obstetric haemorrhages. Radiol Med. 2014;119(8):607–15.
73. Zwart JJ, Dijk PD, van Roosmalen J. Peripartum hysterectomy and arterial embolization for major obstetric hemorrhage: a 2-year nationwide cohort study in the Netherlands. Am J Obstet Gynecol. 2010;202(2):150.e1–7.
74. Mercier FJ, Van de Velde M. Major obstetric hemorrhage. Anesthesiol Clin. 2008;26(1):53–66.
75. Ferrer P, Roberts I, Sydenham E, Blackhall K, Shakur H. Anti-fibrinolytic agents in postpartum haemorrhage: a systematic review. BMC Pregnancy Childbirth. 2009;9:29.
76. Sentürk MB, Cakmak Y, Yildiz G, Yildiz P. Tranexamic acid for cesarean section: a double-blind, placebo-controlled, randomized clinical trial. Arch Gynecol Obstet. 2013;287(4):641–5.
77. Xu J, Gao W, Ju Y. Tranexamic acid for the prevention of postpartum hemorrhage after cesarean section: a double-blind randomization trial. Arch Gynecol Obstet. 2013;287(3):463–8.
78. WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with postpartum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet. 2017;389(10084):2105–16.
79. Jain R. Recombinant activated factor vii in obstetrics & gynaecology. J Res Obstet Gynaecol Infertil. 2016;2(1):14–6.
80. Welsh A, McLintock C, Gatt S, Somerset D, Popham P, Ogle R. Guidelines for the use of recombinant activated factor VII in massive obstetric haemorrhage. Aust N Z J Obstet Gynaecol. 2008;48(1):12–6.
81. Levi M, Levy JH, Andersen HF, Truloff D. Safety of recombinant activated factor VII in randomized clinical trials. N Engl J Med. 2010;363(19):1791–800.
82. O'Connell KA, Wood JJ, Wise RP, Lozier JN, Braun MM. Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. JAMA. 2006;295(3):293–8.
83. Franchini M, Lippi G, Franchi M. The use of recombinant activated factor VII in obstetric and gynaecological haemorrhage. BJOG. 2007;114:8–15.
84. Kalina M, Tinkoff G, Fulda G. Massive postpartum hemorrhage: recombinant factor VIIa use is safe but not effective. Del Med J. 2011;83(4):109–13.
85. Phillips LE, McLintock C, Pollock W, et al. Recombinant activated factor VII in obstetric hemorrhage: experiences from the Australian and New Zealand haemostasis registry. Anesth Analg. 2009;109(6):1908–15.
86. Collins P, Abdul-Kadir R, Thachil J. Management of coagulopathy associated with postpartum hemorrhage: guidance from the SSC of the ISTH. J Thromb Haemost. 2016;14(1):205–10.
87. Collis RE, Collins PW. Haemostatic management of obstetric haemorrhage. Anaesthesia. 2015;70:78–86.
88. Neal MD, Hoffman MK, Cuschieri J, Minei JP, Maier RV, Harbrecht BG, Billiar TR, Peitzman AB, Moore EE, Cohen MJ, Sperry JL. Crystalloid to packed red blood cell transfusion ratio in the massively transfused patient: when a little goes along way. J Trauma Acute Care Surg. 2012;72(4):892–8.
89. Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, Del Junco DJ, Brasel KJ, Bulger EM, Callcut RA, Cohen MJ. Transfusion of plasma, platelets, and red blood cells in a 1: 1: 1 vs a 1: 1: 2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. JAMA. 2015;313(5):471–82.
90. Janelle GM, Shore-Lesserson L, Smith CE, Levy JH, Shander A. What is the PROPPR transfusion strategy in trauma resuscitation? Anesth Analg. 2016;122(4):1216–9.
91. Fung KF, Eason E, Crane J, Armson A, De La Ronde S, Farine D, Keenan-Lindsay L, Leduc L, Reid GJ, Aerde JV, Wilson RD. Prevention of Rh alloimmunization. J Obstet Gynaecol Can. 2003;25(9):765–73.

92. So-Osman C, Cicilia J, Brand A, Schipperus M, Berning B, Scherjon S. Triggers and appropriateness of red blood cell transfusions in the postpartum patient-a retrospective audit. Vox Sang. 2010;98(1):65–9.
93. Patterson JA, Roberts CL, Bowen JR, Irving DO, Isbister JP, Morris JM, Ford JB. Blood transfusion during pregnancy, birth, and the postnatal period. Obstet Gynecol. 2014;123(1):126–33.
94. Burtelow M, Riley E, Druzin M, Fontaine M, Viele M, Goodnough LT. How we treat: management of life-threatening primary postpartum hemorrhage with a standardized massive transfusion protocol. Transfusion. 2007;47(9):1564–72.
95. National Blood Authority (NBA). Patient blood management guidelines: module 1—critical bleeding massive transfusion. 2011. https://www.blood.gov.au/system/files/documents/pbm-module-1.pdf. Accessed 27 Aug 2018.
96. National Blood Authority (NBA). Patient blood management guidelines: module 5—obstetrics and maternity. 2015. https://www.blood.gov.au/system/files/documents/20180426-Module5-WEB.pdf. Accessed 27 Aug 2018.
97. Afshari A, Wikkelsø A, Brok J, Møller AM, Wetterslev JT. Thromboelastography (TEG) or thromboelastometry (ROTEM) to monitor haemotherapy versus usual care in patients with massive transfusion. Cochrane Database Syst Rev. 2011;(3):CD007871.
98. Cortet M, Deneux-Tharaux C, Dupont C, Colin C, Rudigoz RC, Bouvier-Colle MH, Huissoud C. Association between fibrinogen level and severity of postpartum haemorrhage: secondary analysis of a prospective trial. Br J Anaesth. 2012;108(6):984–9.
99. de Lange NM, Lancé MD, de Groot R, Beckers EA, Henskens YM, Scheepers HC. Obstetric hemorrhage and coagulation: an update. Thromboelastography, thromboelastometry, and conventional coagulation tests in the diagnosis and prediction of postpartum hemorrhage. Obstet Gynecol Surv. 2012;67(7):426–35.
100. O'Brien KL, Uhl L. How do we manage blood product support in the massively hemorrhaging obstetric patient? Transfusion. 2016;56(9):2165–71.
101. Jansen AJ, van Rhenen DJ, Steegers EA, Duvekot JJ. Postpartum hemorrhage and transfusion of blood and blood components. Obstet Gynecol Surv. 2005;60(10):663–71.
102. Collins PW, Bruynseels D, Mallaiah S, Dick J, Elton C, Weeks A, et al. Viscoelastometry guided fresh frozen plasma infusion for postpartum haemorrhage: OBS2 , an observational study. Br J Anaesth. 2017;119(3):422–34.
103. Shaylor R, Weiniger CF, Austin N, Tzabazis A, Shander A, Goodnough LT, et al. National and international guidelines for patient blood management in obstetrics. Anesth Analg. 2017;124(1):216–32.
104. Gutierrez MC, Goodnough LT, Druzin M, Butwick AJ. Postpartum hemorrhage treated with a massive transfusion protocol at a tertiary obstetric center: a retrospective study. Int J Obstet Anesth. 2012;21(3):230–5.
105. Mercier FJ, Bonnet MP. Use of clotting factors and other prohemostatic drugs for obstetric hemorrhage. Curr Opin Anaesthesiol. 2010;23(3):310–6.
106. Young PP, Cotton BA, Goodnough LT. Massive transfusion protocols for patients with substantial hemorrhage. Transfus Med Rev. 2011;25(4):293–303.
107. Lier H, Krep H, Schroeder S, Stuber F. Preconditions of hemostasis in trauma: a review. The influence of acidosis, hypocalcemia, anemia, and hypothermia on functional hemostasis in trauma. J Trauma. 2008;65(4):951–60.
108. El Kenz H, Van der Linden P. Transfusion-related acute lung injury. Eur J Anaesthesiol. 2014;31(7):345–50.
109. Teofili L, Bianchi M, Zanfini BA, Catarci S, Sicuranza R, Spartano S, Zini G, Draisci G. Acute lung injury complicating blood transfusion in post-partum hemorrhage: incidence and risk factors. Mediterr J Hematol Infect Dis. 2014;6(1):e2014069.
110. Toy P, Popovsky MA, Abraham E, Ambruso DR, Holness LG, Kopko PM, McFarland JG, Nathens AB, Silliman CC, Stroncek D, National Heart, Lung and Blood Institute Working Group on TRALI. Transfusion-related acute lung injury: definition and review. Crit Care Med. 2005;33(4):721–6.
111. Vlaar AP, Juffermans NP. Transfusion-related acute lung injury: a clinical review. Lancet. 2013;382(9896):984–94.
112. Gosmann F, Nørgaard A, Rasmussen MB, Rahbek C, Seeberg J, Møller T. Transfusion-associated circulatory overload in adult, medical emergency patients with perspectives on early warning practice: a single-centre, clinical study. Blood Transfus. 2018;16(2):137–44.
113. Murphy EL, Kwaan N, Looney MR, Gajic O, Hubmayr RD, Gropper MA, Koenigsberg M, Wilson G, Matthay M, Bacchetti P, Toy P. Risk factors and outcomes in transfusion-associated circulatory overload. Am J Med. 2013;126(4):357–e29.
114. James AH. Venous thromboembolism in pregnancy. Arterioscler Thromb Vasc Biol. 2009;29(3):326–31.
115. McLintock C, Brighton T, Chunilal S, et al. Recommendations for the prevention of pregnancy-associated venous thromboembolism. Aust N Z J Obstet Gynaecol. 2012;52(1):3–13.
116. Chou MH, Chen YC, Hwang KS, Yu MH, Su HY. Myocardial infarction and ischaemic hepatitis complicated by postpartum haemorrhage. Taiwan J Obstet Gynecol. 2016;55(3):437–40.

Fluid Management

7

Kim Ekelund, Morten Hylander Møller, and Arash Afshari

Bullet Points

- Fluid resuscitation remains a mainstay of therapy for noncardiac causes of acute circulatory failure in all critically ill adult patients, including patients with sepsis, trauma and burns, and is therefore an important aspect of treatment of critically ill pregnant women as well.
- Pregnancy is a dynamic state.
- During pregnancy, osmoregulation is adjusted to a lower "set point".
- Decisions regarding the choice of fluids for pregnant women should adhere to international guidelines for resuscitation of adult critically ill patients.
- Synthetic colloids have been associated with an increased risk of renal dysfunction in septic populations and have not been evaluated for treatment of pregnant women.
- As there is little to no evidence to guide fluid administration in pregnant women, treatment should be individually targeted.
- Fluid administration should be guided by frequent reassessment of haemodynamic status and the specific maternal and foetal physiology of each case.
- In acute but controlled bleeding, transfusions can be guided by viscoelastic haemostatic assays (i.e. TEG® or ROTEM®).
- Plasma volume is reduced in women with pre-eclampsia; fluid restriction (conservative fluid management) is recommended.

K. Ekelund · A. Afshari (✉)
Department of Anaesthesia, Copenhagen University Hospital Rigshospitalet, Juliane Marie Centret, Copenhagen, Denmark
e-mail: kim.ekelund@regionh.dk; arash.afshari@regionh.dk

M. H. Møller
Department of Intensive Care, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark
e-mail: morten.hylander.moeller@regionh.dk

7.1 Normal Maternal Physiology

Fluid resuscitation is a pivotal part of management of some critically ill pregnant women. As fluid therapy of these patients differs somewhat from critically ill patients in general, clinicians need to be familiar with the altered physiology in pregnant women.

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_7

7.1.1 Gain in Weight, Total Water and Plasma Volume During Pregnancy

Healthy pregnant women gain an average 12 kg (range 1–21 kg) during pregnancy [1]. Approximately 60% of the weight gain is due to excess water, less than 10% is due to protein, and accumulation of fat will account for the remaining 30% [2]. The increase in water during pregnancy is almost equally distributed between maternal and foetal-placental compartments, and more than 75% of the maternal fluid increment is retained within the ECF space [3].

Total body water (TBW) normally constitutes 45–65% of the total body weight. Two-thirds of this water is sequestrated in the intracellular fluid (ICF) space, and the remaining is in the extracellular fluid (ECF) space. The ECF space includes intravascular and interstitial volumes with a ratio between the two of 1:3. The clinical relevance of this distribution is in that the excess interstitial water can be difficult to mobilize by diuretics.

During pregnancy, total blood volume also gradually increases by approximately 1.5–2.0 L from 4.0 to 5.5–6 L. This increase is secondary to an increase in plasma volume (from 2.7–4.0 L) [4]. At the same time, the erythrocyte volume increases by only 0.4 L [4]. This disproportional increase leads to a physiological drop in haematocrit and haemoglobin concentration. The physiological increase in plasma volume also leads to decreased concentrations of plasma albumin (−20%) and plasma protein (−10 to 15%). The increment in interstitial fluid is only partly explained by the decrease in plasma albumin (i.e. oncotic pressure). Oestrogen-induced hydration of the mucopolysaccharide ground substance in connective tissue leading to potential absorption of water is thought to be another part of the explanation [5].

Contrary to normal physiology, women with pre-eclampsia often have a reduced plasma volume (see below) [6].

7.1.2 The Urogenital and Renin-Angiotensin System and Plasma Osmolality During Pregnancy

Renal plasma flow and glomerular filtration rate (GFR) rise in early pregnancy; this increase persists until term [7]. Creatinine clearance typically increases compared to non-pregnant women, rising from 120 to 200 mL/min (+50%) [8]. The reference level of serum creatinine remains unchanged, whereas the blood urea nitrogen concentration falls from 2.5–7 to 1–4 mmol/L [9].

The renin-angiotensin-aldosterone system, progesterone, oestrogen, prostaglandin and deoxycorticosterone are all thought to play a role in electrolyte homeostasis during pregnancy and the postpartum period. The interaction of these regulatory system components is not yet fully understood [3, 10, 11]. Daily sodium filtration is increased by 50% [3], resulting in reabsorption of 3–4 mmols of sodium daily and overall reabsorption of around 900–1000 mmol of sodium during pregnancy [3]. The net result is a minor decrease in the reference level of sodium during pregnancy from 136–146 to 130–148 mmol/L. In comparison, the total body potassium stores increase by approximately 320 mmol, leaving the reference level of potassium unaltered during pregnancy.

Total protein excretion (including albumin excretion) exceeds pre-pregnant levels [12].

As almost half of the total calcium is bound to serum protein (mostly albumin), augmented absorption of calcium from the small intestine counteracts the increased demand during pregnancy. The level of unbound ionized calcium (the physiological active form) is not affected by the increased excretion of albumin. Therefore the level of ionized calcium during pregnancy remains stable between 1.1 and 1.3 mmol/L, which is comparable to non-pregnant levels.

Plasma osmolality (Posm) decreases during normal pregnancy to values approximately 10 mOsmol/kg below the norm for non-pregnant

women [13]. In non-pregnant subjects, a similar decrement in Posm would halt secretion of the antidiuretic hormone AVP (arginine vasopressin), resulting in a state of continuous diuresis. During pregnancy, even at the lower basal Posm, urine can still undergo concentration and dilution. Therefore the osmoregulatory system must be reset (i.e. the threshold for AVP secretion is adapted to the lower Posm) [13, 14] (Figs. 7.1 and 7.2).

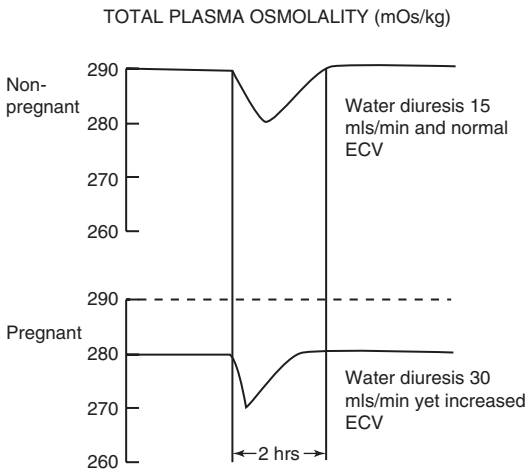


Fig. 7.1 Change in total plasma osmolality in non-pregnant and pregnant women after drinking 1 L of water. *ECV* extracellular volume

7.1.3 Maternal Haemodynamic and Uteroplacental Blood Flow During Pregnancy

Cardiac output is increased by approximately 50% due to an increase in heart rate (+25%) and stroke volume (+25%) throughout pregnancy [15, 16]. There is an equal rise in ejection fraction secondary to increased left ventricular end-diastolic volume and unchanged end-systolic volume [16]. The increase in cardiac output corresponds to an increased demand for perfusion of several organs, namely, the uterus, the kidneys and the skin [17, 18].

The blood pressure drops approximately 10 mmHg by the second trimester despite the rise in cardiac output as a consequence of decreased systemic vascular resistance [19, 20]. For a detailed description of the physiological cardiovascular changes in pregnancy, see Chap. 9.

Placental circulation is characterized by a lack of capillary microcirculation and a high-flow low-resistance system of spiral arteries. The uteroplacental vascular bed is usually maximally dilated. This vascular bed is characterized and has a potent alpha-adrenergic receptor system, which is highly sensitive towards endogenous or exogenous stimulation. It is this characteristic

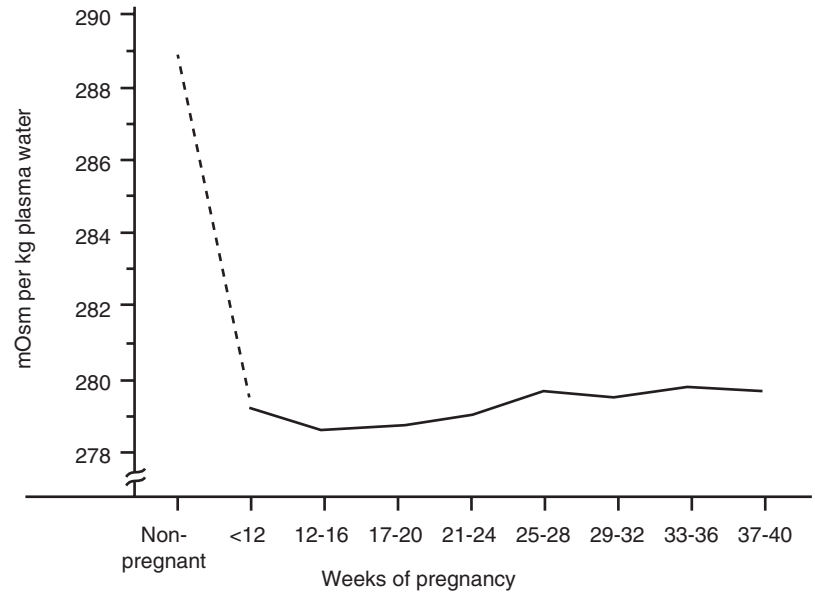


Fig. 7.2 Effect of pregnancy on plasma osmolality

that can lead to a marked decrease in uteroplacental blood flow in critically ill mothers, particularly in the presence of severe hypotension [21, 22]. The uteroplacental blood flow is responsible for the delivery of oxygen and nutrients to the foetus. Hence an acute reduction in uteroplacental blood flow may rapidly threaten foetal viability. Such a drop may occur due to sympathetic blockade during neuraxial anaesthesia, hypovolaemia, haemorrhage and/or supine positioning with aortocaval compression.

7.2 Fluid Management

7.2.1 State-of-the- Art Care Regarding Fluid Therapy in Critically Ill Adult Patients in General

Given the lack of evidence for fluid management specifically in critically ill pregnant patients, fluid management should currently be guided by existing recommendations for adult critically ill patients in general. Fluid resuscitation is a mainstay therapy for noncardiac causes of acute circulatory failure in critically ill adult patients, including patients with sepsis, trauma and burn injury [23]. Fluid resuscitation is given with the specific aim of improving the circulation, i.e. increasing cardiac output thereby reducing hypoperfusion.

Restrictive versus *liberal fluid administration:* A common approach to fluid therapy in critically ill adult patients suffering from hypotension is to give 250–500 mL boluses followed by regular reassessments of the circulation [23]. If the patient has suffered fluid loss, a fixed volume may be given to replace this loss. Many patients improve their circulation after bolus fluid administration. However, some are at particular risk of harm from excess fluid resuscitation [24–26]. For ongoing fluid therapy, increasing evidence suggests that a more restrictive approach is probably more beneficial than a more liberal one [27].

Type of fluid: Crystalloid solutions are generally the preferred type of fluid for critically ill patients and should therefore be used as the first line of therapy (Table 7.1). Synthetic colloid solu-

Table 7.1 Composition of intravenous fluids, including normal plasma reference values for pregnant and non-pregnant adult

Solute	Plasma, non-pregnant[a]	Plasma, third trimester[a]	Crystalloid				Colloid[b]		
			NaCl 0.9%	Ringer's lactate	Hartmann's solution	Plasma-lyte	4% Human[c] albumin	5% Human[c] albumin	20% Human[c] albumin
Sodium	136–146	130–148	154	130	131	140	130–160	130–160	48–160
Potassium	3.5–5.0	3.3–5.1	–	4.0	5.4	5.0	–		–
Calcium	1.13–1.33	1.13–1.33	–	1.5	1.8	–	–		–
Magnesium	0.63–0.95	0.46–0.92	–	–	–	1.5	–		–
Chloride	102–109	97–109	154	109	112	98	128	100–160	48–160
Acetate	0	0	–	–	–	27	–		–
Lactate	<2[d]	<2[d]	–	28	28	–	–		–
Bicarbonate	22–30	18–26	–	–	–	–	–		–
Osmolarity	275–295	278–280	308	273	277	294	250–260	265–330	210–260

Osmolarity (mOsm/L), all other solutes (mmol/L)
Similarly gelatin should not be used in critically ill patients

[a]Lewis SR, Pritchard MW, Evans DJW, Butler AR, Alderson P, Smith AF, Roberts I. Colloids versus crystalloids for fluid resuscitation in critically ill people. Cochrane Database of Systematic Reviews 2018, Issue 8. Art. No.: CD000567. https://doi.org/10.1002/14651858.CD000567. pub7.

[b]The European Medicine Agency (EMA) and the US Food and Drug Administration (FDA) both endorse that hydroxyethyl starch solutions should NOT to be used in critically ill patients:EMA: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Hydroxyethyl_starch-containing_solutions/human_referral_prac_000012.jsp&mid=WC0b01ac05805c516fFDA: https://wayback.archive-it.org/7993/20170112164508/http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm358349.htm

[c]Human albumin is produced by different companies with different concentration of the registered solutes

[d]Singer M, Deutschman C, Seymour C, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801–10

tions are associated with adverse outcomes in critically ill patients in general [28–31]. Albumin is probably safe, but has no obvious benefits and is an expensive and limited resource [32].

As for crystalloid solutions, isotonic saline and buffered solutions can be used, as they appear equally safe [33]. It may be rational to give patients with severe acidosis buffered solutions and those at risk of severe hyponatraemia isotonic solutions [34]. However, overcorrection should be avoided, since baseline sodium is lower during pregnancy.

7.2.2 Fluid Management During Massive Transfusion

Pregnant women have a particular ability to compensate for hypovolaemia, including obstetric haemorrhage. This compensation is a potential source of errors when assessing pregnant women, as the normal monitored values belie the volume of loss. For example, blood pressure may remain stable even during acute haemorrhage. Furthermore, as noted above, pregnancy is accompanied by a physiological increase in heart rate, which may mask impending collapse. When uncontrolled bleeding occurs, it is a life-threatening condition which requires prompt intervention, including some fluid resuscitation [35]. Therefore the threshold of suspicion for haemorrhage should be lower than usual in pregnant women.

There are currently no high-quality data on the optimal transfusion strategy in obstetric haemorrhage. Instead, lessons learned from trauma settings apply for the management of uncontrolled haemorrhage [36, 37]. The initial treatment of uncontrolled haemorrhage includes administration of intravenous crystalloids, since anaemia is better tolerated than hypovolaemia regardless of the cause of fluid loss [38]. However, fluid resuscitation is a short-lived temporizing measure, since coagulopathy can develop as a consequence of dilution and exhaustion of clotting factors if these are not replaced.

Transfusion with O rhesus (D)-negative blood must be prioritized. O-negative blood may be transfused even prior to obtaining either the initial haemoglobin count or any other standard laboratory tests in case of massive bleeding. Transfusion of packed red blood cells (PRBC), fresh frozen plasma (FFP) and platelets should follow a balanced transfusion protocol in accordance with national or international transfusion guidelines [39, 40].

In the setting of acute but controlled bleeding, implementation of haemostatic control strategies based on the use of transfusion packages with PRBCs, FFPs and platelets guided by viscoelastic haemostatic assays (i.e. TEG® or ROTEM®) appear to be associated with reduced transfusion requirements in the peri- and postoperative period, with reduced mortality [41]. Early replacement of coagulation factors and platelets may be of particular importance in the management of bleeding maternal patients [42, 43].

Fibrinogen and tranexamic acid may also have a central role in the treatment of postpartum haemorrhage supplementing uterotonics (oxytocin, methergine and prostaglandin F2a (carboprost), prostaglandin E1 (misoprostol)) and surgical intervention including ligation of arteries, B-Lynch sutures and implementing of a Bakri balloon [44–51]. These are detailed in Chap. 6.

7.2.3 Fluid Management During Pre-Eclampsia/Eclampsia

Plasma volume is reduced in women with pre-eclampsia [6]. This association has led to the suggestion that plasma volume expansion with fluids might improve maternal and uteroplacental circulation, thereby improving outcome for both the woman and the foetus. However, not all women with pre-eclampsia are fluid responders [52]. A Cochrane review comprising three trials of women with pre-eclampsia and no acute kidney injury who required volume expansion concluded that the quantity and quality of evidence supporting fluid resuscitation in woman with pre-eclampsia remain very low with no firm evidence for either benefit or harm [53]. The three included trials had an overall high risk of bias and included very few women (altogether 61), which may lead

to imprecision. Furthermore, not all of the women included had hypertension. Women with hypertension often require less volume expansion. Therefore the external validity of the findings of these studies may be low. These trials also only evaluated colloid solutions and did not examine relevant clinical outcomes such as acute kidney injury, renal placement therapy, acute pulmonary oedema, coagulopathy, admission to lCU or perinatal morbidity.

Intravenous fluid transfusion decreases the colloid oncotic pressure [54]. Redundant fluid administration may therefore potentially increase the risk of cerebral and pulmonary oedema in patients with pre-eclampsia [55]. Consequently, fluid restriction (conservative fluid management) is recommended internationally [56, 57], including limiting maintenance fluids to 80 mL/h [56].

While colloids—compared with crystalloids—theoretically may result in less decrease in the colloid oncotic pressure, there is no evidence of any clinical relevant benefit of colloids over crystalloids for the pregnant woman [58].

7.2.4 Fluid Management During Severe Sepsis

Around 15–30% of maternal admissions to the ICU are due to sepsis. Sepsis also remains a leading cause of maternal morbidity and mortality, accounting for up to 28% of maternal deaths [59–63]. Furthermore, recent reports show a rising incidence of pregnancy-associated sepsis and septic shock and a rise in sepsis-associated morbidity and mortality in the pregnant population [64, 65].

Unfortunately, septic pregnant women are rarely included in clinical trials. The causes for their exclusion are many, including concerns for the developing foetus and the marked physiologic alternations associated with pregnancy [66].

Until recently, the treatment of sepsis included early goal-directed therapy (EGDT) with early initiation and continuation of haemodynamic resuscitation. The primary goal of EGDT is correction of the physiological abnormalities associated with sepsis (i.e. hypotension, hypoxaemia, reduced tissue oxygenation). The "therapeutic bundle" recommended in the early stages of treatment to achieve this goal was initially based on a publication by Rivers et al. [67]. In this landmark single-centre study, the authors randomized 263 patients at a US emergency department to a 6-h protocol of intravenous fluid optimization, use of vasopressors, inotropes and red blood cell transfusions to achieve predefined targets of arterial blood pressure, haemoglobin level, central venous pressure and central venous oxygen saturation vs standard care. EGDT resulted in a significant in-hospital mortality reduction from 46.5 to 30.5% [67].

The findings of the Rivers study prompted initiation of subsequent large multicentre RCTs: ProCESS (Protocolized Care for Early Septic Shock), ARISE (Australasian Resuscitation in Sepsis Evaluation) and ProMISe (Protocolized Management in Sepsis) [68–70]. In the ProCESS study, 1341 septic patients across 31 US emergency departments were randomized, of whom 439 were assigned to protocol-based EGDT, 446 were allocated to a protocol-based standard therapy and 456 to usual care. The authors failed to demonstrate a beneficial effect of EGDT [67]. The ARISE study enrolled 1600 patients with early septic shock presenting at emergency departments across 51 centres mostly in Australia and New Zealand. The patients were assigned to be treated by either usual care or an EGDT protocol. The use of EGDT resulted in administration of more intravenous fluids, use of vasopressors and inotropes and red blood cell transfusions but failed to show any survival benefit at 90 days [68]. In the ProMISe study, 1260 patients with septic shock were included at 56 hospitals across England to receive either EGDT (a 6-h resuscitation protocol) or usual care. As indicated by findings of the ARISE study, the authors found that EGDT resulted in increased use of intravenous fluids, vasoactive drugs and red blood cell transfusions. However, there was no survival benefit (90 days mortality), and EGDT resulted in significantly worse organ failure scores, more days receiving advanced cardiovascular support and longer stays in the intensive care unit [69]. These studies were followed by a comprehensive patient-level meta-

analysis of EGDT that similarly failed to demonstrate better outcomes than usual care but showed an association with higher hospitalization costs in patients with sepsis and septic shock [71]. Finally, a more recent assessment of the impact of rapid implementation of sepsis bundles in emergency departments within 3 h (i.e. fluid resuscitation, blood cultures, broad-spectrum antibiotic agents and lactate measurement) also showed no association with lower risk-adjusted in-hospital mortality [72]. These later findings demonstrating a lack of effect of EGDT are often attributed to the changes in "usual care" that have occurred since publication of the original Rivers study; aggressive initial fluid resuscitation, rapid administration of antibiotics and measurement of lactate and intravascular volume assessment have become mainstays of care [66].

Currently, no trial has been published on the benefits of EGDT among pregnant women. As a consequence, a great deal of uncertainty exists about the timing and amount of fluids needed in pregnant women. Lacking available data in this population, one can only extrapolate from the general septic population (i.e. Surviving Sepsis Campaign (SSC) guidelines). Summarized in brief, the most recent guidelines as of the time of this writing suggest crystalloids (balanced crystalloids or saline) should be used for initial resuscitation and subsequent intravascular volume replacement. Crystalloids are preferred over gelatins, and administration of hydroxyethyl starches is not recommended. Within 3 h of the first manifestation of hypoperfusion, at least 30 mL/kg of intravenous crystalloid fluid should be administered. Additional fluid administration (including fluid challenges) should be guided by haemodynamic measurements, and albumin may be added when large volumes of crystalloids are required [73].

Increased lactate seems to be as strongly associated with adverse outcomes in septic pregnant patients as in the general septic population [73]. However, one must bear in mind that no single clinical or physiological parameter can accurately provide information on the intravascular volume of the septic mother, emphasizing the importance of close monitoring and early assessment and treatment of this population [74, 75].

Blood pressure, pulse rate, capillary refill time, mental status evaluation, urinary output, central venous oxygen saturation, arterial- and central venous gas measurements, lactate, respiratory variables and foetal status should all guide the assessment of fluid responsiveness [76].

Serum lactate values above 2 mmol/L in absence of hypovolaemia may indicate septic shock, and in septic patients, isolated hyperlactatemia is associated with worse adjusted 90-day mortality than those with isolated refractory hypotension [76–78]. Serum lactate values above four are associated with increased mortality in the general population with sepsis [76, 77]. However, like in any other patient, isolated increased lactate values among pregnant critically ill patient may also indicate other conditions such as tissue hypoxia, adverse effects of drugs and toxins and metabolic diseases [75].

In contrast, central venous pressure (CVP) or pulmonary artery wedge pressure monitoring has been shown to lack measurement reproducibility and has poor diagnostic accuracy in the pregnant septic patient [76, 77]. Additionally, uncertainty still surrounds the reliability of fluid responsiveness measurement in spontaneously breathing patients and during low-tidal volume ventilation. The reliability of such measurements has been contested in studies comparing these measurements to other measurement strategies based on cardiac output monitoring, pulse pressure or stroke volume variation, interior vena cava diameter measurements and even stroke volume assessment by echocardiography and veno-arterial CO_2 difference calculations [79].

A pragmatic approach to treatment of sepsis with compensated shock in pregnant patients would be to use fluid boluses with caution, bearing in mind that all fluids cause interstitial oedema in septic patients. Fluid challenges (i.e. 20–30 mL/kg of crystalloids or less) have been proposed to diagnose fluid responsiveness [80]. However, clinicians should ultimately use the smallest bolus volume necessary to treat hypovolaemia; fluids may cause more harm than benefit if an excessive amount is administered.

Regardless of intravascular volume measurements, clinicians should consider early initiation

of inotropes in maternal sepsis if the pregnant patient fails to respond to a fluid challenge. The choice of inotropes should adhere to general recommendations from Surviving Sepsis Guidelines as in the general septic population.

Clinicians should consider both serum osmolality and acid-base status when selecting a resuscitation fluid for the septic pregnant patient. International fluid administration guidelines may be adapted to local settings based on evidence-based practices and knowledge about maternal and foetal physiology. A balanced crystalloid should be the first choice of fluids for resuscitation of the pregnant woman with sepsis. Crystalloid solutions have been associated with improved outcomes in critically ill patients despite conflicting evidence [33, 81]. When considering normal saline, one should be aware of the potential (albeit debated) risk of hyperchloraemic acidosis and renal dysfunction due to decreased glomerular filtration and immune dysfunction.

Colloids should only be considered the second line of fluids for resuscitation. If a decision is made to use colloids, only albumin should be used during pregnancy. Synthetic colloids have not been evaluated in the pregnant population and are associated with increased risk of renal dysfunction in the general septic population [32, 82].

7.2.5 Fluid Management and Potential Impact on the Foetus

In general, resuscitation of the critically ill mother is bound to affect the well-being of the foetus. Not only does the outcome of the mother affect the unborn child, but one may also argue that whatever intervention is deemed beneficial for the mother will inherently be beneficial for the child. Maternal physiological responses to hypotension and shock favour maternal vital organs (i.e. heart, kidney, brain and liver) rather than the foetus. This response may be deleterious for placental circulation and foetal oxygen delivery, as cardiac output may be shifted away from the uteroplacental vasculature. Thus, adequate maternal resuscitation and treatment may directly benefit the child not only by postponing delivery but also by reducing the risk of postnatal complications [e.g. respiratory distress syndrome (RDS), mechanical ventilation, intraventricular haemorrhage (IVH), systemic infections, necrotizing enterocolitis] and demise [60, 83, 84].

There is very limited knowledge about the factors related to foetal and neonatal outcomes in critically ill mothers admitted to the ICU. However, it is clear that not only the choice and amount of fluid administered will affect this outcome. Therapies such as inotropes and vasopressors, mechanical ventilation and drugs (e.g. sedatives) may all affect placental perfusion. The outcome of the child depends on placental perfusion, drug migration across the placenta, serum foetal concentration of drugs, foetal electrolyte disturbances, glycaemic status, acid-base balance, anaemia and coagulation status [85].

Little is also known about the specific effect of maternal fluid treatment during critical maternal illness on the foetus/neonate. As a consequence, decisions in regard to appropriate choice of fluids should adhere to international guidelines for resuscitation of adult critically ill patients [32, 73, 86]. Of note, caution should be exerted when considering synthetic colloids since the risk of adverse events is not only applicable to the mother. Theoretically, the foetus, who a priori has a reduced kidney function and an immature coagulation system, may also be affected.

Routine foetal monitoring by the obstetric team is highly recommended during the maternal stay in the ICU [87]. Such monitoring not only provides valuable information about foetal well-being but may add information regarding the adequacy of maternal resuscitation. The adequacy of resuscitation should be assessed periodically or continuously depending on maternal status and on a case-by-case basis.

7.3 Summary

The general principles guiding fluid management in critically ill adult patients should also guide fluid therapy during maternal fluid resuscitation.

Improving maternal condition will ultimately also optimize the likelihood of foetal survival. Lack of evidence requires that the treating team make individualized decisions based on in-depth knowledge of the details of the case at hand.

References

1. Thomson A, Billewicz W. Clinical significance of weight trends during pregnancy. Br Med J. 1957;1(5013):243–7.
2. Hytten F. Total body water in normal pregnancy. J Obstet Gynaecol Br Commonw. 1966;73(4):553–61.
3. Barron WM, Lindheiner MD. Renal sodium and water handling in pregnancy. Obstet Gynecol Annu. 1984;13:35–69.
4. Hytten F, Painitin D. Increase in plasma volume during normal pregnancy. J Obstet Gynaecol Br Emp. 1963;70:402–7.
5. Robertson EG. The natural history of oedema during pregnancy. J Obstet Gynaecol Br Commonw. 1971;78:520–9.
6. Redman C. Maternal plasma volume and disorders of pregnancy. Br Med J. 1984;288:955–6.
7. Dunlop W. Serial changes in renal haemodynamics during normal human pregnancy. Br J Obstet Gynaecol. 1981;88(1):1–9.
8. Davison J, Hytten F. Glomerular filtration during and after pregnancy. J Obstet Gynaecol Br Emp. 1974;88(8):588–95.
9. Larsson A, Palm M, Hansson L-O, Axelsson O. Reference values for clinical chemistry tests during normal pregnancy. BJOG. 2008;115(7):874–81.
10. Brown M, Sinosich M, Saunders D, Gallery E. Potassium regulation and progesterone-aldosterone interrelationships in human pregnancy: a prospective study. Am J Obstet Gynecol. 1986;155(2):349–53.
11. Tapia HR, Johnson C, Strong CG. Renin-angiotensin system in normal and in hypertensive disease of pregnancy. Lancet. 1972;6:847–50.
12. Higby K, Suiter CR, Phelps JY, Siler-Khodr T, Langer O. Normal values of urinary albumin and total protein excretion during pregnancy. Am J Obstet Gynecol. 1994;171(4):984–9.
13. Davison JM, Vallotton MB, Lindheimer MD. Plasma osmolality and urinary concentration and dilution during and after pregnancy: evidence that lateral recumbency inhibits maximal urinary concentrating ability. Br J Obstet Gynaecol. 1981;88(5):472–9.
14. Lind T. Fluid balance during labour: a review. J R Soc Med. 1983;76(10):870–5.
15. Clark C. Central hemodynamic assessment of normal term pregnancy. Am J Obstet Gynecol. 1989;161(6 Pt 1):1439–42.
16. Laird-Meeter K, van de Ley G, Bom TH, Wladimiroff JW, Roelandt J. Cardiocirculatory adjustments during pregnancy—an echocardiographic study. Clin Cardiol. 1979;2(5):328–32.
17. Thaler I, Manor D, Itskovitz J, Rottem S, Levit N, Timor-Tritsch I, et al. Changes in uterine blood flow during human pregnancy. Am J Obstet Gynecol. 1990;162(1):121–5.
18. Katz M, Sokai M. Skin perfusion in pregnancy. Am J Obstet Gynecol. 1980;137(1):30–3.
19. Jellema J, Balt J, Broeze K, Scheele F, Weijmer M. Hyponatraemia during pregnancy. Int J Gynecol Obstet. 2009;12(1):1–6.
20. Cheung KL, Lafayette RA. Renal physiology of pregnancy. Adv Chronic Kidney Dis. 2013;20(3):209–14.
21. Assali N. Dynamics of the uteroplacental circulation in health and disease. Am J Perinatol. 1989;6:105–9.
22. Wilkening R, Meschia G. Effect of occluding one umbilical artery on placental oxygen transport. Am J Phys. 1991;260:H1319–25.
23. Myburgh JA, Mythen MG. Resuscitation fluids. N Engl J Med. 2013;369(13):1243–51.
24. Hjortrup P, Haase N, Bundgaard H, Thomsen S, Winding R, Pettila V, et al.; Scandinavian Critical Care Trials Group. Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial. Intensive Care Med 2016;42:1695–705.
25. Maitland K, Kiguli S, Opoka R, Engoru C, Olupot-Olupot P, Akech S, et al. Mortality after fluid bolus in African children with severe infection. N Engl J Med. 2011;364:2483–95.
26. The National Heart Lung and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wiedemann H, Wheeler A, Bernard G, Thompson B, Hayden D, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006;354(24):2564–75.
27. Silversides J, Major E, Ferguson A, Mann E, McAuley D, Marshall J, et al. Conservative fluid management or deresuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: a systematic review and meta-analysis. Intensive Care Med. 2017;43:155–70.
28. Perner A, Haase N, Guttormsen A, Tenhunen J, Klemenzson G, Aneman A, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med. 2012;367(2):124–34.
29. Haase N, Perner A, Hennings L, Siegemund M, Lauridsen B, Wetterslev M, et al. Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis. BMJ. 2013;346:f839.
30. Rochwerg B, Alhazzani W, Gibson A, Ribic C, Sindi A, Heels-Ansdell D, et al. Fluid type and the use of renal replacement therapy in sepsis: a systematic review and network meta-analysis. Intensive Care Med. 2015;41:1561–71.
31. Moeller C, Fleischmann C, Thomas-Rueddel D, Vlasakov V, Rochwerg B, Theurer P, et al. How safe is gelatin? A systematic review and meta-analysis of gelatin-containing plasma expanders vs crystalloids and albumin. J Crit Care. 2016;35:75–83.

32. Perner A, Junttila E, Haney M, Hreinsson K, Kvale R, Vandvik P, et al. Scandinavian clinical practice guideline on choice of fluid in resuscitation of critically ill patients with acute circulatory failure. Acta Anaesthesiol Scand. 2015;59:274–85.
33. Young P, Bailey M, Beasley R, Henderson S, Mackle D, McArthur C, et al. Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the intensive care unit: the SPLIT randomized clinical trial. JAMA. 2015;314(6):1701–10.
34. Burdett E, Dushianthan A, Bennett-Guerrero E, Cro S, Gan T, Grocott M, et al. Perioperative buffered versus non-buffered fluid administration for surgery in adults. Cochrane Database Syst Rev. 2012;12:CD004089.
35. Johansson PI, Ostrowski SR, Secher NH. Management of major blood loss: an update. Acta Anaesthesiol Scand. 2010;54(9):1039–49.
36. Saule I, Hawkins N. Transfusion practice in major obstetric haemorrhage: lessons from trauma. Int J Obstet Anesth. 2011;21(1):79–83.
37. Xue X, Liu L, Rao Z. Management of postpartum hemorrhagic shock and disseminated intravascular coagulation with damage control resuscitation. Am J Emerg Med. 2013;31(8):1291.e1–2.
38. Ickx BE. Fluid and blood transfusion management in obstetrics. Eur J Anaesthesiol. 2010;27(12):1031–5.
39. Gaarder C, Naess PA, Frischknecht Christensen E, Hakala P, Handolin L, Stensballe J. Scandinavian guidelines—"the massively bleeding patients". Scand J Surg. 2008;97:15–36.
40. Kozek-Langenecker SA, Ahmed AB, Afshari A, Albaladejo P, Aldecoa C, Barauskas G, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: first update of 2016. Eur J Anaesthesiol. 2017;34(6):332–95.
41. Johansson PI, Stensballe J. Effect of haemostatic control resuscitation on mortality in massively bleeding patients: a before and after study. Vox Sang. 2009;96(2):111–8.
42. Ahonen J, Stefanovic V, Lassila R. Management of post-partum haemorrhage. Acta Anaesthesiol Scand. 2010;54(10):1164–78.
43. Kozek-Langenecker SA, Afshari A, Albaladejo P, Santullano CAA, De Robertis E, Filipescu DC, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. Eur J Anaesthesiol. 2013;30(6):270–382.
44. ACOG Committee on Practice Bulletins, Zelop CM, Herbert WNP. Postpartum hemorrhage. Obstet Gynecol. 2006;108(4):1039–47.
45. Mavrides E, Allard S, Chandraharan E, Collins P, Green L, Hunt BJ, Riris S, Thomson AJ on behalf of the Royal College of Obstetricians and Gynaecologists. Prevention and management of postpartum haemorrhage. BJOG. 2016;124:e106–e149.
46. Leduc D, Senikas V, Lalonde AB, Ballerman C, Biringer A, Delaney M, et al. Active management of the third stage of labour: prevention and treatment of postpartum hemorrhage. Int J Gynecol Obstet. 2010;108(3):258–67.
47. Springhall E, Wallace EM, Stewart L, Knight M, Mockler JC, Davies-tuck M. Customised management of the third stage of labour. ANZJOG. 2016;57(3):302–7.
48. Girard T, Mörtl M, Schlembach D. New approaches to obstetric hemorrhage: the postpartum hemorrhage consensus algorithm. Curr Opin Anaesthesiol. 2014;27(3):267–74.
49. Sentilhes L, Vayssiere C, Deneux-tharaux C, Aya AG, Bayoumeu F, Bonnet M-P, et al. European Journal of Obstetrics & Gynecology and reproductive biology postpartum hemorrhage : guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF) in collaboration with the French Society of Anesthesiology. Eur J Obstet Gynecol Reprod Biol. 2017;198(2016):12–21.
50. Dahlke JD, Mendez-figueroa H, Maggio L, Hauspurg AK, Sperling JD, Chauhan SP, et al. Prevention and management of postpartum hemorrhage: a comparison of 4 national guidelines. Am J Obstet Gynecol. 2015;213(76):e1–10.
51. Shakur H, Roberts I, Fawole B, Chaudhri R, El-Sheikh M, Akintan A, et al. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet. 2017;6736(17):1–12.
52. Brun C, Zieleskiewicz L, Textoris J, Muller L, Bellefleur JP, Antonini F, et al. Prediction of fluid responsiveness in severe preeclamptic patients with oliguria. Intensive Care Med. 2013;39(4):593–600.
53. Duley L, Williams J, Henderson-Smart D. Plasma volume expansion for treatment of women with pre-eclampsia. Cochrane Database Syst Rev. 2000;(2):CD001805.
54. Gonik B, Cotton D. Peripartum colloid osmotic pressure changes: influence of intravenous hydration. Am J Obstet Gynecol. 1984;150:99–100.
55. Cotton D, Gonik B, Spillman T, Dorman K. Intrapartum to postpartum changes in colloid osmotic pressure. Am J Obstet Gynecol. 1984;149:174–7.
56. National Institute for Health and Clinical Excellence. Hypertension in pregnancy: diagnosis and management. Clinical guideline. www.nice.org.uk/guidance/cg107. Accessed 4 Mar 2018.
57. Harding K, Redmond P, Tuffnell D, On behalf of the MBRRACE-UK. Hypertensive disorders of pregnancy chapter writing group. Caring for women with hypertensive disorders of pregnancy. In: Knight M, Nour M, Tuffnell D, Kenyon S, Shakespear J, Brocklehurst P, Kurinczuk JJ (Eds) on behalf of MBRRACE-UK. Saving lives, improving mothers' care—surveillance of maternal deaths in the UK 2012-14 and lessons learned to inform maternity care from. 2016. pp 69–75.
58. Jones M, Longmire S, Cotton D, Dorman K, Skjonsby B, Joyce T 3rd. Influence of crystalloid versus col-

loid infusion on peripartum colloid osmotic pressure changes. Obstet Gynecol. 1986;68:659–61.
59. Ronsmans C, Graham W. Lancet maternal survival series steering group. Maternal mortality: who, when, where, and why. Lancet. 2006;368(9542):1189–200.
60. Pollock W, Rose L, Dennis C-L. Pregnant and postpartum admissions to the intensive care unit: a systematic review. Intensive Care Med. 2010;36(9):1465–74.
61. Oud L. Patterns of the demographics, clinical characteristics, and resource utilization among maternal decedents in Texas, 2001–2010: a population-based cohort study. J Clin Med Res. 2015;7(12):937–46.
62. Oud L. Contemporary trends of reported sepsis among maternal decedents in Texas: a population-based study. Infect Dis Ther. 2015;4(3):321–35.
63. Bauer M, Lorenz R, Bauer S, Rao K, Anderson F. Maternal deaths due to sepsis in the state of Michigan, 1999–2006. Obstet Gynecol. 2015;126(4):747–52.
64. Oud L, Watkins P. Evolving trends in the epidemiology, resource utilization, and outcomes of pregnancy-associated severe sepsis: a population-based cohort study. J Clin Med Res. 2015;7(6):400–16.
65. Bauer M, Bateman B, Bauer S, Shanks A, Mhyre J. Maternal sepsis mortality and morbidity during hospitalization for delivery: temporal trends and independent associations for severe sepsis. Anesth Analg. 2013;117(4):944–50.
66. Guinn D, Abel D, Tomlinson M. Early goal directed therapy for sepsis during pregnancy. Obstet Gynecol Clin North Am. 2007;34(3):459–79.
67. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345(19):1368–77.
68. ProCESS Investigators, Yealy D, Kellum J, Huang D, Barnato A, Weissfeld L, et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med. 2014;370:1683–93.
69. ARISE Investigators, ANZICS Clinical Trials Group, Peake S, Delaney A, Bailey M, Bellomo R, et al. Goal-directed resuscitation for patients with early septic shock. N Engl J Med. 2014;371(16):1496–506.
70. Mouncey P, Osborn T, Power G, Harrison D, Sadique M, Grieve R, et al. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med. 2015;372(14):1301–11.
71. PRISM Investigators, Rowan K, Angus D, Bailey M, Barnato A, Bellomo R, et al. Early, goal-directed therapy for septic shock—a patient-level meta-analysis. N Engl J Med. 2017;376(23):2223–34.
72. Seymour CW, Gesten F, Prescott HC, Friedrich ME, Iwashyna TJ, Phillips GS, et al. Time to treatment and mortality during mandated emergency care for sepsis. N Engl J Med. 2017;376:2235–44.
73. Rhodes A, Evans L, Alhazzani W, Levy M, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock. Intensive Care Med. 2016;43(3):304–77.
74. Albright C, Ali T, Lopes V, Rouse D, Anderson B. Lactic acid measurement to identify risk of morbidity from sepsis in pregnancy. Am J Perinatol. 2015;32(5):481–6.
75. Suetrong B, Walley KR. Lactic acidosis in sepsis: it's not all anaerobic. Chest. 2016;149(1):252–61.
76. Singer M, Deutschman C, Seymour C, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):801–10.
77. Gotmaker R, Peake SL, Forbes A, Bellomo R. Mortality is greater in septic patients with hyperlactatemia than with refractory hypotension. Shock. 2017;48(3):294–300.
78. April MD, Donaldson C, Tannenbaum LI, Moore T, Aguirre J, Pingree A, et al. Emergency department septic shock patient mortality with refractory hypotension vs hyperlactatemia: a retrospective cohort study. Am J Emerg Med. 2017;35(10):1474–9.
79. Seymour C, Rosengart M. Septic shock: advances in diagnosis and treatment. JAMA. 2015;314(7):708–17.
80. Myburgh J. Fluid resuscitation in acute medicine: what is the current situation? J Intern Med. 2015;277(1):58–68.
81. Raghunathan K, Bonavia A, Nathanson B, Beadles C, Shaw A, Brookhart M, et al. Association between initial fluid choice and subsequent in-hospital mortality during the resuscitation of adults with septic shock. Anesthesiology. 2015;123(6):1385–93.
82. Serpa Neto A, Veelo D, Peireira V, de Assunção M, Manetta J, Espósito D, et al. Fluid resuscitation with hydroxyethyl starches in patients with sepsis is associated with an increased incidence of acute kidney injury and use of renal replacement therapy: a systematic review and meta-analysis of the literature. J Crit Care. 2014;29(1):185.e1–7.
83. Roberts D, Brown J, Medley N, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2017;21(3):CD004454.
84. Cartin-Ceba R, Gajic O, Iyer V, Vlahakis N. Fetal outcomes of critically ill pregnant women admitted to the intensive care unit for nonobstetric causes. Crit Care Med. 2008;36(10):2746–51.
85. James F 3rd, Greiss FJ, Kemp R. An evaluation of vasopressor therapy for maternal hypotension during spinal anesthesia. Anesthesiology. 1970;33:25–34.
86. Marx G, Schindler A, Mosch C, Albers J, Bauer M, Gnass I, et al. Intravascular volume therapy in adults: guidelines from the Association of the Scientific Medical Societies in Germany. Eur J Anaesthesiol. 2016;33(7):488–521.
87. Aoyama K, Seaward P, Lapinsky S. Fetal outcome in the critically ill pregnant woman. Crit Care. 2014;18(3):307.

8 Management and Prevention of Thrombotic and Embolic Phenomena During Pregnancy: Deep Vein Thrombosis, Pulmonary Embolism, and Amniotic Fluid Embolism

Leslie Moroz and Vivek Kumar Moitra

Bullet Points

- Compression ultrasound (CUS) is the initial test of choice for pregnant women who present with symptoms of deep vein thrombosis (DVT).
- Chest x-ray is the initial test of choice for pregnant women who present with symptoms of pulmonary embolism in the absence of symptoms of DVT.
- D-dimer levels should not be used as an initial screening tool for VTE.
- Empiric anticoagulation is recommended in pregnant women with high suspicion of PE.
- Pregnant/postpartum women with pulmonary embolism should receive therapeutic doses of unfractionated (UFH) or low-molecular-weight heparin (LMWH).
- In pregnant/postpartum women treated with LMWH, antifactor Xa levels should be monitored.
- For pregnant/postpartum women with massive pulmonary embolism, treatment should proceed as in nonpregnant patients.
- Pregnant/postpartum women with submassive pulmonary embolism should be treated on an individual basis with multidisciplinary specialist consultation (e.g., cardiology, pulmonology, cardiothoracic surgery, interventional radiology).

8.1 Introduction

Venous thromboembolic (VTE) phenomena, specifically deep venous thrombosis (DVT) and pulmonary embolism (PE), are a significant cause of maternal morbidity and mortality worldwide. The World Health Organization (WHO) estimates that VTE accounted for 3.2% of maternal deaths between 2003 and 2012 [1].

Widespread attention to thromboprophylaxis has reduced the rate of maternal death from thromboembolic complications during pregnancy and the peripartum period in developed countries. Data

L. Moroz
Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, New York Presbyterian/Columbia University Medical Center,
New York, NY, USA
e-mail: lm3000@cumc.columbia.edu

V. K. Moitra (✉)
Division of Critical Care Medicine, Department of Anesthesiology, College of Physicians and Surgeons of Columbia University, New York, NY, USA
e-mail: vm2161@cumc.columbia.edu

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_8

from the 1990s suggested that VTE surpassed hemorrhage and hypertension as a leading cause of maternal mortality in the United States and parts of Western Europe [2]. In the subsequent decade, recommendations for thromboprophylaxis from the professional societies of obstetricians and gynecologists in both the United Kingdom and the United States were followed by significant reductions in the incidence of morbidity and mortality from VTE in both countries [3–5]. The cornerstones of addressing VTE in obstetric patients are a high index of suspicion, early treatment, and systems-based strategies for prevention.

In contrast to the well-defined entity of VTE and the progress that has been made in decreasing the burden of VTE, amniotic fluid embolism (AFE) remains a rare but potentially catastrophic complication of pregnancy. The mortality rate of AFE approximates 50%, and there is potential for significant morbidity. It is difficult to estimate the true incidence of AFE because the diagnosis is clinical and there are as yet no consensus criteria to classify this condition [6]. There are also no screening tests or definitive diagnostic tests for AFE, and the management of this condition is entirely supportive.

This chapter will review the diagnosis and management of DVT, PE, and AFE and will specifically address the clinical approach to critically ill pregnant and peripartum women with these conditions.

8.2 Venous Thromboembolism

8.2.1 Physiologic Changes Associated with Pregnancy: Hypercoagulable State

Changes in the maternal hemostatic system begin with conception and persist for at least 12 weeks postpartum. Procoagulant factors I (fibrinogen), VII, VIII, and X, von Willebrand factor, and plasminogen activator inhibitor-1 and -2 are increased, and the anticoagulant free protein S is decreased [5]. The net result is a hypercoagulable state manifested in a rate of VTE that is increased at least fourfold during pregnancy and the postpartum period (see also Chap. 5) [7–10].

8.2.2 Prevention

A VTE (DVT and PE) risk assessment should be performed multiple times during pregnancy. Assessments should be performed during prenatal visits, upon hospitalization for antepartum indications and delivery, and during the postpartum period, from the time immediately following delivery through the 6-week follow-up visit. Administration of prophylactic anticoagulation for prevention of VTE is indicated during most obstetric admissions. Pregnant women admitted antepartum for 72 h or more for any reason should be given pharmacologic prophylactic anticoagulation. For women at high risk of bleeding, mechanical prophylaxis with sequential compression devices (SCDs) should be used as an alternative. The American College of Obstetricians and Gynecologists (ACOG) recommends use of SCDs for all women undergoing cesarean delivery [5]. Pharmacologic prophylactic anticoagulation should be added postoperatively for women with risk factors such as obesity, postpartum infection, prolonged bedrest, thrombophilia, or other pregnancy complications.

The need for antenatal pharmacologic prophylactic anticoagulation for VTE prevention is determined by a woman's history of prior VTE and the presence of thrombophilia [11]. The low-risk thrombophilias include factor V Leiden heterozygosity, prothrombin G20210A heterozygosity, and protein C and protein S deficiencies [11]. The high-risk thrombophilias include antithrombin deficiency, double heterozygosity for prothrombin G20210A mutation and factor V Leiden mutation, factor V Leiden mutation homozygosity, and prothrombin G20210A mutation homozygosity. Pregnant women with a personal history of VTE or a high-risk thrombophilia should receive prophylactic anticoagulation throughout pregnancy [5, 11]. At this time, should other risk factors arise during pregnancy (e.g., prolonged hospitalization or critical illness), there is no evidence to support increasing the dose of anticoagulation drugs to a therapeutic range.

Women with a history of two or more episodes of VTE should receive therapeutic anticoagulation throughout pregnancy regardless of whether

they were receiving long-term anticoagulation therapy before pregnancy or not [11]. In such cases, anticoagulation should be continued for at least 6 weeks postpartum.

8.3 Thromboembolic Events

8.3.1 Clinical Presentation

Clinicians caring for pregnant and postpartum women must maintain a high index of suspicion for DVT because many of the classic presenting symptoms of this condition, such as lower extremity pain and swelling, overlap with common symptoms of pregnancy. Other symptoms may include erythema, warmth, and lower abdominal, flank, buttock, or back pain.

8.3.2 Diagnosis

The screening tools used in nonpregnant patients (e.g., the Wells and modified Wells scores) often perform best in populations in which the frequency of the disease is low. These risk assessment scores have not been validated in pregnancy when the pretest probability of VTE is higher [12]. The LEFt clinical prediction rule (presence of left leg symptoms, calf circumference difference of ≥2 cm, and first trimester presentation) is a risk assessment tool that has been studied in pregnant patients, but it performs poorly as a stand-alone test for ruling out DVT [13].

D-dimer levels often play a role in screening nonpregnant patients for DVT. However, D-dimer levels increase physiologically during pregnancy [14]. Higher cutoff levels may improve specificity, but the adjustment required for this laboratory parameter has not been clarified for pregnant women [15–17]. D-dimer levels are therefore not recommended as an initial screening tool in pregnancy [5].

The primary modality for diagnosing DVT during pregnancy is compression ultrasonography (CUS) of the proximal veins. Visualization of material with mixed echogenicity within the vessel lumen, a noncompressibile segment, and absent Doppler flow indicates the presence of a thrombus [18]. Both ACOG and the American College of Chest Physicians (ACCP) currently recommend that when a pregnant woman has signs or symptoms of DVT, CUS should be the initial diagnostic test [5, 19]. Depending on the results of the initial CUS, additional imaging, either with serial CUS, iliac Doppler US, or venous magnetic resonance imaging (MRI), may be considered (Fig. 8.1) [20].

In women presenting with postpartum pain or fever, the performance of a venous MRI or a pelvic computed tomography (CT) may reveal the presence of an ovarian or pelvic vein thrombosis. In such cases, the diagnosis is usually made while seeking other etiologies for the presenting symptoms (e.g., workup for VTE or sepsis). In some severe cases of septic pelvic thrombophlebitis (SPT), the thrombosed vein may be seeded with bacteria, and the woman may present with symp-

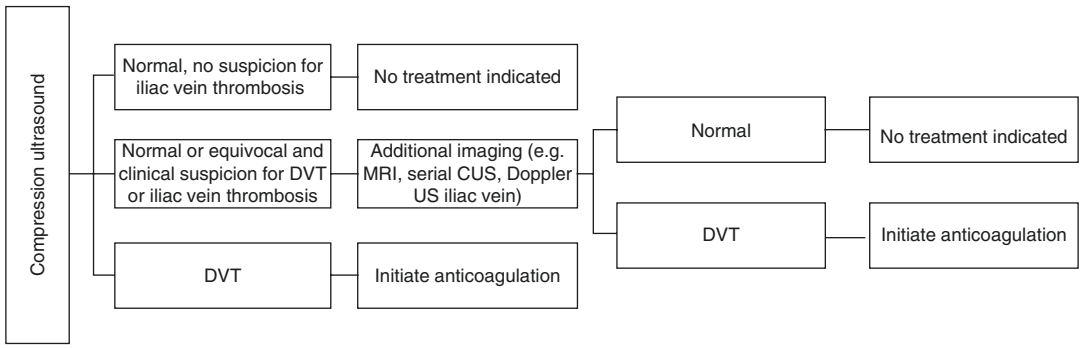


Fig. 8.1 Clinical flow chart for evaluation of obstetric patients with symptoms of DVT

toms of distributive shock. Therefore, although pelvic vein thrombosis and SPT are uncommon, clinicians should remember to include these options in the differential diagnosis [21–23]. Radiology should be consulted prior to imaging with CT, as the intravenous administration of contrast may be timed to evaluate the pelvic vasculature for evidence of thrombosis. In rare cases, organ infarction has been reported, particularly in women with a diagnosis of antiphospholipid syndrome (APS). Evidence of clotting and/or shower emboli may be seen on CT with appropriately timed contrast administration and possibly on MRI. Lactate may be elevated due to systemic sepsis or specific organ ischemia.

Myocardial infarction (MI) is exceedingly rare during pregnancy. The initial evaluation for all patients in whom a diagnosis of MI is considered includes sampling of the blood for cardiac enzymes and performance of an electrocardiogram. This practice should be adhered to regardless of pregnancy. Because of the hemodynamic changes occurring during pregnancy and the potential for undiagnosed structural heart disease in these relatively young patients, the threshold for obtaining an echocardiogram should be low.

While women with isolated DVT do not require ICU admission, those with bacterial seeding of clot (as in septic pelvic thrombophlebitis) or organ infarction (as in the anti-phospolipid syndrome) may present with signs and symptoms of shock. In women diagnosed with DVT, careful attention should be given to the clinical presentation as this will determine when additional testing is indicated. Hemodynamic changes, laboratory abnormalities, symptoms not directly related to the DVT, and pain disproportionate to the diagnosis require further evaluation.

8.4 Pulmonary Embolism

8.4.1 Clinical Presentation

Pregnant women with PE may present with dyspnea, tachycardia, pleuritic chest pain, and, in cases of large proximal clots, syncope and evidence of hemodynamic instability. As is the case for DVT, the use of clinical decision aids for evaluating pregnant patients with symptoms of PE is complicated by the higher incidence of VTE during pregnancy, which may affect test performance. The Wells score for PE, the simplified revised Geneva score (RGS) for PE, and the pulmonary embolism rule-out criteria (PERC rule) have not been validated in pregnant patients [24–26].

As noted above, D-dimer levels should not be used as an initial screening tool in pregnancy due to the alterations in levels throughout pregnancy [5]. As in nonpregnant patients, PaO_2 is not a reliable indicator of PE. Electrocardiographic (ECG) changes are nonspecific and may include atrial fibrillation, T-wave inversion in the anterior chest leads, right bundle-branch block, or the S_1-Q_3-T_3 pattern (large S wave in lead I, a pathologic Q-wave and T-wave inversion in lead III). Furthermore, the ECG has a poor sensitivity for diagnosing PE since these changes tend to occur only with large pulmonary artery occlusions.

Computed tomographic pulmonary angiography (CTPA) and ventilation-perfusion (VQ) scan are the primary modalities employed in diagnosis of PE [5, 27, 28]. Chest x-ray (CXR) imaging should not be used for screening because 25% of patients with PE may have a normal CXR [29]. However, a negative CXR decreases the likelihood of nondiagnostic results from VQ and CTPA scanning. Radiographic findings suggestive of PE include an enlarged pulmonary artery, dilation of pulmonary vessels proximal to the embolus and collapse of distal vessels (Westermark's sign), a wedge-shaped peripheral airspace opacity (Hampton hump), and pleural effusion. A homogenous perfusion scan is very accurate for ruling out PE [30]. If the perfusion scan is not normal and a ventilation study is performed, the study results may be positive or indeterminate, which is a limitation of this imaging modality. Conversely, in the general patient population, the sensitivity and specificity of CTPA approximate 90% regardless of pretest probability [31], and the main advantage of CTPA is that it can also demonstrate other pulmonary pathologies with symptoms similar to PE that may be in the differential diagnosis.

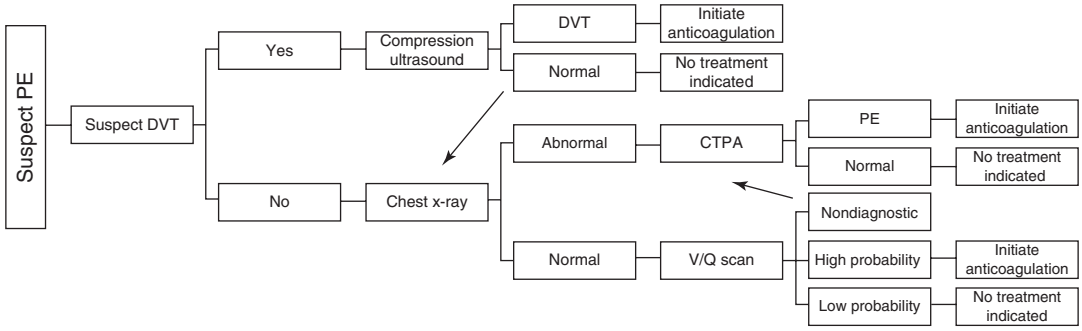


Fig. 8.2 Clinical flow chart for evaluation of obstetric patients with symptoms of PE

Figure 8.2 outlines a systematic approach to the evaluation of a pregnant patient with suspected PE supported by the American Thoracic Society/Society of Thoracic Radiology and ACOG [5, 28]. Proximal vein CUS can be used to minimize the risk of radiation exposure since management will include anticoagulation whether the diagnosis is a DVT or PE [32, 33]. The amount of radiation from CXR, VQ scanning, and CTPA is low (0.001, 0.031, and 0.013 rad, respectively, versus an increased risk for miscarriage, teratogenicity, and perinatal complications at 5 rads), and all modalities are appropriate for pregnant patients with possible PE [34].

8.4.2 Anticoagulation Management of Thromboembolic Events

Anticoagulation with low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) is the mainstay of treatment for acute VTE [5, 35]. Anticoagulation should be started promptly upon diagnosis and, in cases of a high suspicion for PE, may also be initiated empirically [5].

For UFH, therapeutic anticoagulation should be achieved with an activated partial thromboplastin time (aPTT) 1.5–2.5 times the control [36, 37]. Heparin dosing during pregnancy can be challenging because procoagulant plasma levels are increased. An intravenous infusion will allow rapid achievement of therapeutic levels while preserving the option of reversing anticoagulation on short notice [38]. After achievement of steady state, the total 24-h intravenous heparin dose can be calculated and divided into two to three doses to be administered subcutaneously every 12 or 8 h, accordingly.

LMWH is usually the therapy of choice as it provides more reliable anticoagulation. Antifactor Xa levels should be monitored periodically and maintained between 0.6 and 1.2 U/mL. Antifactor Xa levels are first checked 4 h after the fourth dose following initiation or titration [5].

Oral anticoagulation with warfarin is generally not recommended for management of VTE during pregnancy, all the more so during a critical illness. From the maternal perspective, long-acting anticoagulants should not be used until systemic stability has been ensured. Among other issues, warfarin has been associated with an increased risk for maternal and fetal hemorrhage during pregnancy. From the fetal perspective, warfarin crosses the placenta and has been associated with embryopathy when exposure occurs during the period of organogenesis between 7 and 12 weeks gestation [39]. However, conversion to warfarin should be considered in the postpartum period [5]. Warfarin is not concentrated in breast milk and is safe to use during lactation.

Pregnancy is considered a transient nonsurgical risk factor for VTE. The recommended duration of anticoagulation treatment is 3 months for DVT and PE that have been diagnosed during pregnancy [40]. For patients with recurrent VTE, extended anticoagulation may be appropriate.

8.4.3 Management of Massive Pulmonary Embolism

In addition to the specific anticoagulation considerations and treatment presented above, the management of acute PE depends on clot burden and hemodynamic stability. The American Heart Association (AHA) characterizes the presentation of a massive PE as persistent hypotension, profound bradycardia, or pulselessness. Submassive PE is characterized by evidence of right ventricular dysfunction or myocardial necrosis in the absence of hemodynamic changes. In the absence of markers of massive and submassive PE, the PE may be classified as low-risk [41]. In addition to careful assessment of hemodynamic status, an echocardiogram can guide risk assessment and treatment [42, 43].

Multidisciplinary care with involvement of specialists in critical care, cardiology, pulmonology, interventional radiology, and thoracic surgery is essential for the timely delivery of optimal therapy (including surgery when required) for submassive and massive PE.

Critical care management of acute PE focuses on restoring circulatory perfusion and oxygen delivery before organ dysfunction worsens. Perfusing and resuscitating the right ventricle are an important treatment goals. After administration of oxygen (with appropriate airway management) and heparin, the initial hemodynamic treatment should include expansion of the circulating volume with fluid boluses and recurrent assessment of fluid responsiveness. Fluid resuscitation without assessment of fluid responsiveness should be avoided because aggressive fluid administration to a non fluid-responsive patient increases cardiac filling pressures, which can worsen right ventricular failure. If hemodynamic instability persists after fluid administration, vasoconstricting agents such as norepinephrine and vasopressin should be administered to increase coronary (and specifically right coronary) artery perfusion, and an echocardiogram should be obtained. Continued right ventricular failure is managed by inotropes such as dobutamine, milrinone, or epinephrine and pulmonary vasodilators such as nitric oxide [44]. See Fig. 8.3.

Pregnant women with massive PE, and some with submassive PE, may be candidates for systemic thrombolysis. Such women may also require invasive interventions such as catheter-based intra-arterial thrombolytic infusion, mechanical clot disruption, or surgical embolectomy.

Systemic thrombolytic therapy (e.g., tissue-type plasminogen activator [tPA]) during pregnancy poses a risk for hemorrhage. A retrospective study of tPA use during pregnancy reported a mortality rate of 1.2% and a rate of hemorrhagic complications of 8% [45]. There are no controlled studies examining the efficacy and safety of thrombolytic therapy in pregnancy. Obstetric outcomes following catheter-directed procedures and embolectomy are based on case reports. There is therefore insufficient evidence to recommend a management strategy applicable to all pregnant and peripartum women with massive PE. The risks and benefits of the various treatment options must be weighed per individual case by a multidisciplinary care team. Patient presentation and the resources and expertise available should all be considered. However, reports of massive PE treated with thrombolysis, surgical embolectomy, percutaneous embolectomy, and extracorporeal membrane oxygenation (ECMO) describe high rates of maternal and fetal survival (i.e., 86–100% and 75–100%, respectively) in selected cases [46, 47]. Management of ECMO in pregnant and postpartum patients may be complex, particularly during the perioperative period [48, 49]. Consideration of this treatment option requires prompt evaluation by an experienced ECMO team (see Fig. 8.3). For further details regarding.

ECMO treatment during pregnancy and the peripartum period, see Chap. 14.

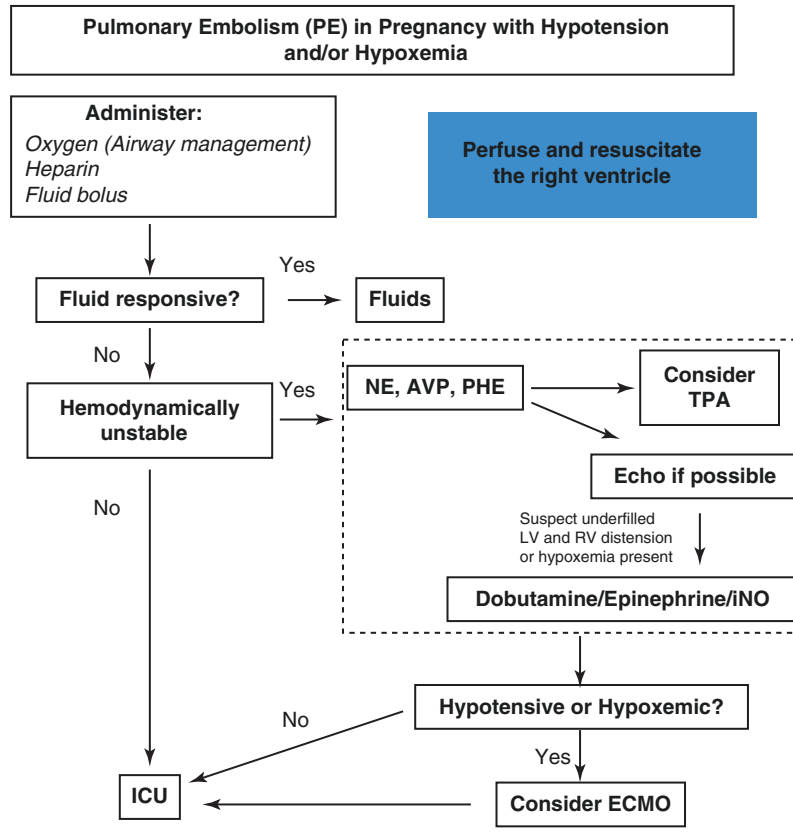


Fig. 8.3 Management of pulmonary embolism with hypotension and/or hypoxemia in pregnancy

8.5 Amniotic Fluid Embolism

8.5.1 Clinical Presentation and Diagnosis

Clinically, AFE presents as rapid onset of hypoxia and hypotension, followed in most cases by evidence of coagulopathy such as bleeding from venipuncture and surgical sites. The diagnosis of AFE is based on the triad of (1) respiratory failure, (2) cardiogenic shock, and (3) disseminated intravascular coagulation (DIC) in the absence of other likely causes (e.g., massive hemorrhage) [6].

AFE usually presents with few or no early warning signs and symptoms. The woman may exhibit altered mental status or agitation, and fetal monitoring may demonstrate loss of variability or decelerations. In most cases AFE occurs during labor, particularly following rupture of fetal membranes. However, presentation during vaginal delivery, cesarean delivery, and in the immediate postpartum period is also possible [50]. Cases of severe maternal morbidity and mortality have also been attributed to AFE during dilation and evacuation in the midtrimester, as well as during external cephalic version [51].

The pathophysiology of AFE is thought to be related to the maternal response to either placental thromboplastin, fetal antigens, or both. Historically, AFE was thought to be an accumulation of fetal cells in the maternal pulmonary vasculature that resulted in acute pulmonary hypertension and right ventricular failure. However, the hemodynamic changes observed with central monitoring and echocardiogram are more complex. More recent studies have shown

that initial systemic and pulmonary hypertension is followed by left ventricular dysfunction [51]. The mechanism for depressed cardiac function is unknown; some studies have proposed myocardial hypoxia due to pulmonary injury, while others have proposed coronary artery spasm [50].

Evidence to support the diagnosis of AFE may include laboratory results suggesting a consumptive coagulopathy, i.e., prolonged PT and aPTT, hypofibrinogenemia (normal values in the third trimester of pregnancy >350 mg/dL), and thrombocytopenia. However, lacking specific diagnostic tests, AFE remains a clinical diagnosis [52].

8.5.2 Management of Amniotic Fluid Embolism

Management of suspected AFE is supportive. High-quality cardiopulmonary resuscitation (CPR) should be initiated immediately in women who develop cardiac arrest due to suspected AFE. Basic life support (BLS) and advanced cardiac life support (ACLS) should be implemented if required [52]. Chest compression, defibrillation, ventilator support, and vasoactive drugs should be utilized as indicated for nonpregnant patients. Defibrillation and medication doses are similar to those administered to nonpregnant individuals [52]. Failure to obtain spontaneous circulation after 4 min of CPR is an indication for cesarean delivery of a fetus ≥20 weeks gestation to improve resuscitative efforts for the mother. Communication with the blood bank is essential as massive hemorrhage may occur with or without surgery. If hemorrhage does occur, a massive transfusion protocol should be activated to ensure that adequate blood products are available for resuscitation. For additional information regarding maternal cardiopulmonary resuscitation, see Chap. 28.

AFE is an unpredictable and rare complication. As such, the resources immediately available to deal with this situation on the labor and delivery unit may be limited. In responding to such events, it is important to anticipate the need to obtain vasopressors and inotropes and potentially to involve cardiologists with expertise in mechanical cardiac support devices. In centers with the requisite expertise, ECMO with venoarterial cannulation may be required for cardiorespiratory support. However, in this specific condition, several unique difficulties may arise. These include questions regarding systemic anticoagulation with profound coagulopathy and the potential for circuit obstruction by embolic material [53].

For patients who have not undergone cardiac arrest or those who have been successfully resuscitated, management should be guided by a careful assessment of hemodynamics, preferably guided by echocardiogram. Central venous access may be required to facilitate ongoing hemodynamic support. One management strategy that has been proposed is the combination of anti-serotonin, antithromboxane, and vagolytic therapy, for example, with atropine, ondansetron, and ketorolac. At least one case report describing the use of this protocol has been described in the literature. However, in this case, patient presentation did not meet the criteria for AFE as proposed by Clark et al. [6, 54] At the time of this publication, there is therefore insufficient evidence to recommend this management strategy for women with suspected AFE.

8.5.3 Prevention

At present, there are no strategies for prevention of AFE. The risk of AFE is increased in those circumstances in which the maternal and fetal compartments are more likely to come into communication, e.g., cesarean or operative vaginal delivery, placental abruption, and placenta accreta [50]. While other associations have been described, these have been reported inconsistently, and the literature may be complicated by a tendency to overdiagnose AFE in cases involving other causes of obstetric hemorrhage [52]. There are no data to indicate that altering obstetric management would impact the diagnosis or outcomes of AFE [52].

8.6 Conclusion

Pregnancy places women at increased risk for venous thromboembolic events, and clinicians must maintain a high index of suspicion for such events. Rare forms of thromboembolic disease should be considered in pregnant women with atypical clinical presentations and those who are critically ill. Anticoagulation treatment should be administered to pregnant patients with acute thromboembolic events as in nonpregnant patients. When LMWH is used, antifactor Xa levels should be monitored to ensure adequate anticoagulation. Pregnant women presenting with hemodynamic instability attributed to massive PE should be managed with thrombolytics regardless of pregnancy status. Multidisciplinary collaboration is essential for optimizing the management of cases of submassive and massive PE. These cases typically differ, and the circumstances of each case require that each be carefully considered individually. In emergency situations, circulatory support should be directed toward optimizing the likelihood of maternal survival.

The mechanism of amniotic fluid embolism remains poorly understood, which limits current ability to predict this catastrophic event. Diagnosis is based on clinical circumstances combined with the findings of respiratory failure, cardiogenic shock, and DIC. Supportive care includes hemodynamic and respiratory optimization and correction of coagulopathy.

References

1. Alkema L, Chou D, Hogan D, et al. Global, regional, and national levels and trends in maternal mortality between 1990 and 2015, with scenario-based projections to 2030: a systematic analysis by the UN Maternal Mortality Estimation Inter-Agency Group. Lancet. 2016;387(10017):462–74.
2. Chang J, Elam-Evans LD, Berg CJ, et al. Pregnancy-related mortality surveillance: United States, 1991-1999. MMWR Surveill Summ. 2003;52:1–8.
3. The Royal College of Obstetricians and Gynaecologists. Reducing the risk of thrombosis and embolism during pregnancy and puerperium. Green-Top Guideline No. 37a. 2015. https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-37a.pdf. Accessed 12 Dec 2018.
4. Centre for Maternal and Child Enquiries (CMACE). Saving mothers' lives: reviewing maternal deaths to make motherhood safer: 2006-08. The eighth report of the confidential enquiries into maternal deaths in the United Kingdom. BJOG. 2011;118(Suppl 1):1–203.
5. James A. Committee on Practice Bulletins—Obstetrics. Practice bulletin no. 123: thromboembolism in pregnancy. Obstet Gynecol. 2011;118(3):718–29.
6. Clark SL, Romero R, Dildy GA, et al. Proposed diagnostic criteria for the case definition of amniotic fluid embolism in research studies. Am J Obstet Gynecol. 2016;215(4):408–12.
7. James AH, Jamison MG, Brancazio LR, Myers MR. Venous thromboembolism during pregnancy and the postpartum period: incidence, risk factors, and mortality. Am J Obstet Gynecol. 2006;194:1311–5.
8. Bourjeily G, Paidas M, Khalil H, Rosene-Montella K, Rodger M. Pulmonary embolism in pregnancy. Lancet. 2010;375:500–12.
9. Gabbe SG, Niebyl JR, Simpson JL, et al. Thromboembolic disorders. In: Obstetrics: normal and problem pregnancies. 5th ed. Philadelphia: Churchill Livingstone Elsevier; 2007. p. 1064–76.
10. Gherman RB, Goodwin TM, Leung B, et al. Incidence, clinical characteristics, and timing of objectively diagnosed venous thromboembolism during pregnancy. Obstet Gynecol. 1999;94:730–4.
11. American College of Obstetricians and Gynecologists Women's Health Care Physicians. ACOG Practice Bulletin No. 138. Inherited thrombophilias in pregnancy. Obstet Gynecol. 2013;122:706–17.
12. Wells PS, Hirsh J, Anderson DR, et al. A simple clinical model for the diagnosis of deep-vein thrombosis combined with impedance plethysmography: potential for an improvement in the diagnostic process. J Intern Med. 1998;243:15–23.
13. Chan WS, Lee A, Spencer FA, et al. Predicting deep venous thrombosis in pregnancy: out in "LEFt" field? Ann Intern Med. 2009;151(2):85–92.
14. Kovac M, Mikovic Z, Rakicevic L, et al. The use of d-dimer with new cutoff can be useful in diagnosis of venous thromboembolism in pregnancy. Eur J Obstet Gynecol Reprod Biol. 2010;148:27–30.
15. Chan WS, Lee A, Spencer FA, et al. D-dimer testing in pregnant patients: towards determining the next 'level' in the diagnosis of deep vein thrombosis. J Thromb Haemost. 2010;8:1004–11.
16. Chan WS, Chunilal S, Lee A, Crowther M, Rodger M, Ginseberg JS. A red blood cell agglutination D-dimer test to exclude deep venous thrombosis in pregnancy. Ann Intern Med. 2007;147(3):1165–70.
17. Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED Ddimer. Thromb Haemost. 2000;83:416–20.
18. Gaitini D. Current approaches and controversial issues in the diagnosis of deep venous thrombosis

via duplex Doppler ultrasound. J Clin Ultrasound. 2006;34(6):289–97.
19. Bates SM, Jaeschke R, Stevens SM, et al. Diagnosis of DVT: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence based practice guidelines. Chest. 2012;141(2 Suppl):e351S–418S.
20. Catalano C, Pavone P, Laghi A, et al. Role of MR venography in the evaluation of deep venous thrombosis. Acta Radiol. 1997;38(5):907–12.
21. Wysokinska EM, Hodge D, McBane RD 2nd. Ovarian vein thrombosis: incidence of recurrent venous thromboembolism and survival. Thromb Haemost. 2006;96(2):126–31.
22. Witlin AG, Sibai BM. Postpartum ovarian vein thrombosis after vaginal delivery: a report of 11 cases. Obstet Gynecol. 1995;85(5 pt 1):775–80.
23. Brown CE, Stettler RW, Twickler D, Cunningham FG. Puerperal septic pelvic thrombophlebitis: incidence and response to heparin therapy. Obstet Gynecol. 1999;181(1):143–8.
24. Kline JA, Mitchell AM, Kabrhel C, Richman PB, Courtney DM. Clinical criteria to prevent unnecessary diagnostic testing in emergency department patients with suspected pulmonary embolism. J Thromb Haemost. 2004;2:1247–55.
25. Klok FA, Mos IC, Nijkeuter M, Righini M, Perrier A, Le GG, et al. Simplification of the revised Geneva score for assessing clinical probability of pulmonary embolism. Arch Intern Med. 2008;168(19):2131–6.
26. Kline JA, Courtney DM, Kabrhel C, et al. Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. J Thromb Haemost. 2008;6(5):772–80.
27. Cahill AG, Stout MJ, Macones GA, Bhalla S. Diagnosing pulmonary embolism in pregnancy using computed-tomographic angiography or ventilation-perfusion. Obstet Gynecol. 2009;114:124–9.
28. Leung AN, Bull TM, Jaeschke R, et al. An official American Thoracic Society/Society of Thoracic Radiology Clinical Practice Guideline: evaluation of suspected pulmonary embolism in pregnancy. Am J Respir Crit Care Med. 2011;184:1200–8.
29. Elliott CG, Goldhaber SZ, Visani L, DeRosa M. Chest radiographs in acute pulmonary embolism: results from the international cooperative pulmonary embolism registry. Chest. 2000;118:33–8.
30. Kline JA, Kabrhel C. Emergency evaluation for pulmonary embolism, part 2: diagnostic approach. J Emerg Med. 2015;49(1):104–17.
31. Mos IC, Klok FA, Kroft LJ, DE Roos A, Dekkers OM, Huisman MV. Safety of ruling out acute pulmonary embolism by normal computed tomography pulmonary angiography in patients with an indication for computed tomography: systematic review and meta-analysis. J Thromb Haemost. 2009;7:1491–8.
32. Tzoran I, Saharov G, Brenner B, et al. Silent pulmonary embolism in patients with proximal deep vein thrombosis in the lower limbs. J Thromb Haemost. 2012;10:564–71.
33. Daniel KR, Jackson RE, Kline JA. Utility of the lower extremity venous ultrasound in the diagnosis and exclusion of pulmonary embolism in outpatients. Ann Emerg Med. 2000;35:547–54.
34. Brent RL. The effect of embryonic and fetal exposure to x-ray, microwaves, and ultrasound: counseling the pregnant and nonpregnant patient about these risks. Semin Oncol. 1989;16:347–68.
35. Greer IA. Prevention and management of venous thromboembolism in pregnancy. Clin Chest Med. 2003;24:123–37.
36. Raschke RA, Reilly BM, Guidry JR, Fontana JR, Srinivas S. The weight-based heparin dosing nomogram compared with a "standard care" nomogram. A randomized controlled trial. Ann Intern Med. 1993;119:874–81.
37. Prandoni P, Bagatella P, Bernardi E, et al. Use of an algorithm for administering subcutaneous heparin in the treatment of deep venous thrombosis. Ann Intern Med. 1998;129(4):299–302.
38. Horlocker TT, Vandermeuelen E, Kopp SL, Gogarten W, Leffert LR, Benzon HT. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (fourth edition). Reg Anesth Pain Med. 2018;43(3):263–309.
39. Hall JG, Pauli RM, Wilson KM. Maternal and fetal sequelae of anticoagulation during pregnancy. Am J Med. 1980;68(1):122–40.
40. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease CHEST guideline and expert panel report. Chest. 2016;149(2):315–52.
41. Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation. 2011;123:1788–830.
42. Gibson NS, Sohne M, Buller HR. Prognostic value of echocardiography and spiral computed tomography in patients with pulmonary embolism. Curr Opin Pulm Med. 2005;11(5):380–4.
43. Leibowitz D. Role of echocardiography in the diagnosis and treatment of acute pulmonary thromboembolism. J Am Soc Echocardiogr. 2001;14(9):921–6.
44. Moitra VK, Einav S, Thies KC, et al. Cardiac arrest in the operating room: resuscitation and management for the anesthesiologist: part 1. Anesth Analg. 2018;126(3):876–88.
45. Turrentine MA, Braems G, Ramirez MM. Use of thrombolytics for the treatment of thromboembolic disease in pregnancy. Obstet Gynecol Surv. 1995;50:534–41.
46. te Raa GD, Ribbert LS, Snijder RJ, Biesma DH. Treatment options in massive pulmonary embolism during pregnancy; a case-report and review of the literature. Thromb Res. 2009;124(1):1–5.

47. Martillotti G, Boehlen F, Robert-Ebadi H, et al. Treatment options for severe pulmonary embolism during pregnancy and the postpartum period: a systematic review. J Thromb Haemost. 2017;15(10):1942–50.
48. Fernandes P, Allen P, Valdis M, Guo L. Successful use of extracorporeal membrane oxygenation for pulmonary embolism, prolonged cardiac arrest, post-partum: a cannulation dilemma. Perfusion. 2015;30(2):106–10.
49. McDonald C, Laurie J, Janssens S, et al. Successful provision of inter-hospital extracorporeal cardiopulmonary resuscitation for acute post-partum pulmonary embolism. Int J Obstet Anesth. 2017;30:65–8.
50. Clark SL, Hankins GD, Dudley DA, Dildy GA, Porter TF. Amniotic fluid embolism: analysis of the national registry. Am J Obstet Gynecol. 1995;172:1158–69.
51. Clark SL. Amniotic fluid embolism. Obstet Gynecol. 2014;123(2 Pt 1):337–48.
52. Society for Maternal-Fetal Medicine (SMFM), Pacheco LD, Saade G, Hankins GD, Clark SL. Amniotic fluid embolism: diagnosis and management. Am J Obstet Gynecol. 2016;215: B16–24.
53. Biderman P, Carmi U, Setton E, Fainblut M, Bachar O, Einav S. Maternal salvage with extracorporeal life support: lessons learned in a single center. Anesth Analg. 2017;125(4):1275–80.
54. Rezai S, Hughes AC, Larsen TB, Fuller PN, Henderson CE. Atypical amniotic fluid embolism managed with a novel therapeutic regimen. Case Rep Obstet Gynecol. 2017;2017: 8458375.

Part III

The Cardiovascular System

9 Cardiovascular Changes in Pregnancy

Shuangbo Liu, Davinder S. Jassal, and Carolyn M. Zelop

Bullet Points

- The maternal system undergoes significant physiologic changes during pregnancy to allow the body to adapt to increased metabolic demands and to support a growing fetus.
- Blood volume increases during pregnancy to approximately 50% above baseline values. Higher increase in blood volume compared to red blood cell mass leads to the physiological anemia of pregnancy.
- Mean arterial pressure decreases in pregnancy, paralleling a decrease in diastolic blood pressure. Systolic blood pressure remains relatively unchanged.
- Heart rate increases during pregnancy and can be 10–20 beats per minute above prepregnancy values.
- Stroke volume increases during pregnancy by 20–30% above baseline values due to an increase in preload and decrease in afterload.
- Cardiac output increases during pregnancy and peaks at 40–60% higher than prepregnancy values and can be as high as 6.2–7.6 L/min.
- Systemic vascular resistance decreases during pregnancy to a nadir of 30–35% less than baseline.
- During labor, cardiac output rises, along with heart rate and blood pressure. Within minutes after delivery, stroke volume and cardiac output increase further. These physiologic changes may take 24 weeks to normalize.
- Brain natriuretic peptide and N-terminal pro-brain natriuretic peptide levels are higher in pregnant than nonpregnant females; however, they are constant throughout gestation. Abnormally high levels are associated with disease processes.

S. Liu · D. S. Jassal
Section of Cardiology, Department of Internal Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada

C. M. Zelop (✉)
The Valley Hospital, Ridgewood, NJ, USA

NYU School of Medicine, New York, NY, USA
e-mail: cmzelop@comcast.net

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_9

9.1 Introduction

The maternal cardiovascular system undergoes significant physiologic changes during pregnancy to adapt to increased metabolic demands and to support a growing fetus. Although the magnitude of these changes can vary depending on underlying maternal and fetal characteristics, there are several common key features. To accurately detect disease states in pregnancy, a firm understanding of normal physiologic changes is important. This chapter reviews the physiologic changes that occur during pregnancy, labor, delivery, and the postpartum period.

9.2 Physiologic Changes During Pregnancy

9.2.1 Blood Volume

In pregnancy, activation of the renal-angiotensin-aldosterone system (RAAS) and the placenta acting as an arteriovenous fistula [1] cause higher levels of aldosterone and sodium retention [2]. The RAAS plays a major role in the increase of blood volume in pregnancy. This increase can be as high as 10% at 7 weeks and 20% at 15 weeks (Table 9.1) [3, 4]. It continues gradually until the third trimester, at which time blood volume plateaus at 4700–5200 mL (Table 9.2), approximately 50% above baseline values [4–11]. This physiological increase in blood volume is important, as lack of an increase has been associated with poor outcomes such as intrauterine growth restriction and preeclampsia [12, 13].

In the last trimester, blood volume may start to decrease [7, 8, 10]. Although both blood volume and red blood cell (RBC) mass increase during pregnancy, blood volume tends to increase more than RBC mass [8]. This discrepancy leads to the physiologic anemia of pregnancy whereby individuals demonstrate a low hemoglobin, hematocrit, and RBC count [8, 14]. In addition to the extra blood volume in pregnancy, colloid oncotic pressure decreases during the first and second trimester, with a nadir at 30–34 weeks before it starts to rise [15]. Collectively, Starling forces favor a narrowing of the oncotic pressure-wedge pressure gradient which increases the tendency for pregnant women to develop pulmonary edema [16].

9.2.2 Blood Pressure

The systolic blood pressure (BP) remains relatively unchanged throughout pregnancy, until the

Table 9.1 Normal physiologic changes during pregnancy, labor, delivery, and postpartum

Parameter	First trimester Week 1–12	Second trimester Week 13–27	Third trimester Week 28–birth	Labor	Delivery	Immediately postdelivery	Postpartum
Blood volume, mL	+10%	+20 to 50%	Decrease/ unchanged	Unchanged	Unchanged	Decrease	Decrease
SBP, mmHg	Unchanged	−5%/ unchanged	+5 to 10%	Increase	Increase	Unchanged	Decrease
DBP, mmHg	−5%	−5 to 10%	+10 to 15% or unchanged	Increase	Increase	Unchanged	Decrease
HR, bpm	+10 to 15%	+15 to 20%	+15 to 20%	Increase	Increase	Decrease	Decrease
SV, mL	+5 to 20%	+25 to 30%	+25 to 30%	Increase	Increase	Increase	Decrease
CO, L/min	+10 to 30%	+30 to 40%	+40 to 60%	Increase	Increase	Increase	Decrease
SVR, dynes/ sec/cm^{-5}	−10 to 20%	−30 to 35%	−30 to 35%	–	–	–	Increase

SBP systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *SV* stroke volume, *CO* cardiac output, *SVR* systemic vascular resistance

Adapted from the following sources: Refs. [6, 18]

Table 9.2 Normal physiologic changes during pregnancy, labor, delivery, and postpartum

Parameter	First trimester Week 1–12	Second trimester Week 13–27	Third trimester Week 28–birth	Labor	Delivery	Immediately postdelivery	Postpartum
Blood volume, mL	2768	2820–3751	3730–4022	Unchanged	Unchanged	3530	2699–3525
SBP, mmHg	92–98	90–98	96–100	115	Increase	Unchanged	Decrease
DBP, mmHg	50–53	52–55	55–60	71	Increase	Unchanged	Decrease
HR, bpm	70–77	77–80	78–85	80	Increase	75	66–71
SV, mL	90–91	79–86	78–82	75	Increase	96	80–81
CO, L/min	6.8–7.01	6.55–7.2	5.6–6.67	6.3	Increase	7.22	5.27–5.71
SVR, dynes/sec/cm^{-5}	1069–1270	912–1070	880–1027	–	–	–	1228–1423

SBP systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *SV* stroke volume, *CO* cardiac output, *SVR* systemic vascular resistance
Adapted from the following sources: Refs. [6, 17, 18]

36th week of gestation, when there can be a slight increase (Tables 9.1 and 9.2) [18]. On the other hand, the diastolic BP starts to decrease as early as 7 weeks of gestation [18–20] and reaches a nadir by the 20th week, before starting to increase again until term [18, 21]. The lower diastolic BP results in a fall of the mean arterial pressure in early pregnancy, with a decrease by nearly 10% (Table 9.1) [3, 22]. After the 20th–24th week of gestation, the mean arterial pressure increases parallel to the diastolic BP [23, 24].

9.2.3 Heart Rate

Heart rate (HR) increases gradually during pregnancy, starting at 5 weeks of gestation (Table 9.1) [18, 25]. In early pregnancy (up to 15 weeks), the HR can increase by approximately 20% [3, 26]. HR continues to increase until the third trimester when it plateaus. At 32 weeks of gestation, the HR can be 10–20 beats per minute above pre-pregnancy values (Table 9.2) [6, 21, 27].

9.2.4 Stroke Volume

Stroke volume (SV) represents the amount of blood ejected from the heart with each beat. It is dependent on preload and afterload. Preload is increased during pregnancy due to an increase in plasma volume. Afterload is reduced due to a decrease in peripheral vascular resistance. These changes lead to an increase in SV during pregnancy, approximately 20–30% above baseline values (Table 9.1) [28, 29]. This increase in SV starts as early as 8 weeks gestation, peaks at 20 weeks, and is maintained until the 38th week when it begins to decrease (Tables 9.1 and 9.2) [18, 23].

9.2.5 Cardiac Output

Cardiac output (CO) is the product of SV and HR. Due to an increase in both SV and HR, CO increases accordingly during pregnancy. Toward the end of the first trimester (10–13 weeks), the CO increases sharply up to 20–40% above pre-pregnancy values (Table 9.1) [18, 30, 31]. This continues during the second trimester, and CO tends to peak by the beginning of the third trimester (24–29 weeks) [30, 32, 33]. Studies have demonstrated that CO can be 40–60% higher than baseline values [18, 20, 30, 32, 34] and as high as 6.2–7.6 L/min during pregnancy (Table 9.2) [20, 23, 26, 35]. Initially, the increase in SV, rather than HR, contributes more to the increase in CO in pregnancy [33, 36]. However, in late pregnancy,

the increase in HR plays a larger role in CO [18, 20]. Throughout the third trimester, the rise in CO starts to slow down [30, 32] .

The increased CO associated with pregnancy is unevenly distributed throughout the organ systems. During the first trimester, there is a significant increase in blood flow to the kidneys and uterus [37–40]. With advanced gestational age, the blood flow to the skin and breasts are also increased [41, 42]. Regional blood flow to the uterus is increased with uterine arterial flow recorded as high as 600–1000 mL/min at term [6, 21, 43], representing 15–20% of the overall maternal cardiac output.

9.2.6 Systematic Vascular Resistance

An increase in prostacyclin and nitric oxide levels during pregnancy leads to a significant decrease in systemic vascular resistance (SVR) [44]. SVR decreases during the first trimester by approximately 10% [19] and reaches a nadir of 30–35% less than baseline by weeks 10–24 (Tables 9.1 and 9.2) [6, 18, 26, 45, 46].

9.2.7 Cardiac Structural Changes

Several cardiac structures remodel during pregnancy. Left ventricular (LV) mass increases during pregnancy, from a baseline of 110–120 g to 183 g at term [18, 35, 47]. This declines to normal values by 3 months postpartum [35]. While LV end-systolic dimension remains relatively stable, LV end-diastolic dimension increases during pregnancy from baseline values of 45 mm to 52–55 mm by the third trimester [35]. Cardiac magnetic imaging studies have shown that both right ventricular end-diastolic dimension and volume increase with pregnancy [35]. Pulmonary artery pressure appears to remain unaffected [35]. Left atrial and right atrial volumes are both higher than baseline during pregnancy [35, 48]. LV systolic function is unchanged and the LV ejection fraction can remain constant or increase slightly during pregnancy [18, 35, 47, 48]. LV diastolic function remains within the normal range throughout pregnancy due to a shift from early to late diastolic filling [47, 49, 50].

9.2.8 Aortocaval Compression

Aortocaval compression was traditionally believed to occur when a woman in late pregnancy lies supine, leading to a decrease in CO. However, studies have shown that this can occur as early as 20 gestational weeks [48]. Initially, aortocaval compression is due mainly to the gravid uterus compressing on the inferior vena cava [51, 52], and the aorta is less affected. However, ongoing compression of the aorta eventually leads to an increase in afterload which compromises cardiac performance. This results in hypotension and tachycardia, a decrease in SV, and a decrease in CO by 17–25% [48, 53–57]. Aortocaval compression has been associated with supine hypotensive syndrome [58, 59] and symptoms including sweating, nausea, and dizziness. Given these findings, it is important to consider positioning particularly in hemodynamically unstable pregnant patients, as supine positioning may contribute to worsening hypotension. Lateral decubitus positioning can help correct the hemodynamic instability by increasing overall CO [60].

9.3 Physiologic Changes During Labor and Delivery

Significant hemodynamic changes can occur during labor and delivery. CO increases during labor. This increase may be as great as 1 L/min, rising from 6.99 L/min pre-labor to 7.88 L/min when ≥8 cm cervical dilatation is reached (Tables 9.1 and 9.2) [61]. Several mechanisms are responsible for this increase, including uterine contractions, elevated HR, and elevated BP from increased sympathetic tone. With each uterine contraction, an additional 300–500 mL of blood from the uterus enters the maternal circulation [21, 62–64]. This increase in SV leads to an increase in CO [53]. There is a progressive

increase of CO with ongoing contractions, with an average increase of 1.14 L/min at ≤3 cm, 1.75 L/min at 4–7 cm, and 2.69 L/min at ≥8 cm of cervical dilatation [61].

During the second stage of labor, maternal pushing efforts can increase CO by a further 50% [64]. Due to the increased sympathetic tone associated with pain and anxiety, both HR and BP increase, contributing to the higher CO [65]. BP increases during delivery, especially with contractions [6, 61]. The degree of increase varies with patient position, duration and frequency of contractions, and the amount of pain and anxiety the pregnant woman experiences. During labor, pregnant women are hemodynamically more stable (SV and CO) between contractions in the lateral recumbent position than in the supine position [53, 64]. The increase in CO is more pronounced in patients with local anesthesia (e.g., paracervical block, pudendal block) than in patients with regional analgesia [64]. It is likely that the increase in HR, which is more significant in patients with local anesthesia, contributes to the higher CO [64]. While cesarean delivery can mitigate some of these hemodynamic fluctuations, surgery carries additional risks unto itself [21, 64]. Vaginal delivery is therefore still favored. Therefore, in the setting of cardiopulmonary disease, the route of delivery should be individualized for each pregnant woman.

9.4 Physiologic Changes Postpartum

Mean arterial pressure is often unchanged until 24–48 h after delivery [23, 24]. However, within minutes after delivery, the SV and CO increase rapidly by 60–80%. This occurs due to transfer of uterine blood back into the systemic circulation, decreased compression of the inferior vena cava, and movement of extravascular fluid into intravascular spaces (Tables 9.1 and 9.2) [28, 64, 66, 67]. At 1 h postpartum, SV and CO remain elevated by 50–60%, while the HR decreases and BP remains unchanged [68]. This effect can last 1–2 h after delivery, during which time women may be susceptible to pulmonary edema [18]. Conversely, the hypervolemia associated with pregnancy appears to have a protective effect with regard to potential hemorrhage; the usual amount of blood loss associated with delivery does not cause significant hemodynamic compromise [14]. Healthy pregnant women can lose up to 30% of blood volume at delivery without a decrease in the hematocrit [14, 69, 70].

The maternal cardiovascular system continues to change in the weeks following delivery. At 6 weeks postpartum, the CO and HR continue to decrease [71] while the SVR increases [23]. Mean arterial pressure and SV begin to return to baseline values by 12 weeks postpartum [23], but this process can take as long as 24 weeks [24, 28].

9.5 Brain Natriuretic Peptide

Brain natriuretic peptide (BNP) is a hormone released from the heart due to increased transmural ventricular wall stress [72]. Increased values of plasma BNP have been identified in heart failure [73]. The BNP levels found in pregnancy are higher than baseline BNP levels (12 pg/mL prepregnancy vs. 16–18 pg/mL during pregnancy) [74], but these high levels are fairly constant throughout gestation [75]. During the early postpartum period (4 days postpartum), the measured values of BNP can be even higher (up to 43 pg/mL) [74]. They decrease over the next month but still remain elevated 1 month postpartum (16 pg/mL) [74]. N-terminal pro-BNP (NT-proBNP) levels are also elevated during pregnancy, increasing by up to 31% compared to nonpregnant levels [76]. Abnormally high levels of BNP are associated with preeclampsia, gestational hypertension, and gestational diabetes. There appears to be a spectrum of BNP elevation with higher plasma values in more severe preeclampsia [75]. Elevated levels of serum NT-proBNP are also associated with these maternal conditions [76] (65 pg/mL in patients with gestational hypertension and 89–190 pg/mL in patients with preeclampsia in comparison to 37–59 pg/mL) [76, 77].

The role of BNP in diagnosing heart failure and cardiomyopathy in pregnancy is not well-

established. However, BNP has been shown to be higher during pregnancy in patients with underlying heart disease. Plasma BNP levels >100 pg/mL have been associated with adverse cardiovascular outcomes, whereas plasma BNP ≤ 100 pg/mL had a negative predictive value of 100% for adverse events during pregnancy in patients with heart disease [78]. Similarly, NT-proBNP >128 pg/mL have been associated with adverse cardiovascular events in pregnant patients with underlying congenital heart disease [79].

9.6 Conclusion

It is important to understand cardiovascular changes in pregnancy, labor, and delivery in order to appropriately recognize and treat disease states.

References

1. Cockcroft JR, Backx K et al. Cardiac output and related haemodynamics during pregnancy: a series of meta-analyses. Heart 2016;102:518–526
2. Vaklotton MB, Davison JM, Riondel AM, Lindheimer MD. Response of the renin-aldosterone system and antidiuretic hormone to oral water loading and hypertonic saline infusion during and after pregnancy. Clin Exp Hypertens B. 1982;1(2–3):385–400.
3. Clapp JF 3rd, Seaward BL, Sleamaker RH, Hiser J. Maternal physiologic adaptations to early human pregnancy. Am J Obstet Gynecol. 1988;159(6):1456–60.
4. Lund CJ, Donovan JC. Blood volume during pregnancy. Significance of plasma and red cell volumes. Am J Obstet Gynecol. 1967;98(3):394–403.
5. Hytten FE, Paintin DB. Increase in plasma volume during normal pregnancy. J Obstet Gynaecol Br Emp. 1963;70:402–7.
6. Ouzounian JG, Elkayam U. Physiologic changes during normal pregnancy and delivery. Cardiol Clin. 2012;30(3):317–29.
7. Rovinsky JJ, Jaffin H. Cardiovascular hemodynamics in pregnancy: I. Blood and plasma volumes in multiple pregnancy. Am J Obstet Gynecol. 1965;93:1–15.
8. Pritchard JA. Changes in the blood volume during pregnancy and delivery. Anesthesiology. 1965;26:393–9.
9. Ueland K. Maternal cardiovascular dynamics. VII. Intrapartum blood volume changes. Am J Obstet Gynecol. 1976;126(6):671–7.
10. Thomson KJ, Hirsheimer A, Gibson JG II, Evans WA Jr. Studies on the circulation in pregnancy. Am J Obstet Gynecol. 1938;36(1):48–59.
11. McLennan C, Thouin LG. Blood volume in pregnancy; a critical review and preliminary report of results with a new technique. Am J Obstet Gynecol. 1948;55(2):189–200.
12. Salas SP, Rosso P, Espinoza R, Robert JA, Valdes G, Donoso E. Maternal plasma volume expansion and hormonal changes in women with idiopathic fetal growth retardation. Obstet Gynecol. 1993;81(6):1029–33.
13. Salas SP, Marshall G, Gutierrez BL, Rosso P. Time course of maternal plasma volume and hormonal changes in women with preeclampsia or fetal growth restriction. Hypertension. 2006;47(2):203–8.
14. Pritchard JA, Baldwin RM, Dickey JC, Wiggins KM. Blood volume changes in pregnancy and the puerperium: 2. Red blood cell loss and changes in apparent blood volume during and following vaginal delivery, cesarean section, and cesarean section plus total hysterectomy. Am J Obstet Gynecol. 1962;84(10):1271–82.
15. Wu PY, Udani V, Chan L, Miller FC, Henneman CE. Colloid osmotic pressure: variations in normal pregnancy. J Perinat Med. 1983;11(4):193–9.
16. Odutayo A, Hladunewich M. Obstetric nephrology: renal hemodynamic and metabolic physiology in normal pregnancy. Clin J Am Soc Nephrol. 2012;7(12):2073–80.
17. Meah VL, Cockcroft JR, Backx K et al. Cardiac output and related haemodynamics during pregnancy: a series of meta-analyses. Heart 2016;102:518–526
18. Robson SC, Hunter S, Boys RJ, Dunlop W. Serial study of factors influencing changes in cardiac output during human pregnancy. Am J Phys. 1989;256(4 Pt 2):H1060–5.
19. Duvekot JJ, Cheriex EC, Pieters FA, Menheere PP, Peeters LH. Early pregnancy changes in hemodynamics and volume homeostasis are consecutive adjustments triggered by a primary fall in systemic vascular tone. Am J Obstet Gynecol. 1993;169(6):1382–92.
20. Mabie WC, DiSessa TG, Crocker LG, Sibai BM, Arheart KL. A longitudinal study of cardiac output in normal human pregnancy. Am J Obstet Gynecol. 1994;170(3):849–56.
21. Ueland K, Metcalfe J. Circulatory changes in pregnancy. Clin Obstet Gynecol. 1975;18(3):41–50.
22. Capeless EL, Clapp JF. When do cardiovascular parameters return to their preconception values? Am J Obstet Gynecol. 1991;165(4 Pt 1):883–6.
23. van Oppen AC, van der Tweel I, Alsbach GP, Heethaar RM, Bruinse HW. A longitudinal study of maternal hemodynamics during normal pregnancy. Obstet Gynecol. 1996;88(1):40–6.
24. San-Frutos L, Engels V, Zapardiel I, Perez-Medina T, Almagro-Martinez J, Fernandez R, et al. Hemodynamic changes during pregnancy and post-

partum: a prospective study using thoracic electrical bioimpedance. J Matern Fetal Neonatal Med. 2011;24(11):1333–40.
25. Capeless EL, Clapp JF. Cardiovascular changes in early phase of pregnancy. Am J Obstet Gynecol. 1989;161(6 Pt 1):1449–53.
26. Clark SL, Cotton DB, Lee W, Bishop C, Hill T, Southwick J, et al. Central hemodynamic assessment of normal term pregnancy. Am J Obstet Gynecol. 1989;161(6 Pt 1):1439–42.
27. Katz R, Karliner JS, Resnik R. Effects of a natural volume overload state (pregnancy) on left ventricular performance in normal human subjects. Circulation. 1978;58(3 Pt 1):434–41.
28. Tan EK, Tan EL. Alterations in physiology and anatomy during pregnancy. Best Pract Res Clin Obstet Gynaecol. 2013;27(6):791–802.
29. Laird-Meeter K, van de Ley G, Bom TH, Wladimiroff JW, Roelandt J. Cardiocirculatory adjustments during pregnancy—an echocardiographic study. Clin Cardiol. 1979;2(5):328–32.
30. Hamilton HF. The cardiac output in normal pregnancy; as determined by the Cournand right catheterization technique. J Obstet Gynaecol Br Emp. 1949;56(4):548–52.
31. Lees MM, Taylor SH, Scott DB, Kerr MG. A study of cardiac output at rest throughout pregnancy. J Obstet Gynaecol Br Commonw. 1967;74(3):319–28.
32. Bader RA, Bader ME, Rose DF, Braunwald E. Hemodynamics at rest and during exercise in normal pregnancy as studies by cardiac catheterization. J Clin Invest. 1955;34(10):1524–36.
33. Walters WA, MacGregor WG, Hills M. Cardiac output at rest during pregnancy and the puerperium. Clin Sci. 1966;30(1):1–11.
34. Palmer AJ, Walker AH. The maternal circulation in normal pregnancy. Obstet Gynaecol Br Emp. 1949;56(4):537–47.
35. Ducas RA, Elliott JE, Melnyk SF, Premecz S, da Silva M, Cleverley K, et al. Cardiovascular magnetic resonance in pregnancy: insights from the cardiac hemodynamic imaging and remodeling in pregnancy (CHIRP) study. J Cardiovasc Magn Reson. 2014; 16:1.
36. Savu O, Jurcut R, Giusca S, van Mieghem T, Gussi I, Popescu BA, et al. Morphological and functional adaptation of the maternal heart during pregnancy. Circ Cardiovasc Imaging. 2012;5(3):289–97.
37. Jurkovic D, Jauniaux E, Kurjak A, Hustin J, Campbell S, Nicolaides KH. Transvaginal color Doppler assessment of the uteroplacental circulation in early pregnancy. Obstet Gynecol. 1991;77(3):365–9.
38. Jaffe R, Warsof SL. Transvaginal color Doppler imaging in the assessment of uteroplacental blood flow in the normal first-trimester pregnancy. Am J Obstet Gynecol. 1991;164(3):781–5.
39. Palmer SK, Zamudio S, Coffin C, Parker S, Stamm E, Moore LG. Quantitative estimation of human uterine artery blood flow and pelvic blood flow redistribution in pregnancy. Obstet Gynecol. 1992;80(6): 1000–6.
40. Dunlop W. Serial changes in renal haemodynamics during normal human pregnancy. Br J Obstet Gynaecol. 1981;88(1):1–9.
41. Ginsburg J, Duncan SL. Peripheral blood flow in normal pregnancy. Cardiovasc Res. 1967;1(2):132–7.
42. Katz M, Sokal MM. Skin perfusion in pregnancy. Am J Obstet Gynecol. 1980;137(1):30–3.
43. Metcalfe J, Romney SL, Ramsey LH, Reid DE, Burwell CS. Estimation of uterine blood flow in normal human pregnancy at term. J Clin Invest. 1955;34(11):1632–8.
44. Ylikorkala O, Makila UM. Prostacyclin and thromboxane in gynecology and obstetrics. Am J Obstet Gynecol. 1985;152(3):318–29.
45. Carbillon L, Uzan M, Uzan S. Pregnancy, vascular tone, and maternal hemodynamics: a crucial adaptation. Obstet Gynecol Surv. 2000;55(9):574–81.
46. Easterling TR, Benedetti TJ, Schmucker BC, Millard SP. Maternal hemodynamics in normal and preeclamptic pregnancies: a longitudinal study. Obstet Gynecol. 1990;76(6):1061–9.
47. Mesa A, Jessurun C, Hernandez A, Adam K, Brown D, Vaughn WK, et al. Left ventricular diastolic function in normal human pregnancy. Circulation. 1999;99(4):511–7.
48. Rossi A, Cornette J, Johnson MR, Karamermer Y, Springeling T, Opic P, et al. Quantitative cardiovascular magnetic resonance in pregnant women: cross-sectional analysis of physiological parameters throughout pregnancy and the impact of the supine position. J Cardiovasc Magn Reson. 2011; 27;13(1):31.
49. Fok WY, Chan LY, Wong JT, Yu CM, Lau TK. Left ventricular diastolic function during normal pregnancy: assessment by spectral tissue Doppler imaging. Ultrasound Obstet Gynecol. 2006;28(6):789–93.
50. Moran AM, Colan SD, Mauer MB, Geva T. Adaptive mechanisms of left ventricular diastolic function to the physiologic load of pregnancy. Clin Cardiol. 2002;25(3):124–31.
51. Kerr MG, Scott DB, Samuel E. Studies of the inferior vena cava in late pregnancy. Br Med J. 1964;1(5382):532–3.
52. Higuchi H, Takagi S, Zhang K, Furui I, Ozaki M. Effect of lateral tilt angle on the volume of the abdominal aorta and inferior vena cava in pregnant and nonpregnant women determined by magnetic resonance imaging. Anesthesiology. 2015;122(2): 286–93.
53. Ueland K, Hansen JM. Maternal cardiovascular dynamics. II. Posture and uterine contractions. Am J Obstet Gynecol. 1969;103(1):1–7.
54. Bieniarz J, Branda LA, Maqueda E, Morozovsky J, Caldeyro-Barcia R. Aortocaval compression by the uterus in late pregnancy. 3. Unreliability of the

sphygmomanometric method in estimating uterine artery pressure. Am J Obstet Gynecol. 1968;102(8):1106–15.
55. Bamber JH, Dresner M. Aortocaval compression in pregnancy: the effect of changing the degree and direction of lateral tilt on maternal cardiac output. Anesth Analg. 2003;97(1):256–8.
56. Lees MM, Scott DB, Kerr MG, Taylor SH. The circulatory effects of recumbent postural change in late pregnancy. Clin Sci. 1967;32(3):453–65.
57. Easterling TR, Schmucker BC, Benedetti TJ. The hemodynamic effects of orthostatic stress during pregnancy. Obstet Gynecol. 1988;72(4):550–2.
58. Howard BK, Goodson JH, Mengert WF. Supine hypotensive syndrome in late pregnancy. Obstet Gynecol. 1953;1(4):371–7.
59. Kinsella SM, Lohmann G. Supine hypotensive syndrome. Obstet Gynecol. 1994;83(5 Pt 1):774–88.
60. Jeejeebhoy FM, Zelop CM, Lipman S, Carvalho B, Joglar J, Mhyre JM, et al. Cardiac arrest in pregnancy: a scientific statement from the American Heart Association. Circulation. 2015;132(18):1747–73.
61. Robson SC, Dunlop W, Boys RJ, Hunter S. Cardiac output during labour. Br Med J (Clin Res Ed). 1987;295(6607):1169–72.
62. Hendricks CH, Quilligan EJ. Cardiac output during labor. Am J Obstet Gynecol. 1956;71(5):953–72.
63. Burch GE. Heart disease and pregnancy. Am Heart J. 1977;93(1):104–16.
64. Ueland K, Hansen JM. Maternal cardiovascular dynamics. 3. Labor and delivery under local and caudal analgesia. Am J Obstet Gynecol. 1969;103(1):8–18.
65. Sanghavi M, Rutherford JD. Cardiovascular physiology of pregnancy. Circulation. 2014;130(12):1003–8.
66. Robson SC, Dunlop W. When do cardiovascular parameters return to their preconception values? Am J Obstet Gynecol. 1992;167(5):1479.
67. Robson SC, Hunter S, Moore M, Dunlop W. Haemodynamic changes during the puerperium: a Doppler and M-mode echocardiographic study. Br J Obstet Gynaecol. 1987;94(11):1028–39.
68. Kjeldsen J. Hemodynamic investigations during labour and delivery. Acta Obstet Gynecol Scand Suppl. 1979;89:1–252.
69. Newton M, Mosey LM, Egli GE, Gifford WB, Hull CT. Blood loss during and immediately after delivery. Obstet Gynecol. 1961;17:9–18.
70. Wilcox CF 3rd, Hunt AB, Owens CA Jr. The measurement of blood lost during cesarean section. Am J Obstet Gynecol. 1959;77(4):772–9.
71. Atkins AF, Watt JM, Milan P, Davies P, Crawford JS. A longitudinal study of cardiovascular dynamic changes throughout pregnancy. Eur J Obstet Gynecol Reprod Biol. 1981;12(4):215–24.
72. Iwanaga Y, Nishi I, Furuichi S, Noguchi T, Sase K, Kihara Y, et al. B-type natriuretic peptide strongly reflects diastolic wall stress in patients with chronic heart failure: comparison between systolic and diastolic heart failure. J Am Coll Cardiol. 2006;47(4):742–8.
73. Brunner-La Rocca HP, Kaye DM, Woods RL, Hastings J, Esler MD. Effects of intravenous brain natriuretic peptide on regional sympathetic activity in patients with chronic heart failure as compared with healthy control subjects. J Am Coll Cardiol. 2001;37(5):1221–7.
74. Mayama M, Yoshihara M, Uno K, Tano S, Takeda T, Ukai M, et al. Factors influencing brain natriuretic peptide levels in healthy pregnant women. Int J Cardiol. 2017;228:749–53.
75. Resnik JL, Hong C, Resnik R, Kazanegra R, Beede J, Bhalla V, et al. Evaluation of B-type natriuretic peptide (BNP) levels in normal and preeclamptic women. Am J Obstet Gynecol. 2005;193(2):450–4.
76. Tihtonen KM, Koobi T, Vuolteenaho O, Huhtala HS, Uotila JT. Natriuretic peptides and hemodynamics in preeclampsia. Am J Obstet Gynecol. 2007;196(4):328.e1–7.
77. Sadlecki P, Grabiec M, Walentowicz-Sadlecka M. Prenatal clinical assessment of NT-proBNP as a diagnostic tool for preeclampsia, gestational hypertension and gestational diabetes mellitus. PLoS One. 2016;11(9):e0162957.
78. Tanous D, Siu SC, Mason J, Greutmann M, Wald RM, Parker JD, et al. B-type natriuretic peptide in pregnant women with heart disease. J Am Coll Cardiol. 2010;56(15):1247–53.
79. Kampman MA, Balci A, van Veldhuisen DJ, van Dijk AP, Roos-Hesselink JW, Sollie-Szarynska KM, et al. N-terminal pro-B-type natriuretic peptide predicts cardiovascular complications in pregnant women with congenital heart disease. Eur Heart J. 2014;35(11):708–15.

Preexisting Heart Disease in Pregnancy

10

Sigal Sviri, Avraham Abutbul, and Amiram Nir

Bullet Points

- Heart disease is present in 1–4% of all pregnancies and is emerging as the leading indirect cause of obstetric morbidity and mortality.
- The risk for complications during pregnancy in women with congenital and acquired heart disease can be estimated using several models.
- While most lesions carry a small risk, pregnancy carries a prohibitory risk in selected situations.
- Main anticipated complications are decompensated heart failure due to volume overload and severe arrhythmias. Therefore, pregnant women with high-risk CHD should be monitored and managed in high care units pre-, during, and postdelivery.
- Pregnancy in women with high-risk congenital heart disease (CHD) is a life-threatening event that should be carefully planned including preconception evaluation and decision-making by a multidisciplinary team of obstetricians, cardiologists, and anesthesiologists.
- Risk assessment and close follow-up and cooperation between multidisciplinary teams for the management of pregnancy and delivery are required in these patients.
- Risks should be discussed with the mother at the time of preconception evaluation and during all stages of pregnancy and delivery.
- Valvular heart disease is a leading cause of pregnancy-related maternal morbidity and mortality.
- Regurgitant left-sided valvular lesions are better tolerated in pregnancy than stenotic lesions due to the reduction in afterload during pregnancy.
- Women with prosthetic mechanical valves pose a special high risk in view of the anticoagulation required to avoid stuck valve and thromboembolic complications and minimize fetal risks.

S. Sviri (✉) · A. Abutbul
Medical Intensive Care Unit, Hadassah-Hebrew University Medical Centre, Jerusalem, Israel
e-mail: Sigals@hadassah.org.il

A. Nir
Pediatric Cardiology and Adult Congenital Heart Disease, Shaare Zedek Medical Center, Jerusalem, Israel

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_10

10.1 Epidemiology of Preexisting Heart Disease

Heart disease is present in 1–4% of all pregnancies [1] and is emerging as the leading cause of obstetric mortality, overtaking traditional direct causes of hemorrhage and thromboembolism in some countries [2]. Hospitalizations due to congenital heart disease, arrhythmias, cardiomyopathy, and congestive heart failure in pregnancy have been noted to be steadily increasing in both the United States and the United Kingdom [2–5]. The overall rate of mortality from cardiac disease has risen from 7.3/million births in 1982–1984 to 22.7/million births in 2003–2005 [5].

The causes of heart disease in pregnant women vary geographically. In the last decades, congenital heart disease (CHD) has become the leading cause of cardiac problems in pregnancy as women reach childbearing age in countries with facilities for advanced care [6, 7]. CHD now comprises more than 50% of cardiac lesions observed during pregnancy in developed countries [8], including 74% of the pregnancies among women with preexisting heart disease in Canada [9] and 66% in a European registry [10]. In Brazil, however, rheumatic heart disease remains the leading cause of preexisting heart disease (56%) with only 19% having CHD [11]. In China, among women with preexisting heart disease, only 30% of the women have CHD, 9% have rheumatic heart disease, and arrhythmias (38%) have been described as the most prevalent complication [12].

Using delivery-related discharge records in US community hospitals, Kuklina et al. [13] reported a significant linear increase in the prevalence of CHD from 6.4 to 9.0 per 10,000 delivery hospitalizations from 2000 to 2010. Importantly, most women had simple cardiac lesions. However, the prevalence of severe heart disease in the United States may have been underestimated in this study as it only examined community hospitals, and many of the women were referred to deliver in tertiary hospitals. The same study reported an in-hospital mortality rate of 17.8 per 10,000 deliveries among women with a history of CHD, 22 times higher than in women without CHD [13]. There was a significantly increased need for mechanical ventilation, transfusions, and treatment of deep vein thrombosis for women with CHD, and the risk for myocardial infarction was 35 times higher [3].

Peripartum complications account for a considerable number of intensive care unit (ICU) admissions. Among 765,598 admissions for antepartum, delivery, or postpartum conditions in Maryland, United States (1999–2008), cardiac disease was present in 18.3% of the 2927 women admitted to the ICU (ICU admission rate of 419.1 per 100,000 deliveries) [14]. A literature review from 2007 suggested that 11% of all pregnant women with a history of CHD have pregnancy or peripartum cardiac complications [15]. Heart failure accounted for 4.8% of this patient group, and arrhythmias, especially supraventricular, were present in 4.5% of CHD cases [15, 16].

10.2 Infertility and Complicated Valvular Lesions

Pregnant women with complicated valvular lesions are rarely seen in developed countries. Complicated valvular lesions have traditionally been associated with an increased rate of primary infertility [17, 18] and miscarriage [19]. However, assisted reproductive techniques have facilitated pregnancies in these women at a greater prevalence [20].

10.3 Risk Assessment for Heart Disease

The complexity of CHD pathologies varies considerably, ranging from simple septal defects that result in left to right shunt to valvular pathologies with significant pressure and/or volume overload. More complex types of CHD include Tetralogy of Fallot (TOF); even after repair, these patients may exhibit significant pulmonary valve regurgitation and right ventricular pressure and volume load [21]. Complex lesions, such as congenitally corrected transposition or atrial repair of transposition of the great arteries, result in a right ventricle that serves as the systemic pumping chamber. This anatomic right ventricle may fail

to sustain the hemodynamic challenges of late pregnancy. Women with one functional ventricle or "univentricular heart" may be cyanotic due to mixing of oxygenated and unoxygenated blood. Many women with a univentricular heart have undergone the Fontan palliation, which directs systemic venous return directly to the pulmonary arteries, thus alleviating cyanosis. This unique hemodynamic state may be compatible with pregnancy but is associated with a significant risk for maternal morbidity, as well as for fetal loss and early delivery [7, 22–24]. This great variability in physiology demands that standard tools be used to assess the risk and severity of the maternal condition prior to and during pregnancy and the peripartum period in women with CHD.

Several tools have been developed for predicting the risk for complications during pregnancy in women with congenital and preconception acquired heart disease, including cardiomyopathies [1]. The *CARPREG*, developed from 599 pregnancies [9], assigns a score according to the presence of risk factors: 1 point for prior cardiac events or arrhythmia, 1 point for NYHA >2 or cyanosis, 1 point for left ventricular outflow tract obstruction (gradient >30 mmHg or aortic valve area < 1.5 cm^2), or mitral valve stenosis (mitral valve area < 2 cm^2), and 1 point for reduced systemic ventricular systolic function (EF < 40%). The final score is the sum of points assigned. The risk for maternal cardiac complications during pregnancy has been described as 27% for women assigned 1 point and 75% for those with more than 1 point [9]. This score was recently updated to include ten additional predictors [25]. The *ZAHARA* model was developed from 1302 pregnancies in women with congenital heart disease [26]. It assigns different weights to the risk factors: 0.75 points to NYHA ≥ II before pregnancy, and moderate or severe systemic or pulmonary atrioventricular valve regurgitation; 1 point to corrected or uncorrected cyanotic heart disease; 1.5 points to history of arrhythmia and cardiac medications before pregnancy; 2.5 points to left ventricular outflow tract gradient >50 mmHg or aortic valve area <1 cm^2, and 4.5 points to mechanical valves. In the *ZAHARA* model, the risk for cardiovascular complications is 43% if the sum of points was >2.5 and 70% if it is greater than 3.5 [26].

The *WHO* classification integrates all known maternal cardiovascular risk factors into a single score estimating the pregnancy risk for women with congenital heart disease (Table 10.1). Importantly, this classification includes pulmonary hypertension, which is not included in the

Table 10.1 Modified WHO classification of maternal cardiovascular risk [1, 27]

WHO I
Uncomplicated, small or mild – Pulmonary stenosis – Patent ductus arteriosus – Mitral valve prolapse
Successfully repaired simple lesions – Atrial septal defect – Ventricular septal defect – Patent ductus arteriosus – Anomalous pulmonary venous drainage
Isolated atrial or ventricular ectopic beats
WHO II
Unoperated atrial or ventricular septal defect
Repaired Tetralogy of Fallot
Most arrhythmias (if otherwise well and uncomplicated)
WHO II–III
Mild left ventricular impairment
Hypertrophic cardiomyopathy
Native or tissue valvular heart disease not considered WHO I or IV Marfan syndrome without aortic dilatation
Aorta <45 mm in aortic disease associated with bicuspid aortic valve
Repaired coarctation
WHO III
Mechanical prosthetic valve
Systemic right ventricle
Fontan circulation
Cyanotic heart disease (unrepaired)
Other complex congenital heart disease
Aortic dilatation 40–45 mm in Marfan syndrome
Aortic dilatation 45–50 mm in aortic disease associated with bicuspid aortic valve
WHO IV
Pulmonary arterial hypertension of any cause
Previous peripartum cardiomyopathy with any residual impairment of left ventricular function
Severe mitral stenosis, severe symptomatic aortic stenosis
Marfan syndrome with aorta dilated >45 mm
Aortic dilatation >50 mm in aortic disease associated with bicuspid aortic valve
Native severe coarctation

LVEF left ventricular ejection fraction, *NYHA* New York Heart Association, *WHO* World Health Organization

other scores [7, 28]. The *WHO* classification divides the severity of maternal condition into four categories: Women in class I have no detectable increased risk of maternal mortality and either no or a mild increase in morbidity; women in class II might have a slight increase in maternal mortality or a moderate increase in morbidity with pregnancy; class III carries a significant increased risk for maternal mortality or severe morbidity; and women in class IV have an extremely high risk for mortality or severe morbidity. Women who have been assessed as belonging to class IV should be advised that pregnancy is contraindicated. If pregnancy occurs, termination of pregnancy should be discussed [7].

A recent study compared these three risk prediction scores on a cohort of 190 women with CHD who had 268 pregnancies and 6.7% had cardiac complications [29]. The c-statistics were comparable for all three scores, with slightly higher area under the curve (0.827) for the WHO classification compared to the other two risk prediction scores.

Table 10.2 summarizes the maternal risk factors for pregnancy in patients with congenital heart disease.

A number of tools for early detection of maternal cardiovascular deterioration during labor and delivery have been designed: In Great Britain, the modified early obstetric warning system (MEOWS) [30], which was adopted from the CEMACH (Confidential Enquiry into Maternal and Child Health) report and in the United States, the Maternal Early Warning Criteria (MERC) [31]. Both systems monitor maternal respiratory rate, pulse rate, blood pressure, temperature, and mental state. Individual parameters of the MEOWS chart were correlated with obstetric morbidity. The MERC score uses a HR > 110/min, mean arterial pressure < 65 mmHg, oxygen saturation ≤ 93%, respiratory rate > 24/min, and altered mental status as warning signs for cardiovascular compromise. Using the MERC system in more than 36,000 deliveries, Shields et al. showed a significant reduction in maternal morbidity as compared to close to 145,000 deliveries not using the system. It is recommended that these scores be used as assessment tools to detect maternal deterioration [31].

Table 10.2 Maternal risk factors for pregnancy in women with congenital heart disease

Systemic right ventricle—risk factors for severe disease pregnancy and delivery risk
• NYHA class III or IV should be advised against becoming pregnant
• Valvular dysfunction
• Arrhythmias, atrial ventricular, and AV block
Cyanotic heart disease without pulmonary hypertension—risk factors for complications during pregnancy and delivery
• Degree of maternal hypoxemia is the most important predictor of fetal outcome. If resting oxygen saturation is less than 85%, a substantial maternal and fetal mortality risk is expected, and pregnancy is contraindicated
• Prothrombotic state, thrombosis, or bleeding in the past
Single-ventricle physiology/Fontan palliation—risk factors for severe disease pregnancy and delivery risk
• Ventricular dysfunction
• Arrhythmia (atrial reentry, flutter)
• Hypoxia at rest <85% saturation
• High pulmonary artery (Fontan) pressures

10.4 Management Strategies in Specific Lesions

The risk for cardiac complications during pregnancy is relatively low for conditions in WHO classes I and II. This chapter will therefore focus on the risk for critical illness and complications in women with higher-risk lesions (congenital and acquired) during pregnancy and the peripartum period. Recent comprehensive guidelines from the European Society of Cardiology discuss these in detail [27].

Pregnant women with preexisting heart disease require an individualized plan that considers their specific lesion, as discussed below. This plan should outline the physiologic goals required to maintain optimal cardiac function throughout pregnancy, labor, and the postpartum period [32]. A detailed history includes family history, genetic counselling, and cardiac symptomatology. Medications may require adjustment for teratogenic drugs, as outlined in Chap. 38. Physical examination and additional investigations such as 12-lead ECG, echocardiography, stress testing, and Holter

monitoring may be indicated in women with palpitations and suspected arrhythmias. The detailed plan should include management recommendations such as peripartum bacterial endocarditis prophylaxis, anticoagulation, surgical or angiographic interventions or repair as required, labor analgesia plans, recommended timing of delivery, optimal delivery mode, indications for postpartum hospitalization in a monitored bed and postpartum recommendations [2, 7, 27, 32]. Table 10.3 summarizes the drugs most commonly used during pregnancy and the peripartum period in women with heart disease.

Table 10.3 Drugs commonly used in women with heart disease during pregnancy and the peripartum period

Drug category	Drug name	FDA pregnancy category	Risk for mother	Risk for fetus
Vasopressors/ inotropes [1]	Norepinephrine	C	Increased PVR [4]	Target MAP to 70 mmHg to maintain adequate placenta perfusion pressure
	Epinephrine	C	Tachycardia	
	Phenylephrine	C	Increased PVR	Possible association with gastroschisis and hemifacial macrosomia
	Dopamine	C	Tachyarrhythmias	
Cardiac glycosides	Digoxin	C	Can be used throughout pregnancy	
Anticoagulants	Low molecular weight heparin	C	Possible maternal osteoporosis [1], maternal bleeding	
	Heparin	C	Possible maternal osteoporosis, monitor coagulation, bleeding, and signs of heparin-induced thrombocytopenia [1]	
	Warfarin[a]	D	Complicated dosing. Preferable dose ≤5 mg daily [33]	Coumarin embryopathy, bleeding Teratogenic during first trimester [1]
	Fondaparinux	B		
Antiarrhythmic	Metoprolol	C		Bradycardia and hypoglycemia in fetus [33]
	Carvedilol	C		Bradycardia and hypoglycemia in fetus [33]
	Atenolol	D		Hypospadias (first trimester), bradycardia and hypoglycemia, in fetus. Risk of IUGR mainly at second and third trimesters [1, 27] Serial fetal sonography recommended. Monitor for neonatal bradycardia
	Labetalol	C		Intrauterine growth retardation, neonatal bradycardia, and hypotension [34]
	Adenosine	C		No adverse effects reported [33]

(continued)

Table 10.3 (continued)

Drug category	Drug name	FDA pregnancy category	Risk for mother	Risk for fetus
	Amiodarone	D	Thyroid insufficiency, hyperthyroidism	Premature birth [33]
	Lidocaine	C		Fetal bradycardia, acidosis, central nervous system toxicity [1]
Vasodilators	Sildenafil	B		
	Nitroglycerine	B		
Diuretics	Furosemide	C		Oligohydramnion. Can result in uteroplacental hypoperfusion [35]
	Amiloride	B		
Antihypertensives	Acetylcholine Esterase inhibitors and Angiotensin II receptor blockers	D		Renal or tubular dysplasia, oligohydramnion, growth retardation, ossification disorders of skull, lung hypoplasia, contractures, large joints, anemia, intrauterine fetal death [1, 33]
	Hydralazine	C	Risk of hypotension, lupus-like symptoms	Fetal tachyarrhythmias [1]

MAP mean arterial pressure, *IUGR* intrauterine growth retardation, *FDA Class: A*—controlled studies showed no risk, *B*—no evidence of risk in controlled studies, *C*—risk cannot be ruled out, *D*—positive evidence of risk
[a]See recommended anticoagulation protocols, Table 10.5

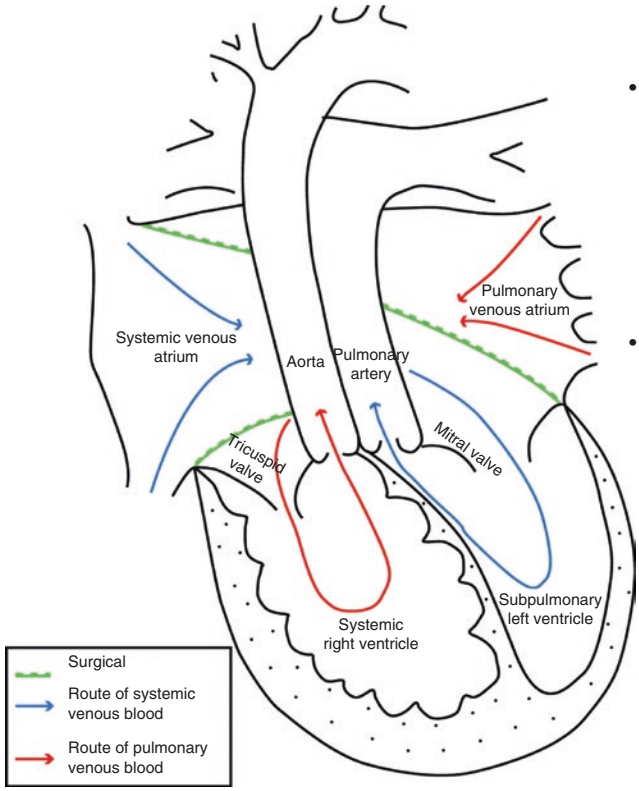
10.4.1 WHO III Congenital Heart Diseases

Systemic right ventricle—there are two main subtypes of systemic right ventricle [2, 7].

1. In dextro-transposition of the great arteries (D-TGA): the aorta arises from the right ventricle outflow tract, and the pulmonary artery arises from the left ventricle outflow tract. Without correction, most patients die during the first months of life. Until the mid-1980s, atrial switch operation (Mustard or Senning repair, Fig. 10.1) was the preferred repair procedure, where blood from the pulmonary veins was directed to the right ventricle which pumps it to the systemic vasculature, and blood from the vena cavae was directed to the left ventricle and the pulmonary arteries. This approach has been subsequently changed to arterial repair (late 1980s and 1990s); therefore, women younger than 30 years may have undergone the arterial repair where the arteries are switched to give rise to a normal circulation.
2. In congenitally corrected transposition of the great arteries (Levo-TGA or ccTGA): the ventricles are transposed; the left atrium is connected to the right ventricle which gives rise to the aorta. The right atrium is connected to the left ventricle which gives rise to the pulmonary arteries.

In both D-TGA postatrial switch or L-TGA, the right ventricle serves as the systemic pumping chamber. This puts the right ventricle under considerable strain, which may result in cardiac failure [33]. Arrhythmias are a major concern. These include sinus node and AV node dysfunction, tachyarrhythmias and brady-arrhythmias [28].

During pregnancy and childbirth, the systemic ventricle is exposed to considerable strain due to dramatic alterations in intravascular volume [7, 36]. The systemic vascular resistance falls, and cardiac output increases secondary to an increased heart rate and stroke volume. A systemic right ventricle may not adequately respond to the



Repair for simple transposition of the great arteries.

- Schematic representation post-Mustard or Senning repair for simple transposition of the great arteries (atrioventricular concordance, ventriculo-arterial discordance). Pulmonary venous blood is directed to the aorta via a morphological tricuspid valve and a systemic right ventricle, and systemic venous blood is directed to the pulmonary artery via a morphological left ventricle.
- **Adapted from SA Thorne. Heart 2004;90: 450-456. With permission from the BMJ Publishing Group Ltd.*

Fig. 10.1 Repair for simple transposition of the great arteries. Schematic representation post-Mustard or Senning repair for simple transposition of the great arteries (atrioventricular concordance, ventriculo-arterial discordance). Pulmonary venous blood is directed to the aorta via a morphological tricuspid valve and a systemic right ventricle, and systemic venous blood is directed to the pulmonary artery via a morphological left ventricle. (*Adapted from SA Thorne. Heart 2004;90:450–456. With permission from the BMJ Publishing Group Ltd.)

demands placed upon it during pregnancy, resulting in symptomatic cardiac failure. Importantly, a "healthy" left ventricle may tolerate high pulmonary pressures, and a high pressured left ventricle may be beneficial to the adjacent systemic right ventricle. In a multicenter study, Canobbio et al. [23] reported cardiac complications among 36% of 70 pregnancies in women who had undergone atrial switch operations. The main complications were arrhythmias, heart failure, and hemoptysis.

10.4.2 Management of Pregnancy with Systemic Right Ventricle

Preconception. Evaluation of the patient with surgically corrected D-TGA or with L-TGA should include echocardiogram, cardiopulmonary exercise testing, and Holter monitoring for evaluation of the ventricular and valvular function and to assess the presence of arrhythmias [7, 23]. Pregnancy is not advised in women with moderate-to-severe ventricular dysfunction (NYHA class III or IV).

During pregnancy. Baseline BNP may be useful as an indicator of ventricular overload. In women with a history of arrhythmias, Holter monitoring should be performed in cases of symptomatic palpitations. Asymptomatic stable women may be followed up every 4–6 weeks in the second trimester and every 2–4 weeks in the third trimester. They should be discouraged from performing strenuous exercise, should restrict their dietary sodium, and should report increasing

peripheral edema or dyspnea [7]. Due to an increased risk of brady-arrhythmias and AV nodal block, beta-blockers should be used very carefully if at all. In the event of symptomatic heart failure or life-threatening arrhythmias, induction of labor should be strongly recommended, especially if gestational age is greater than 37 weeks. At a lower gestational age, risk benefit assessment should guide decision-making by prioritizing the mother's health. Delivery planning should include an anesthetic regimen in the event of Cesarean section and regional anesthesia for pain relief.

Intrapartum. Recommendations for monitoring during active labor include pulse oximetry and cardiac rhythm monitoring, usually with a 3-lead ECG. Vaginal delivery with a facilitated second stage of labor and neuraxial anesthesia is the preferred delivery approach. Neuraxial anesthesia is recommended to minimize hemodynamic changes during labor. Women with a history of arrhythmias or who have had documented arrhythmias during pregnancy should be placed on continuous cardiac monitoring (direct or telemonitoring) throughout labor, delivery, and the postpartum period.

Postpartum. Increased postpartum maternal blood volume (autotransfusion) may result in clinical heart failure even if there were no signs of heart failure during pregnancy. Stroke volume and cardiac output increase immediately by up to 80% after vaginal delivery [7]. For that reason, close cardiac monitoring for the first 48 h postdelivery is warranted [28, 33], with increased vigilance for the requirement of diuretic treatment, followed by observation for another 3–5 days postdelivery, due to the likelihood of volume overload or arrhythmias. Women with signs of significant heart failure or predisposition to arrhythmias will require monitoring in the ICU, with continuous pulse oximetry and telemetric cardiac monitoring. Invasive hemodynamic monitoring is rarely required. High-risk patients will require monitoring and management in an intensive care unit for the first 24–48 h after delivery. Filtered vascular lines should be used in order to prevent paradoxical air embolism. The hemodynamic effects of pregnancy typically resolve within 6–12 weeks postpartum but may persist for up to 6 months [37]; therefore, discharge planning should include follow-up visits with routine postpartum and cardiac evaluation.

See below for the treatment of heart failure and arrhythmias during pregnancy and postpartum.

In conclusion, pregnancy in women with a systemic right ventricle carries a risk of both maternal and neonatal complications. The long-term effect of pregnancy on the systemic right ventricle is unclear, although there are studies suggesting damaging effects. One study recommended discouraging multiple pregnancies in women with a systemic right ventricle due to the potential deleterious effects of pregnancy [28].

10.4.3 Cyanotic Heart Disease Without Pulmonary Hypertension

Cyanosis in CHD patients usually indicates the presence of right-to-left shunt at the atrial, ventricular, or arterial level. As pregnancy progresses, the systemic vascular resistance decreases, thereby causing an increase in the right-to-left shunt and worsening hypoxemia [38]. In cases of documented right-left shunt, as in cases with septal defects and pulmonary hypertension or stenosis in the pulmonary outflow or arteries, systemic pressures must be maintained. It is important to remember that right-to-left shunting may increase if the systemic vascular resistance decreases or the pulmonary vascular resistance increases. This can occur, for example, during the use of prostaglandin analogues, thus leading to worsening hypoxemia and an increase in the risk of maternal and fetal death [7]. Cyanotic CHD is usually corrected during childhood, but some women with uncorrected or palliated lesions reach childbearing age. Most patients have compensatory polycythemia and coagulation abnormalities. The main maternal pregnancy complications anticipated are heart failure, pulmonary or systemic thrombosis, arrhythmias, and infective endocarditis [38]. These complications have been reported to occur in 30% of cyanotic pregnant patients [33]. In a recent study,

Ladouceur et al. reviewed 71 pregnancies in 31 cyanotic women without pulmonary hypertension and with oxygen saturation of 89 ± 2%. There were no patient deaths during pregnancy or the postpartum period. Cardiovascular complications occurred in 27% of completed pregnancies. These included heart failure, supraventricular tachycardia, and worsening hypoxemia. No maternal baseline characteristic was predictive of cardiovascular complications [39].

10.4.4 Management of Pregnancy with Cyanotic Heart Disease Without Pulmonary Hypertension

Preconception. Detailed knowledge of the specific cardiac lesion, surgical procedures, and other interventions, and most recent cardiac evaluations should be examined. The degree of maternal hypoxemia is the most important predictor of maternal and fetal outcome. If resting oxygen saturation is below 85%, the risk of maternal and fetal mortality is expected to be substantial, and pregnancy is contraindicated. When resting maternal blood saturation is 90% or higher, fetal outcome is acceptable (10% fetal loss), and maternal risk is lower. If resting oxygen saturation is 85–90%, it is advisable to measure oxygen saturation during exercise. If the saturation decreases significantly and early, pregnancy carries a poor prognosis for the mother and fetus, and patients should be advised to avoid pregnancy [7, 38].

During pregnancy. Recommendations include restriction of physical activity that will lead to dyspnea or hypoxia and use of supplemental oxygen as necessary [40]. Supplemental oxygen is unlikely to significantly improve saturations or maternal outcomes due to shunting, but it may slightly increase oxygen delivery to the placenta. Red blood cell mass is increased as a compensatory response to cyanosis, causing increased blood viscosity; in addition, the prothrombotic state of pregnancy enhances the risk of clot forming and thrombosis. As a result, these women have a particularly increased risk of both thrombosis and hemorrhage [40]. The reduced resistance on the systemic vasculature poses an increased risk of paradoxical embolism. Unless specifically contraindicated, prophylactic treatment with heparin or low molecular weight heparin [7, 33] should be prescribed. This is particularly important for women assigned to prolonged bed rest or suffering from arrhythmias. See below for anticoagulation protocols.

Delivery. Anesthesia should be planned carefully in view of the elevated risks in this particular population. Ideally, an obstetric anesthesiologist should be consulted at the beginning of pregnancy as in all cases of complex CHD. Vaginal delivery is advised in most cases [7] with neuraxial anesthesia techniques that have the advantage of blunting the hemodynamic response to labor, especially during the second stage [41]. In planned elective cesarean delivery, a neuraxial anesthesia technique with monitored incremental induction may be associated with better maternal outcomes [33, 34]. Particular attention should be given to prevention of venous air embolism. Right-to-left shunting makes air embolism a life-threatening complication from intravenous infusions [42]; special attention and care should be given to prevent air bubble entrance to the circulation through any line. Volume status should be carefully monitored during labor and postpartum, taking into consideration the cardiac lesion present, as these patients are at risk of both volume depletion and volume overload. An emergency plan should be made for early cesarean delivery should maternal decompensation occur or if there are signs of fetal distress. For anesthesia choice, the impacts of changes in venous return, myocardial function, heart rate, and afterload on the specific lesion should be clearly understood in order to create a suitable anesthesia plan.

Postpartum. The critical period for major cardiovascular events postpartum is the first 24–48 h after delivery, as a result of the increase in maternal blood volume following delivery, which may lead to worsening heart failure. Therefore, close cardiac monitoring and follow-up in the intensive care setting are advised. Ideally, this should continue for up to 3–5 days postdelivery, as signs of heart failure may take time to develop [33]. Close monitoring for postpartum hemorrhage is advised, as anemia may reduce oxygen delivery.

Cyanotic patients need higher hemoglobin concentration; a "normal" hemoglobin level may not provide the required oxygen-carrying capacity. Early mobilization with support stockings may reduce the risk of thromboembolism. Cardiology follow-up should be scheduled within 1–2 weeks from discharge [7].

10.4.5 Single-Ventricle Physiology/ Fontan Palliation

The "Fontan procedure" is a palliative surgical procedure used in patients with univentricular hearts. To date, this operation is performed in children 2–4 years of age. Women in their late 20s and 30s may have undergone the Fontan procedure at an older age. In the Fontan procedure, systemic venous blood is routed to the pulmonary arteries either by connecting the right atrium to the pulmonary arteries (in older patients) or via a tube inserted into the right atrium or via an extracardiac tube (in younger patients) [43]. Either way, the end result is that deoxygenated systemic venous flow is directed to the pulmonary arterial circulation, thus alleviating cyanosis (Fig. 10.2). As there is no sub-pulmonary pumping chamber, pulmonary flow stems from the small pressure gradient between the systemic veins and the pulmonary veins [2]. There is limited capacity to increase cardiac output on demand, thus relying on elevated central venous pressures. This unique hemodynamic setup leads to long-term sequelae related to chronically elevated systemic venous pressure, diminished cardiac output, and cardiac reserve [43, 44]. Years after the procedure, the main complications

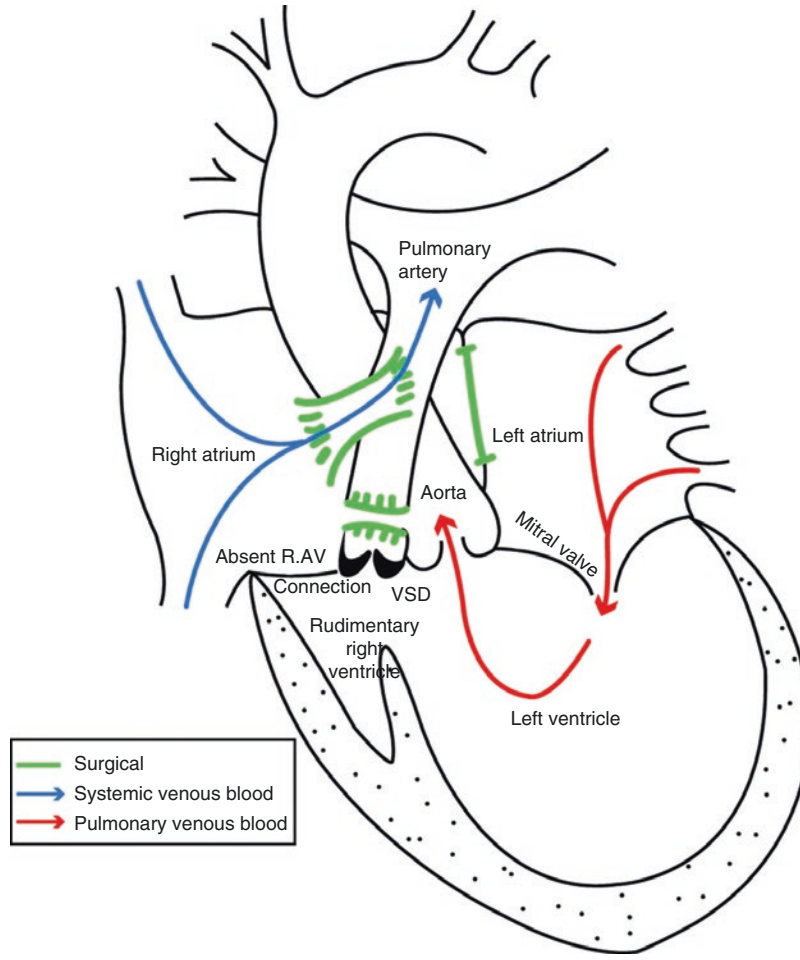


Fig. 10.2 Fontan procedure for tricuspid atresia. Schematic representation of Fontan operation (atriopulmonary connection). The atrial septal defect is closed, thus separating the systemic and pulmonary circulations, the pulmonary artery is ligated and an anastomosis is formed between the right atrium and the pulmonary artery. (*Adapted from SA Thorne. Heart 2004;90:450–456. With permission from the BMJ Publishing Group Ltd.)

are arrhythmias, reduced functional capacity resulting from impaired ventricular function or atrioventricular valve regurgitation, protein-losing enteropathy, thromboembolism, portal hypertension, and liver dysfunction [45]. Compared to pediatric Fontan patients, adults with symptomatic heart failure demonstrate higher central venous pressures but lower systemic vascular resistance, as well as pathological signs of liver disease suggestive of portal hypertension [46].

In single-ventricle physiology, the response to manipulation of preload, afterload, and contractility is abnormal. These patients are very sensitive to changes in preload, as hypovolemia can result in severe hypotension. One of the most difficult aspects of treatment in a patient with single ventricle and shock is fluid management. It is critical to maintain venous return. Hypovolemia and decreased venous tone during critical illness may cause severe hypotension, as high venous pressures are required to maintain cardiac output. On the other hand, hypervolemia from overzealous fluid resuscitation can result in a decreased pressure gradient between systemic arterial and venous systems, thus reducing cardiac output. Similarly, the effect of increased afterload due to vasoconstriction may reduce cardiac output. Resuscitation to very specific targets like CVP or right atrial pressure and continuous hemodynamic monitoring are often required [42].

Single-ventricle physiology presents a unique challenge in the setting of pregnancy given the obligatory increase in heart rate, cardiac output, and plasma volume. Initially, the fixed low cardiac output and decreased blood flow to the uterus and placenta could result in intrauterine growth retardation and a compromised fetal status [47]. Later on, increased plasma volume may lead to heart failure, arrhythmias, and ascites. The thrombogenic state in pregnancy may lead to Fontan pathway and pulmonary artery thrombosis and stroke [48].

Figure 10.3 Summarizes the evaluation required for patients with Fontan physiology and low cardiac output.

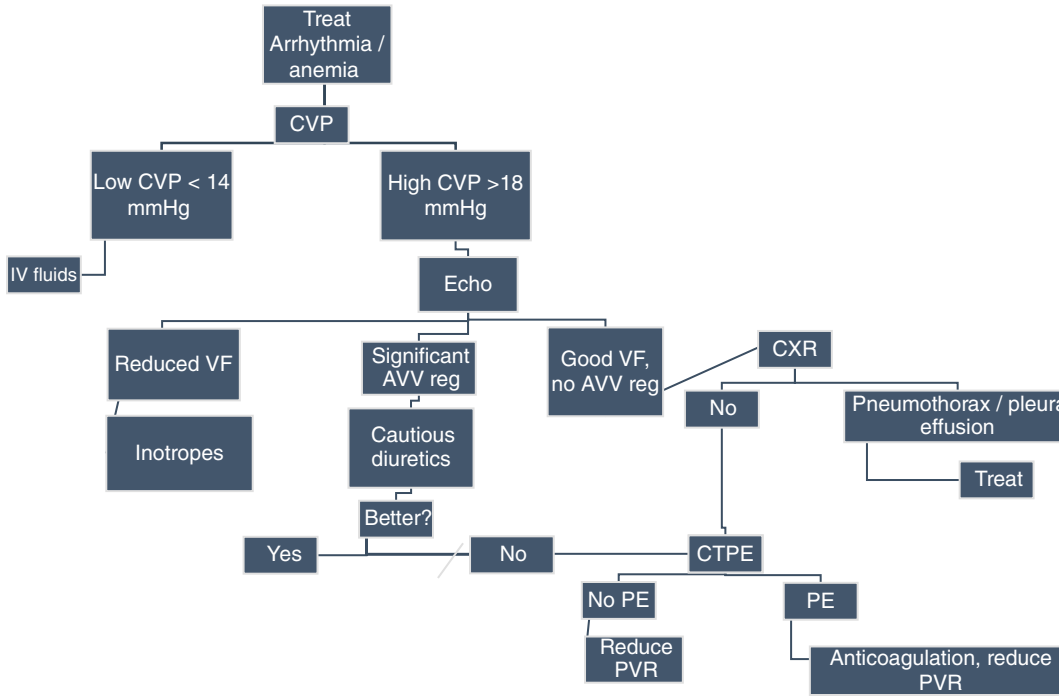


Fig. 10.3 Management guidelines for pregnant women following Fontan procedure presenting with low cardiac output. *CVP* central venous pressure = pulmonary artery pressure in Fontan. Extrapolated from non-pregnant Fontan patients. (** As there may be preferential flow from IVC to one lung and SVC to the other, hand injection of contrast may give a false diagnosis of pulmonary embolism.) *VF* ventricular function, *AV valve reg* atrio ventricular valve regurgitation, *PE* pulmonary embolism, *PVR* pulmonary vascular resistance

10.4.6 Management of Pregnancy with Single-Ventricle Physiology/Fontan Palliation

Preconception. The patient planning to conceive must be informed that pregnancy and delivery are not without risk, fetal loss is high, and that early delivery may be necessary if maternal decompensation occurs [18, 48]. The preconception evaluation should address ventricular function, valve function, the risk for arrhythmia, O_2 saturation, and pulmonary artery pressures. In clinically stable women with good ventricular function and no arrhythmia, the risk of pregnancy in the setting of Fontan physiology is not very high and may be well tolerated, including normal vaginal delivery [28]. However, the risk for fetal loss (30%) and early delivery are significantly greater in women after the Fontan palliation. BNP may be a signal for cardiac failure, and an elevated level is correlated with NYHA stage of cardiac function.

During pregnancy. Follow-up is recommended every 4 weeks to assess ventricular function and signs of congestive heart failure [33]. Treatment with Acetylcholine Esterase inhibitors should be stopped. If anticoagulation is indicated in these patients, substituting heparin for warfarin in the first trimester is a good option. Atrial and ventricular arrhythmias are a special area of concern in patients with Fontan circulation, mainly in those with the right atrial to pulmonary artery connections (*see below*). Other cardiac events to be prepared for are venous or arterial thromboembolic events and heart failure [17].

Delivery. A detailed delivery plan should be developed with a multidisciplinary team including both surgical and anesthetic regimens. Because of the vasoplegic effect of anesthesia, blood pressure monitoring is crucial, and vasoconstrictive drugs (e.g., phenylephrine) should be prepared. If the patient has become symptomatic, induction of labor should be considered after week 38 or earlier as indicated by clinical presentation. Both neuraxial and general anesthesia techniques have been described for these patients. One case report presented emergency general anesthesia for cesarean in one pregnancy followed by neuraxial anesthesia for a subsequent elective cesarean delivery [49]. Cesarean delivery should be performed in cases of severe cardiac insufficiency or uncontrolled arrhythmias [28]. Cardiac function and filling pressures should be assessed using a central venous catheter, which acts as a pulmonary artery catheter in women with Fontan [47]. During delivery, central venous pressure increases, and cardiac output decreases. Fluid shifts that may cause systemic congestion should be anticipated [50, 51]. Therefore, treatment of volume overload should be considered, using drugs such as furosemide. However, it is important to maintain adequate preload for passive pulmonary blood flow, as patients with Fontan physiology poorly tolerate hypovolemia and low central venous pressure. The balance between prevention of heart failure due to volume overload and suppression of cardiac output because of low preload is very difficult to maintain [47]. Patients with poor ventricular function or arrhythmia may not tolerate labor well. Peripartum ICU admission is recommended for these women. Hypercarbia, hypoxia, and acidosis should be avoided, and the use of a noninvasive cardiac output monitoring device should be considered.

Postpartum. Guidelines suggest 24–48 hours of postpartum ICU observation for all Fontan circulation women after delivery [7]. Mechanical ventilation may increase pulmonary pressure and be deleterious for Fontan patients; however, some form of ventilator support may be required in severe cases of heart failure. In such cases, noninvasive positive pressure ventilation may be preferred, and pulse contour cardiac output monitoring should be considered.

10.4.7 Valvular Heart Disease in Pregnancy

10.4.7.1 Rheumatic Heart Disease

Rheumatic heart disease is still encountered in developing countries and in disadvantaged populations in developed countries [52–54]. Acute

rheumatic fever causes mainly mitral and aortic regurgitation. Mitral stenosis may ensue years after the acute attack, causing secondary pulmonary hypertension. Although it may have significant implications for maternal health, maternal and fetal death is low [35]. Other causes of valvular heart disease during childbearing age include mitral valve prolapse, prior endocarditis, Marfan syndrome, and autoimmune diseases involving the heart [20]. In the developed world, valvular heart disease accounts for 25% of pregnant women with heart disease and is second only to congenital heart disease [10]. More women reach childbearing age following valve replacement surgery, which poses further pregnancy-related risks, including prosthetic valve malfunction, the need for anticoagulation, and thrombotic complications [54].

Ideally, diagnosis and risk assessment should be performed prior to pregnancy, based on functional capacity, severity and type of valve disease, left ventricular function, and pulmonary pressures. Moderate and high-risk women should be referred to high-risk obstetrics centers with a Pregnancy Heart Team where pregnancy outcomes may be optimized by care throughout the pregnancy [1, 20, 27, 28, 55].

Because of the decline in systemic resistance which occurs during pregnancy, regurgitant lesions are usually better tolerated than stenotic lesions during pregnancy and labor [4, 56]. Because left-sided pressure differences are higher and therefore more prone to acute decompensation, severe left-sided stenotic lesions are the most important lesions to diagnose, evaluate, and treat before conception, during pregnancy, and peripartum. Table 10.4 summarizes the maternal risk classification of pregnancy in women with valvular heart disease.

Table 10.4 Maternal risk classification of pregnancy in women with valvular heart disease

Low risk
Mitral stenosis: mean gradient <5 mmHg, valve area > 1.5 cm^2, no pulmonary hypertension
Mitral or aortic regurgitation: asymptomatic
Aortic stenosis: mean gradient <25 mmHg, valve area > 1.5 cm^2, ejection fraction >50%, asymptomatic
Bioprosthetic valve: asymptomatic
High risk
Mitral stenosis: mean gradient >10 mmHg, valve area < 1 cm^2, NYHA II–IV
Mitral or aortic regurgitation: NYHA III–IV
Aortic Stenosis: mean gradient >40 mmHg, valve area < 1 cm^2
Marfan syndrome: aortic diameter > 4 cm
Prosthetic mechanical valve
Severe pulmonary hypertension

10.4.7.2 Simple Valvular Lesions

The most commonly observed valve lesions in pregnant women are simple valvular lesions such as mitral or aortic stenosis or regurgitation [57]. With proper preventive management and treatment during pregnancy, many of the women with such lesions are not seen in the ICU. However, ongoing neglect based on a single pre-pregnancy assessment suggesting low risk may ultimately endanger the life of the mother and, secondarily, that of the unborn child [55].

10.4.7.3 Mitral Stenosis

Mitral stenosis (MS) is the most common acquired valvular lesion in pregnant women [55, 56] and is a leading cause of maternal morbidity. Maternal mortality in women with mitral stenosis is estimated between 0 and 3% [5].

Symptoms are more likely to occur in women with moderate-to-severe stenosis, with a valve area of less than 1.5 cm^2. Reported rates of pulmonary edema in pregnant women with mild, moderate, and severe MS range between 11 and 24%, 34 and 61%, and 56 and 78%, respectively [1, 58]. The increased stroke volume and tachycardia during pregnancy cause decreased ventricular filling duration and increased left atrial pressure, which result in pulmonary congestion leading to pulmonary edema [2, 28, 55]. Cardiac function may further deteriorate if atrial fibrillation or other tachyarrhythmias occur; this occurs due to the additional decrease in filling time, thus reducing preload and cardiac output. Due to the increase in blood volume during pregnancy, diastolic dysfunction worsens [56, 57]. Symptoms peak at 20–30 weeks gestation, but the risk of

decompensation and pulmonary edema continues throughout the third trimester leading up to the time of delivery[54, 58]. NYHA class has been reported to deteriorate during pregnancy by 1–2 levels in 74% and 40% of women, respectively [54]. During labor and delivery, cardiac output increases due to pain-induced catecholamine release and uterine contractions. These can be alleviated with epidural anesthesia [57]. Volume shifts are also expected, as some blood loss is usual (500 mL with vaginal delivery and 1000 mL with cesarean delivery). However, immediately after delivery, there is a dramatic increase in cardiac output (as high as 80%) because of massive autotransfusion of uterine blood volume and increased vascular resistance. These may lead to decompensated cardiac failure and may last for 2 weeks to even 6 months postpartum [57].

Preconception. Risk assessment should be performed (Table 10.4). Low maternal risk is associated with a mean gradient of less than 5 mmHg and a valve area of greater than 1.5 cm^2 with no evidence of pulmonary hypertension. High risk is associated with a mean gradient >10 mmHg a valve area < 1 cm^2 and NYHA II–IV [54]. A careful history should be taken looking for symptoms such as resting dyspnea, cough, chest pain, or palpitations [20]. Physical examination may reveal a diastolic murmur and signs of heart failure, and electrocardiography may show signs of left atrial enlargement, ventricular hypertrophy, and arrhythmias. Echocardiography is indicated to assess valvular and cardiac function, as well as pulmonary artery pressures. Procedural interventions such as mitral valvuloplasty are indicated in patients with moderate-to-severe stenosis and valve area < 1.0 cm^2 and in those with signs of significant pulmonary hypertension; these should be performed prior to a planned pregnancy [27, 33, 54].

During Pregnancy. High-risk women should be followed up in specialized centers with a Pregnancy Heart Team [27]. Clinical and echocardiographic follow-up is indicated at close intervals. In cases of moderate-to-severe stenosis, monthly or bimonthly follow-up is indicated. In patients with mild stenosis, evaluation is recommended every trimester and prior to delivery [33]. Treatment goals are primarily to diagnose and treat any condition that may worsen the mother's clinical status such as fever, infection, or anemia, to decrease the heart rate in order to prolong filling times, to reduce preload, and to maintain perfusion [20, 59]. When symptoms of heart failure or pulmonary hypertension appear, treatment includes restriction of physical activity, oxygen supplementation, rate control with selective beta-blockers or digoxin (targeting about 60–80 bpm), diuretics, and antibiotics as required. Women with pulmonary edema should be admitted and treated with intravenous beta-blockers and diuretic agents. In cases of arrhythmias, antiarrhythmics are indicated in order to avoid cardiac decompensation, and DC cardioversion may be used if arrhythmias cause hemodynamic compromise. Transesophageal echocardiography should be used in order to rule out left atrial thrombosis prior to cardioversion, as this is a contraindication [1, 54]. Anticoagulation with low molecular weight heparin or intravenous unfractionated heparin may be required in the presence of arrhythmias, an enlarged left atrium, left atrial thrombosis, low cardiac output, or prior embolism [33].

See below for the treatment of heart failure, arrhythmias, and anticoagulation.

Balloon mitral valvuloplasty should be considered when the mother cannot proceed to term because of hemodynamic instability and severe symptoms, despite medical therapy, usually if the valve area is less than 1.5 cm^2 or pulmonary artery pressures are more than 50 mmHg [1, 2, 33, 55]. This procedure is preferably performed after 20 weeks gestation in patients with NYHA class III–IV [2, 36, 60]. Optimized radiation dose with short screening times and abdominal lead shields should be used. Overall results have been favorable [61]; mitral regurgitation may develop following valvotomy, but this is usually well tolerated [55].

Delivery. Vaginal delivery is preferred among patients with mild disease and those without pulmonary hypertension. The second stage of labor should be assisted using forceps or vacuum in order to minimize valsalva maneuvers [54]. Patients with severe disease (NYHA III–IV) and

pulmonary hypertension, as well as those requiring mechanical ventilation or have obstetric indications, should be referred to Cesarean section [57]. The need for monitoring depends on the severity of the disease. In cases of significant stenosis and arrhythmias, telemetric monitoring during delivery is required, as well as blood pressure monitoring, pulse oximetry, and fetal monitoring [20]. Occasionally, a pulmonary artery catheter may need to be inserted in order to measure cardiac output and pulmonary artery pressures. During labor and delivery, heart rate should be targeted at 90–100 bpm using pain management and beta-blockers. Optimal fluid balance is challenging, as preload is required for cardiac function, but fluid overload may exacerbate heart failure. The administration of antibiotic prophylaxis is debatable, but most opinions are supportive, as the risk of antibiotic prophylaxis is smaller than the complications of endocarditis [20, 59].

Postpartum. High-risk women should be monitored in intensive care or cardiac care units for at least 24 h due to expected fluid shifts. Anticoagulation may be resumed where indicated if there is no evidence of postpartum hemorrhage. Cardiac follow-up should be performed at 4–6 weeks postpartum in order to assess cardiac function and to adjust medical treatment.

10.4.7.4 Aortic Stenosis

The most common cause of aortic stenosis in women of childbearing age is congenital bicuspid aortic valve, which occurs in about 2% of the population [54, 55]. Women may be asymptomatic even with severe disease, with signs appearing only during pregnancy. The stenotic valve obstructs blood flow into the aorta; thus cardiac output is fixed and depends on preload. The balance between reduced filling causing under-perfusion and hypervolemia causing pulmonary edema is therefore very fragile. Complications of aortic stenosis include angina, syncope, and congestive heart failure [20, 54]. Further risks for the mother include arrhythmias and cardiovascular events such as myocardial infarction and stroke. Mortality is estimated at 2.5% [15]. Fetal risk includes preterm birth, intrauterine growth retardation, and low birth weight in up to 25% of cases with moderate and severe stenosis [33, 62].

Preconception. All women with known aortic stenosis should undergo assessment of aortic valve dimension using echocardiography prior to conception [33]. Exercise testing can be used to evaluate exercise tolerance, blood pressure changes, arrhythmias, and the need for intervention [63]. Low maternal pregnancy risk includes patients with a good exercise tolerance, a normal blood pressure rise, mean gradient of less than 25 mmHg, valve area greater than 1.5 cm^2, an ejection fraction >50%, and asymptomatic patients. High-risk patients include those with an ejection fraction <40%, mean gradient greater than 40 mmHg and a valve area < 1 cm^2 [55] (Table 10.4). Patients with bicuspid aortic valves may occasionally also suffer from dilatation of the ascending aorta, thus predisposing these women to increased aortic stress during pregnancy and an increased risk for aortic dilatation and dissection, especially in the third trimester. An aortic root diameter of greater than 40 mm is a risk factor for dissection [54]. Asymptomatic women with severe stenosis may tolerate pregnancy with conservative treatment and close follow-up. Women who are high risk, who have a reduced LV ejection fraction of less than 50%, and/or who are symptomatic before pregnancy should be discouraged from pregnancy until they undergo valvuloplasty or surgery prior to conception [27]. Aortic root repair is indicated in women who have an aortic diameter greater than 50 mm [54, 63].

During pregnancy. Follow-up of pregnant women with significant aortic stenosis requires the coordination between a congenital heart disease specialist, an obstetric anesthesiologist and a high-risk obstetrician in a specialized center. Pregnant women with asymptomatic or minimally symptomatic aortic stenosis may be managed conservatively with recommendation for reduced exertion, beta-blockers, and oxygen if required. Follow-up should include monthly or bimonthly echocardiographic evaluation of the ascending aorta and aortic valve until delivery [54]. It is recommended that women with

an aortic diameter larger than 40 mm receive beta-blockers. Symptomatic aortic stenosis during pregnancy often requires prompt medical and occasionally interventional therapy [1, 40, 57]. Medical management includes bed rest, rate control with beta-blockers or non-dihydropyridine calcium channel antagonists, treatment of aggravating conditions, and cautious diuresis if indicated. Afterload-reducing agents may be hazardous, due to the fixed cardiac output through the aortic valve. Pulmonary edema should be treated with diuretic agents; however, hypovolemia, which may cause hypotension and decreased maternal organ perfusion due to a fixed cardiac output, should be avoided. Sinus rhythm should be restored in women who develop arrhythmia. In stable patients, medical therapy of the arrhythmia is an option (see Table 10.3). In hemodynamically unstable patients, cardioversion should be performed [64]. In patients who are symptomatic despite medical management, percutaneous valvulotomy may be indicated in non-calcified valves with minimal regurgitation, preferably prior to delivery [61, 65]. This procedure is associated with maternal and fetal morbidity, and the rate of restenosis and aortic regurgitation is not negligible. Surgical valve replacement is reserved for women in critical condition, such as shock with reduced cardiac output and signs of organ decompensation or intractable pulmonary edema who cannot undergo percutaneous valvulotomy. This should preferably be performed immediately post-cesarean delivery, as this procedure is associated with significant fetal death [20, 66]. Care should be taken to minimize post-surgical hemorrhage associated with full anticoagulation.

Delivery. Labor and delivery should be planned in advance with a multidisciplinary team of cardiologists, obstetricians, and anesthesiologists. In mild to moderate disease, vaginal delivery is preferred, with minimal reduction in systemic vascular resistance during anesthesia and assisted second stage. It has been recommended that severe, symptomatic cases undergo cesarean delivery with general anesthesia, although neuraxial anesthesia has also been reported [33, 67].

10.4.8 Mitral and Aortic Regurgitation

In the childbearing age, these valve disorders are most commonly due to rheumatic or congenital lesions but may also be associated with infective or autoimmune diseases [33]. Mitral valve prolapse is a leading cause of mitral regurgitation in this age group and is associated with connective tissue weakening [54]. Previous valvulotomy may occasionally be a causative factor. As stated earlier, as a result of reduced systemic vascular resistance during pregnancy, left-sided regurgitant lesions are usually less symptomatic than stenotic lesions and have good clinical outcomes [1, 54]. Complication rate is small and is usually due to severe regurgitation or the development of dilated cardiomyopathy and congestive heart failure.

Preconception. A thorough medical history and physical examination is required, together with an electrocardiogram and transthoracic echocardiography, to assess valvular and cardiac function. In moderate-to-severe regurgitation, exercise testing is recommended [33]. In severe cases of mitral valve regurgitation, surgery may be required; however repair is usually preferred in order to avoid the need for anticoagulation [61].

During pregnancy. Women with regurgitant left-sided valves should be followed up by a multidisciplinary team of cardiologists, anesthesiologists high-risk obstetricians. As long as left ventricular function is maintained, only follow-up is required: every trimester in mild to moderate regurgitation and more often in severe regurgitation [33]. Once signs of ventricular failure appear, medical treatment is usually indicated, as pregnancy-related volume overload may exacerbate pulmonary congestion (Table 10.3). This includes diuretics, beta-blockers, and vasodilators such as nitrates and hydralazine. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are contraindicated in pregnancy due to teratogenicity [57]. Physical activity should be restricted as well as sodium intake. In cases of severe chronic mitral regurgitation, left atrial enlargement may occur, and predispose women to arrhythmias, in which case antiarrhythmics and anticoagulation, may be indicated (see below) [54]. In cases of severely reduced left ventricular

failure, inotropic support may be required. Acute valvular regurgitation is poorly tolerated; acute mitral regurgitation, as a result of a ruptured chordae, will present with cardiogenic shock and pulmonary edema. In such cases, initial stabilization may require intra-aortic balloon pump placement and referral for urgent surgery [20]. Acute aortic valve regurgitation, as may occur in cases of infective endocarditis or aortic dissection, is a surgical emergency [20, 57]. Maternal morbidity and mortality during cardiopulmonary bypass may be higher than in nonpregnant women, depending on the type of surgery and severity of disease; fetal morbidity and mortality remain high as well [68]. At 26 weeks gestation, both fetal mortality and neurological impairment are estimated at 20% [33, 68]. It is therefore recommended that beyond 26 weeks, cesarean delivery is performed prior to cardiac surgery.

Delivery. Vaginal delivery is preferable with epidural anesthesia, and a shortened second stage is advisable [33]. As in all cases of clinically significant heart disease, the obstetric anesthsiologist should be part of the team following the patient from the outset. Severe cases of decompensated heart failure may require cesarean delivery.

10.5 Marfan Syndrome

This autosomal dominant hereditary connective tissue disease has an estimated prevalence of 1:5000. Most patients have cardiovascular involvement, including aortic regurgitation, dilatation, and mitral and tricuspid involvement [69]. Aortic disease, mostly involving the thoracic aorta, predisposes to aortic aneurysm and dissection, which leads to a high risk for morbidity and mortality [69, 70]. See Table 10.4.

Preconception. Pregnancy poses a high risk for worsening of diseases of the aorta due to hemodynamic changes, such as increased blood volume and heart rate as well as hormonal changes, leading to increased maternal mortality [33, 70, 71]. Therefore, all women with diagnosed Marfan syndrome or dilated aortic root are at risk during pregnancy and should be counselled accordingly prior to conception. Imaging of the entire aorta using magnetic resonance imaging (MRI) or computerized tomography (CT) scans should be performed. Echocardiography (transthoracic or transesophageal) should enable assessment of left ventricular function, diameter of the aortic root, and the ascending and descending aorta [69].

The risk of dissection is about 1% in the absence of aortic root dilatation [55]. An aortic root diameter of 4 cm and over, or an increasing aortic root diameter during pregnancy, carries up to 10% risk of dissection [55, 69]. With an aortic root diameter of over 4.5 cm, pregnancy without prior repair should be discouraged [20, 27]. Aortic dissection occurs mostly in the third trimester or in the early postpartum period [70]. Repair of aortic dissection during pregnancy carries a significant risk for fetal loss; therefore aortic root replacement should ideally be conducted electively before pregnancy if indicated [61, 70]. Women with an aortic root diameter of more than 4.5 cm should be considered for surgical correction prior to pregnancy [33, 61, 72]. Pregnancy in women with Marfan syndrome is associated with a high rate of obstetric complications, such as premature delivery, premature rupture of membranes, intrauterine growth retardation, and neonatal mortality [69, 72]. Maternal and fetal risk should be evaluated by a multidisciplinary team including a cardiologist, obstetrician, and genetic specialist. The woman needs to be informed of the risk of dissection throughout pregnancy and the peripartum period, and that even a normal aortic root diameter does not guarantee an uneventful pregnancy.

During pregnancy. Women should be followed up by a cardiologist, an anesthsiologist and a high-risk obstetrician. Echocardiography should be performed at 4 to 8-week intervals during pregnancy according to aortic diameter and at 3–6 months postpartum [69]. Women who had surgical correction of the aortic dilatation are still at higher risk for dissection and should be monitored as well. Treatment with selective beta-blockers such as metoprolol is indicated throughout pregnancy as they reduce the shear forces acting on the aortic root, thereby decreasing the rate of aortic dilatation and dissection [27, 33, 69, 70]. Beta-blocker dose should be titrated to reduce heart rate by at least 20 bpm with close

follow-up of intrauterine growth. Hypertension should be prevented using vasodilative drugs (Table 10.3). In cases of increasing aortic diameter during pregnancy, aortic repair should be performed either with the fetus in utero or following Cesarean delivery. Because of their high morbidity and the risk for postoperative bleeding, these procedures should be performed in specialized centers with adult cardiothoracic and neonatal intensive care facilities [69]. There has been a decrease in maternal and fetal mortality in these cases, with reported maternal mortality decreasing from 30% in the 1990s to 0% in 2004 [36]. Aortic dissection during pregnancy is a surgical emergency and requires the cooperation of a multidisciplinary team, including urgent Cesarean delivery by specialist anesthesiologists, obstetricians, and neonatologists, followed by urgent aortic repair by cardiothoracic surgeons [69].

Delivery. Vaginal delivery is recommended in women with an aortic diameter of less than 4 cm. This should ideally be performed under beta-blocker treatment and epidural anesthesia in order to reduce hypertension, pain, and stress during labor. Assisted shortening of the second stage of labor is also recommended. In cases where the aortic diameter exceeds 4.5 cm, or with progressive dilatation of the aorta, the risk of dissection is high, and Cesarean delivery should be performed [55]. Elective surgery with epidural anesthesia is a good option in order to minimize hemodynamic changes during vaginal delivery. It should be noted that patients with Marfan syndrome sometimes have dural ectasia precluding regional anesthesia [33]. As stated above, in case of aortic dissection, urgent aortic repair is indicated. Postoperative hemorrhage is a reported complication and should be anticipated [72]. Postpartum women should be followed up closely by a cardiologist: weekly for high risk and monthly for low risk until 4–6 months postdelivery [69].

10.6 Antiarrhythmic Treatment in Pregnancy

Ectopic beats often occur during pregnancy and do not require specific treatment. However, patients with congenital heart disease, cardiomyopathy and valvular heart disease are often prone to clinically significant supraventricular tachycardia (SVT), atrial fibrillation, and ventricular arrhythmias [73, 74]. The incidence of SVTs in pregnancy has been reported to be 24/100,000, ventricular arrhythmias 2/100,000, and AV block 1.5/100,000 [75]. The incidence is higher in women with a previous history of arrhythmias.

Supraventricular tachyarrhythmias such as AV nodal reentrant tachycardia without hemodynamic decompensation may be treated with antiarrhythmic drugs or AV nodal blocking drugs, such as adenosine, beta-blockers, calcium channel blockers, or digoxin (Table 10.3) [33, 76]. Initially, adenosine is the agent of choice at a dose of 6–12 mg. Cases of atrial tachycardia (non-AV nodal reentrant tachycardia) and fibrillation should be treated with antiarrhythmics or DC cardioversion. DC cardioversion is safe in all stages of pregnancy, but fetal monitoring is required [73, 74]. Rate control can be achieved using selective beta-blockers such as metoprolol (starting dose 5 mg intravenously over 5 min), digoxin, or verapamil. Care must be taken to avoid hypotension. For rhythm control, sotalol is the antiarrhythmic of choice, but flecainide is a second-line option [76]. In cases of refractory or poorly tolerated SVT, catheter ablation should be considered in experienced centers [27].

Ventricular arrhythmias with hemodynamic instability require prompt DC cardioversion. In stable patients, wide complex tachycardia should be presumed to be ventricular tachycardia, and verapamil should not be used. Lidocaine and sotalol are considered safe during pregnancy; however amiodarone has considerable fetal toxicity and should be used with caution [73].

Anticoagulation is indicated for at least 3 weeks before and 4 weeks after elective cardioversion of atrial fibrillation. In cases of documented atrial fibrillation lasting less than 48 h, pre-conversion intravenous heparin or subcutaneous low molecular weight heparin may be sufficient. Women with risk factors for recurrent arrhythmias and stroke require prolonged anticoagulation and rhythm control [33].

Women with asymptomatic bradycardia usually tolerate pregnancy and delivery well. However, pacemaker insertion may be required

in severe cases of AV block, ideally after the first trimester [76]. Delivery requires monitoring; spinal anesthesia during delivery may precipitate bradycardia and is therefore not recommended [74].

Insertion of implantable electronic devices, such as cardioverter-defibrillators, pacemakers, or cardiac re-synchronization devices may be indicated before pregnancy in high-risk arrhythmia cases (such as long QT syndrome, dilated and hypertrophic cardiomyopathy, etc.) and is not a contraindication for pregnancy [73, 77]. Delivery requires a joint obstetric, cardiologic, and anesthetic monitoring and treatment plan, aiming at minimizing hemodynamic compromise and exacerbation of arrhythmias. Monitoring includes cardiac heart rate and ECG monitoring, pulse oximetry, and intra-arterial catheter in higher-risk patients. If indicated, transcutaneous or transvenous pacing and external defibrillators should be available. Vaginal delivery with a neuraxial analgesia and assisted second stage is preferred [77]. If surgery is indicated, bipolar diathermy is safer than unipolar diathermy to limit electrical interference. Occasionally, reprogramming of certain devices may be indicated to reduce electromagnetic interference [77]. Postpartum monitoring in a high dependency unit with the ability to provide pacing or defibrillation is required.

10.7 Management of Heart Failure in Pregnant Women with Preexisting Heart Disease

Thorough knowledge of patient anatomy and physiology should be obtained and treated accordingly. In case of ICU admission because of heart decompensation, one has to remember that most patients with congenital heart diseases do not tolerate well either increases in pulmonary vascular resistance (PVR) or rises in systemic vascular resistance. Physiologic influences of hypoxemia, hypercapnia, acidosis, positive pressure ventilation, and high PEEP will increase the PVR and should be avoided and corrected if possible. Low tidal volumes and low PEEP may be indicated. Pharmacologic treatments frequently given in ICU like phenylephrine, norepinephrine, and dopamine may result in increased PVR and should be administered carefully. Drugs such as dobutamine, milrinone, and inhaled NO are pulmonary artery vasodilators which reduce PVR and are therefore better tolerated [42].

Management of postpartum decompensation of heart failure in the intesive care setting includes the following [78]:

- Diagnosis and correction of any exacerbating factors such as infection, anemia, and arrhythmias. Saturation should be kept above 90%, and supplemental oxygen may be required.
- Monitoring includes arterial blood pressure (invasive or noninvasive), telemetric cardiac monitoring, and occasionally central venous pressure measurement. Echocardiogram is important to determine volume status, ventricular function, and valve stenosis or regurgitation.
- Fluid balance should be carefully optimized. In cases of fluid overload, which may worsen left ventricular failure, preload may be reduced by administering intravenous diuretics. Fluid administration is indicated in cases of suspected hypovolemia.
- Pharmacologic reduction of pulmonary vascular resistance (PVR) in cases of pulmonary hypertension by using drugs such as prostaglandins, PDE-5 inhibitors or inhaled NO, or systemic vasodilators in cases of left ventricular failure may improve ventricular function.
- Ventricular contractility may be improved by using dobutamine targeting a $ScvO_2 > 70\%$ or a cardiac index >2.0 L/min/m^2. However, this drug may cause tachyarrhythmias. Alternatives are levosimendan or milrinone.
- If there is significant hypotension, adding noradrenaline may be necessary to achieve a MAP >65 mmHg in order to optimize perfusion pressure. This should be done with caution, as vasoconstriction may increase afterload, causing further deterioration of ventricular function. The alternative to noradrena-

lin, vasopressin, has the advantage of not increasing pulmonary vascular resistance.
– In extreme measures, if all of the above fails, consider extracorporeal support.

10.8 Prosthetic Valves

Prosthetic valves are used to treat severe congenital and acquired valve lesions. The two types of valves in use are mechanical and biological prostheses [79]. Valve selection is challenging in women of childbearing age, which is why both mechanical and biological valves may be encountered in this age group [80]. It is therefore recommended that valve selection be performed in consultation with a Pregnancy Heart Team. Mechanical valves have better long-term durability, but the need for full anticoagulation is associated with increased maternal and fetal morbidity and mortality. Bioprosthetic valves are less thrombogenic and have reasonable hemodynamic performance. However, their long-term durability is decreased due to structural changes over time [1]. Accelerated valve degeneration has been associated with younger age [20] and reaches 80% of cases at 10 years follow-up. Mitral valves are more vulnerable than aortic valves [79]. Early mortality may reach 4.5% in patients undergoing redo aortic valve surgery and 4.7–7.4% in those undergoing redo mitral valve surgery [1].

Patients with bioprosthetic valves are usually treated similarly to patients with native valve pathologies. Pregnancy is well tolerated in patients with well-functioning bioprosthetic valves [33]. Lawley et al. [81] studied the prognosis of pregnancies of mothers with both mechanical and tissue prosthetic heart valves during the years 2000–2011 in Australia. They found 136 cases (1 per 10,000 pregnancies). The relative risk for severe maternal cardiovascular events was 34.6, preterm birth 2.77 and small for gestational age infants 2.03. There were no cases of maternal mortality. There was a tendency toward higher morbidity in mothers with mechanical prosthetic valves. The higher rate of complications in patients with mechanical prosthetic valves was mostly related to the mandatory use of anticoagulation [1, 82].

Women with mechanical prosthetic valves carry a higher rate of morbidity and mortality. As pregnancy induces thrombogenesis, these women have an increased risk of thromboembolic events (13%), heart failure (7.5%), and arrhythmias (3.3%) [79, 82]. Anticoagulation, which is required with mechanical valves, is associated with a higher risk of peripartum hemorrhage (10.4%) [79]. Maternal mortality ranges between 1 and 15% in different series [79]. Perinatal complications include fetal loss, preterm delivery, low birth weight, and teratogenicity from anticoagulants [82]. These maternal and fetal risk factors mandate management in tertiary medical centers, as well as very close follow-up of such patients during pregnancy, labor and delivery, and the postpartum period.

10.8.1 Anticoagulation

Women with mechanical valves require continuous anticoagulation throughout pregnancy. This requires close monitoring and adjustment, depending on the anticoagulation dosing, monitoring, and effectiveness [33, 57]. Finding the safest anticoagulation regimen for the mother and fetus is challenging; most regimens require conversion from one drug to the other, requiring careful observation and extra vigilance. Some even indicate admission for intravenous administration and monitoring. At this time, there is no consensus regarding the ideal treatment protocol; therefore different medical centers use different protocols [57] (Table 10.5).

Valve thrombosis risk has been found to be lowest with the use of oral anticoagulants such as warfarin throughout pregnancy (2.4–3.9%) and highest with the use of unfractionated heparin (9.2–10.3%) [56, 79]. Warfarin dosing is similar to that of nonpregnant women and is targeted to an INR of 2.5 (range 2.0–3.0) [83]. Warfarin, however, crosses the placenta and is teratogenic when taken in the first trimester (5–10% risk of fetal defects); this condition is termed warfarin embryopathy [84]. Its use is associated with an

Table 10.5 Anticoagulation protocols for pregnant women with a mechanical valve prosthesis[a]

First trimester
1. Warfarin dose ≤5 mg daily, close INR monitoring, targeting 2.0–3.0 IU
Or
2. Low molecular weight heparin, twice daily, targeting anti-Xa levels 0.8–1.2 U/mL, 4–6 h post dosing, trough levels >0.6 IU/mL
Or
3. Continuous infusion of unfractionated heparin, targeting aPTT of >2 controls
Second and third trimester
1. Aspirin 75–100 mg daily plus
Warfarin targeted to INR 2.0–3.0 IU
2 weeks before planned delivery
Continuous infusion of unfractionated heparin, targeting aPTT of >2 controls
Or
2. Low molecular weight heparin, twice daily, targeting anti-Xa levels 0.8–1.2 U/mL, 4–6 h post dosing, trough levels >0.6 IU/mL
36 h before planned delivery
Continuous infusion of unfractionated heparin, targeting aPTT of >2 controls[b]

aPTT activated partial thromboplastin time, *INR* international normalized ratio, *LMWH* low molecular weight heparin

[a]Pregnant women on LMWH or unfractionated heparin should perform weekly anti-Xa level monitoring or aPTT monitoring with dose adjustment

[b]Heparin infusion should be withheld 4–6 h prior to anticipated delivery, and aPTT should be normal before neuraxial anesthesia is performed

increased risk of fetal intracerebral hemorrhage in the third trimester [20, 54] A reduced rate of fetal complications has been reported with doses less than 5 mg a day [1, 55]. Fetal risk has been found to be similar between a warfarin dose of 5 mg daily or lower and low molecular weight heparin [85].

Heparin does not cross the placenta and is a safer option for the mother and the fetus. However, administration and monitoring of adequate anticoagulation is difficult. Intravenous administration is required, using devices that can target specific doses, as well as frequent aPTT measurements, which usually require admission. A target of aPTT which is twice that of the control value is required [83]. There are also concerns about associated infections, osteoporosis, and thrombocytopenia. Subcutaneous heparin administration is not recommended by the 2014 American Heart Association/American College of Cardiology guidelines, as it is associated with a high risk of thromboembolic phenomena [83]. Admission to hospital and conversion to treatment with intravenous heparin is generally recommended from week 36 onward unless delivery is planned for an earlier date. A review of 1234 pregnancies with mechanical valve prostheses compared three anticoagulation regimens: oral anticoagulation throughout pregnancy, oral anticoagulation substituted with heparin in the first trimester, and heparin throughout pregnancy [84]. The lowest thromboembolic complications were found in the oral coagulation group (3.9%), but this group also demonstrated the highest rates of teratogenic complications (6.4%) in live births and 21.1% spontaneous abortions. The rate of thromboembolic complications was the highest: 33.3% in the heparin regimen and only 9.2% using the combined oral anticoagulation and heparin regimen [84]. Combination therapy reduced the risk of teratogenic complications to zero if heparin was used before week 6 and to 11.1% if heparin was used after week 6. Overall maternal mortality was 2.9%; 1.8% in the group using the oral anticoagulation regimen; 4.2% in those using the combined regimen; and 15% in the group using the heparin regimen.

Low molecular weight heparin is an alternative to unfractionated heparin; its use in pregnancy is becoming more common, as it is associated with a more predictable dose response [1, 79, 86]. However, pregnancy is associated with an increase in dosing requirements, and maternal and fetal complications still occur depending on dosing, compliance, and monitoring [33, 79, 87] In one report, 34 pregnancies of women with mechanical valves treated with enoxaparin were followed up. Thrombotic complications were reported in 10.6% patients. More women experienced live births than those treated with warfarin [86]. In a meta-analysis of studies looking at the risk of postpartum hemorrhage with the use of low molecular weight heparin, 1320 women were included [88]. The risk for postpartum hemor-

rhage was higher in this group of women (RR 1.45), but there was no difference in blood loss during delivery. Dosing and level monitoring of low molecular weight heparin has also been studied. The American College of Cardiology recommends monitoring peak plasma anti-Xa levels with a target of 0.8–1.2 U/mL–6 h post-dose delivery [83]. In a study by Goland et al., trough levels were found to be subtherapeutic (<0.6 U/mL) in 80% of 123 women with therapeutic peak levels. They recommend measuring trough anti-Xa levels as well in this patient population [89]. There is currently not enough evidence to support the use of novel oral anticoagulants during pregnancy [90].

10.8.2 Anticoagulation Protocols

There are several options for anticoagulation regimens in pregnant women with mechanical valve prostheses, and there is no one preferred regimen [33, 79, 83] (Table 10.5).

The American College of Cardiology and the European Society of Cardiology recommend continuing warfarin in the first trimester if the dose required to reach INR targets is less than 5 mg a day. However, if a larger dose is required, it may be replaced with intravenous heparin titrated by weight (1 mg/kg) and anti-Xa adjusted enoxaparin during weeks 6–12. Subsequently, oral anticoagulants may be continued until 36 weeks gestation, or until 2 weeks before a planned or expected delivery, whereupon the regimen should be changed to unfractionated or low molecular weight heparin [79]. Alternatively, low molecular weight heparin can be continued until the third trimester under close monitoring [33, 79, 83]. Aspirin, at a dose of 75–100 mg, is given together with anticoagulants in the second and third trimesters.

Taking all these considerations into account, it is very important to discuss treatment options with the parents including risks for the mother and fetus, previous and potential treatment compliance, and required monitoring. A multidisciplinary team of cardiologists, obstetricians, and anesthesiologists should be involved in planning these women's follow-up, monitoring, and delivery.

During Pregnancy. Follow-up is individualized according to valve and cardiac function, type of valve replaced, and the type of anticoagulation and compliance. Women with bioprosthetic valves and good cardiac function may be followed by a cardiologist and echocardiography every trimester. Patients with mechanical valves should be monitored more closely, including physical and echocardiographic examinations and weekly monitoring and dose adjustments of anticoagulation protocols as necessary [79]. Changes of anticoagulation should be performed under observation in hospital. Women should be educated regarding anticoagulant dosing and monitoring, and a high level of compliance should be encouraged [33].

Delivery. A planned vaginal delivery requires prior changing to intravenous heparin targeting an aPTT of more than two times control. Cesarean section may also be planned or performed in cases where labor begins while still on oral anticoagulants [33]. Oral anticoagulants or LMWH should be stopped and replaced by intravenous unfractionated heparin at least 36 h prior to delivery. The heparin infusion should be held 4–6 h prior to anticipated delivery, and aPTT should be normal before neuraxial anesthesia is performed [27]. Unfractionated heparin can usually be recommenced 4–6 h postpartum provided there is no bleeding [79].

10.8.3 Valve Thrombosis ("Stuck Valve")

Pregnancy presents a considerable risk of prosthetic valve thrombosis, due to a prothrombotic tendency, especially in artificial mitral valves [91]. Prosthetic valve thrombosis is a life-threatening complication [79]. Symptoms of a thrombotic artificial valve include dyspnea, signs of heart failure, arrhythmias, hemodynamic instability, and embolic phenomena. Urgent echocardiography should be performed in all pregnant women with mechanical valves presenting with dyspnea and/or an embolic event [33]. Physical

examination may demonstrate absent valvular click sounds and a new murmur [83]. A transthoracic or transesophageal echocardiography and/or fluoroscopy examination with abdominal shielding is indicated and should be performed urgently. If the diagnosis is confirmed, the thrombus is small (<10 mm), and the mother is clinically stable; intravenous unfractionated heparin is a good option. If the patient is clinically unstable and has an obstructing thrombus, surgical intervention may be required; however, this is associated with a 20–30% risk of fetal loss [79, 91].

Fibrinolytic therapy is also an option. Fibrinolytics (e.g., tPA, streptokinase) do not cross the placenta and are the preferred therapeutic option for right-sided valvular thrombosis [1]. There is an increased risk of subplacental bleeding, however, and the options should be discussed with the parents [33]. Usual dosing is 10 mg IV bolus of tPA followed by 90 mg infused IV over 2 h while holding heparin infusion. Alternatively, a lower dose of 20 mg IV bolus followed by 10 mg per hour for 3 h may be used. A streptokinase regimen includes a loading dose of 500,000 IU in 20 min followed by 1,500,000 IU over 10 h [83]. In a prospective, single center study, low-dose tPA (25 mg over 6 h) was administered to 28 prosthetic valve episodes (mitral valve) under transesophageal echocardiography guidance [92]. Complete thrombus lysis was accomplished in all cases, and one case had placental bleeding. Fibrinolysis may be associated with bleeding and thromboembolic phenomena. Large thrombi (>1 cm in diameter) are associated with a higher rate of complications, especially if the thrombus is mobile or there have been previous thromboembolic events. High risk of bleeding is associated with a history of hemorrhagic stroke, hypertension (systolic BP >200 mmHg), intracranial trauma, or neoplasm or NYHA class III and IV symptoms [83]. Fibrinolysis may therefore be a reasonable option in order to avoid surgery in patients with a small thrombus and NYHA class I or II symptoms. In more severe cases, surgery is indicated [79, 83]. Thrombolysis treatment is followed by intravenous heparin and oral anticoagulants with a target INR of 3.0–4.0 for aortic prosthetic valves and 3.5 to 4.5 for mitral prosthetic valves.

10.9 Conclusion

Due to advances in diagnostics and treatment options, women with complex preexisting heart disease often survive to childbearing age, and their desire for pregnancy poses a challenge to obstetricians, cardiologists anesthesiologists, and intensivists [1]. Heart failure, arrhythmias, and pulmonary hypertension continue to account for most maternal deaths. Preconception evaluation and counselling is extremely important, and risk assessment should be performed according to available risk prediction scores. Appropriate monitoring during pregnancy and planned delivery should be performed according to risk assessment and treatment options. Early collaboration between cardiologists, anesthesiologists, intensivists, neonatologists, pulmonologists, and obstetricians is recommended to optimize maternal outcomes for women with preexisting heart disease who become pregnant [32, 93].

References

1. Elkayam U, Goland S, Pieper PG, Silverside CK. High-risk cardiac disease in pregnancy: part I. J Am Coll Cardiol. 2016;68(4):396–410.
2. Thorne SA. Pregnancy in heart disease. Heart. 2004;90(4):450–6.
3. Thompson JL, Kuklina EV, Bateman BT, Callaghan WM, James AH, Grotegut CA. Medical and obstetric outcomes among pregnant women with congenital heart disease. Obstet Gynecol. 2015;126(2):346–54.
4. Cauldwell M, Dos Santos F, Steer PJ, Swan L, Gatzoulis M, Johnson MR. Pregnancy in women with congenital heart disease. BMJ. 2018;360:k478.
5. Lewis G. Saving mothers' lives: the continuing benefits for maternal health from the United Kingdom (UK) confidential enquires into maternal deaths. Semin Perinatol. 2012;36(1):19–26.
6. Brickner ME. Cardiovascular management in pregnancy: congenital heart disease. Circulation. 2014;130(3):273–82.
7. Canobbio MM, Warnes CA, Aboulhosn J, Connolly HM, Khanna A, Koos BJ, et al. Management of pregnancy in patients with complex congenital heart disease: a scientific statement for healthcare pro-

fessionals from the American Heart Association. Circulation. 2017;135(8):e50–87.
8. Merz WM, Keyver-Paik MD, Baumgarten G, Lewalter T, Gembruch U. Spectrum of cardiovascular findings during pregnancy and parturition at a tertiary referral center. J Perinat Med. 2011;39(3):251–6.
9. Siu SC, Sermer M, Colman JM, Alvarez AN, Mercier LA, Morton BC, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. Circulation. 2001;104(5):515–21.
10. Roos-Hesselink JW, Ruys TP, Stein JI, Thilen U, Webb GD, Niwa K, et al. Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology. Eur Heart J. 2013;34(9):657–65.
11. Avila WS, Rossi EG, Ramires JA, Grinberg M, Bortolotto MR, Zugaib M, et al. Pregnancy in patients with heart disease: experience with 1,000 cases. Clin Cardiol. 2003;26(3):135–42.
12. Liu H, Huang TT, Lin JH. Risk factors and risk index of cardiac events in pregnant women with heart disease. Chin Med J. 2012;125(19):3410–5.
13. Kuklina E, Callaghan W. Chronic heart disease and severe obstetric morbidity among hospitalisations for pregnancy in the USA: 1995-2006. BJOG. 2011;118(3):345–52.
14. Wanderer JP, Leffert LR, Mhyre JM, Kuklina EV, Callaghan WM, Bateman BT. Epidemiology of obstetric-related ICU admissions in Maryland: 1999-2008*. Crit Care Med. 2013;41(8):1844–52.
15. Drenthen W, Pieper PG, Roos-Hesselink JW, van Lottum WA, Voors AA, Mulder BJ, et al. Outcome of pregnancy in women with congenital heart disease: a literature review. J Am Coll Cardiol. 2007;49(24):2303–11.
16. Ntiloudi D, Giannakoulas G, Parcharidou D, Panagiotidis T, Gatzoulis MA, Karvounis H. Adult congenital heart disease: a paradigm of epidemiological change. Int J Cardiol. 2016;218:269–74. Epub 2016/05/31.
17. Cauldwell M, Patel RR, Steer PJ, Swan L, Norman-Taylor J, Gatzoulis M, et al. Managing subfertility in patients with heart disease: what are the choices? Am Heart J. 2017;187:29–36.
18. Drenthen W, Pieper PG, Roos-Hesselink JW, van Lottum WA, Voors AA, Mulder BJ, et al. Pregnancy and delivery in women after Fontan palliation. Heart. 2006;92(9):1290–4.
19. Cauldwell M, Steer PJ, Bonner S, Asghar O, Swan L, Hodson K, et al. Retrospective UK multicentre study of the pregnancy outcomes of women with a Fontan repair. Heart. 2018;104(5):401–6.
20. Stout KK, Otto CM. Pregnancy in women with valvular heart disease. Heart. 2007;93(5):552–8.
21. Greutmann M, Pieper PG. Pregnancy in women with congenital heart disease. Eur Heart J. 2015;36(37):2491–9.
22. Canobbio MM, Mair DD, van der Velde M, Koos BJ. Pregnancy outcomes after the Fontan repair. J Am Coll Cardiol. 1996;28(3):763–7.
23. Canobbio MM, Morris CD, Graham TP, Landzberg MJ. Pregnancy outcomes after atrial repair for transposition of the great arteries. Am J Cardiol. 2006;98(5):668–72.
24. Warnes CA. Pregnancy and delivery in women with congenital heart disease. Circ J. 2015;79(7):1416–21.
25. Silversides CK, Grewal J, Mason J, Sermer M, Kiess M, Rychel V, et al. Pregnancy outcomes in women with heart disease: the CARPREG II study. J Am Coll Cardiol. 2018;71(21):2419–30.
26. Drenthen W, Boersma E, Balci A, Moons P, Roos-Hesselink JW, Mulder BJ, et al. Predictors of pregnancy complications in women with congenital heart disease. Eur Heart J. 2010;31(17):2124–32.
27. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, Blomstrom-Lundqvist C, Cifkova R, De Bonis M, et al. 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy. Eur Heart J. 2018;39(34):3165–241.
28. Bianca I, Geraci G, Gulizia MM, Egidy Assenza G, Barone C, Campisi M, et al. Consensus Document of the Italian Association of Hospital Cardiologists (ANMCO), Italian Society of Pediatric Cardiology (SICP), and Italian Society of Gynaecologists and Obstetrics (SIGO): pregnancy and congenital heart diseases. Eur Heart J Suppl. 2017;19(Suppl D):D256–92.
29. Lu CW, Shih JC, Chen SY, Chiu HH, Wang JK, Chen CA, et al. Comparison of 3 risk estimation methods for predicting cardiac outcomes in pregnant women with congenital heart disease. Circ J. 2015;79(7):1609–17.
30. Singh A, Guleria K, Vaid NB, Jain S. Evaluation of maternal early obstetric warning system (MEOWS chart) as a predictor of obstetric morbidity: a prospective observational study. Eur J Obstet Gynecol Reprod Biol. 2016;207:11–7.
31. Shields LE, Wiesner S, Klein C, Pelletreau B, Hedriana HL. Use of maternal early warning trigger tool reduces maternal morbidity. Am J Obstet Gynecol. 2016;214(4):527.e1–6.
32. Rao S, Ginns JN. Adult congenital heart disease and pregnancy. Semin Perinatol. 2014;38(5):260–72.
33. Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM, et al. ESC guidelines on the management of cardiovascular diseases during pregnancy: the task force on the management of cardiovascular diseases during pregnancy of the European Society of Cardiology (ESC). Eur Heart J. 2011;32(24):3147–97.
34. Chambers CE, Clark SL. Cardiac surgery during pregnancy. Clin Obstet Gynecol. 1994;37(2):316–23.
35. Sartain JB, Anderson NL, Barry JJ, Boyd PT, Howat PW. Rheumatic heart disease in pregnancy: cardiac and obstetric outcomes. Intern Med J. 2012;42(9):978–84.
36. Elkayam U, Goland S, Pieper PG, Silverside CK. High-risk cardiac disease in pregnancy: part II. J Am Coll Cardiol. 2016;68(5):502–16.
37. Capeless EL, Clapp JF. When do cardiovascular parameters return to their preconception values? Am J Obstet Gynecol. 1991;165(4 Pt 1):883–6.

38. Presbitero P, Somerville J, Stone S, Aruta E, Spiegelhalter D, Rabajoli F. Pregnancy in cyanotic congenital heart disease. Outcome of mother and fetus. Circulation. 1994;89(6):2673–6.
39. Ladouceur M, Benoit L, Basquin A, Radojevic J, Hauet Q, Hascoet S, et al. How pregnancy impacts adult cyanotic congenital heart disease: a multicenter observational study. Circulation. 2017;135(24):2444–7.
40. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (writing committee to develop guidelines on the management of adults with congenital heart disease). Circulation. 2008;118(23):e714–833.
41. Cauldwell M, Von Klemperer K, Uebing A, Swan L, Steer PJ, Gatzoulis M, et al. The management of the second stage of labour in women with cardiac: a mixed methods study. Int J Cardiol. 2016;222:732–6.
42. Kratzert WB, Boyd EK, Schwarzenberger JC. Management of the critically ill adult with congenital heart disease. J Cardiothorac Vasc Anesth. 2018;32(4):1682–700.
43. Gewillig M. The Fontan circulation. Heart. 2005;91(6):839–46.
44. Gewillig M, Brown SC. The Fontan circulation after 45 years: update in physiology. Heart. 2016;102(14):1081–6.
45. Pundi KN, Johnson JN, Dearani JA, Li Z, Hinck CA, Dahl SH, et al. 40-year follow-up after the Fontan operation: long-term outcomes of 1,052 patients. J Am Coll Cardiol. 2015;66(15):1700–10.
46. Hebson CL, McCabe NM, Elder RW, Mahle WT, McConnell M, Kogon BE, et al. Hemodynamic phenotype of the failing Fontan in an adult population. Am J Cardiol. 2013;112(12):1943–7.
47. Inoue S, Masuyama H, Akagi T, Hiramatsu Y. Pregnancy and delivery in patients with Fontan circulation: a report of two cases. J Obstet Gynaecol Res. 2013;39(1):378–82.
48. Khan A, Kim YY. Pregnancy in complex CHD: focus on patients with Fontan circulation and patients with a systemic right ventricle. Cardiol Young. 2015;25(8):1608–14.
49. Eid L, Ginosar Y, Elchalal U, Pollak A, Weiniger CF. Caesarean section following the Fontan procedure: two different deliveries and different anaesthetic choices in the same patient. Anaesthesia. 2005;60(11):1137–40.
50. Mathney E, Beilin Y. Successful epidural anesthesia for cesarean delivery in a woman with Fontan repair. J Clin Anesth. 2015;27(1):60–2.
51. Tiouririne M, de Souza DG, Beers KT, Yemen TA. Anesthetic management of parturients with a Fontan circulation: a review of published case reports. Semin Cardiothorac Vasc Anesth. 2015;19(3):203–9.
52. Essop MR, Peters F. Contemporary issues in rheumatic fever and chronic rheumatic heart disease. Circulation. 2014;130(24):2181–8.
53. Marijon E, Mirabel M, Celermajer DS, Jouven X. Rheumatic heart disease. Lancet. 2012;379(9819):953–64.
54. Pessel C, Bonanno C. Valve disease in pregnancy. Semin Perinatol. 2014;38(5):273–84.
55. Emmanuel Y, Thorne SA. Heart disease in pregnancy. Best Pract Res Clin Obstet Gynaecol. 2015;29(5):579–97.
56. Lau ES, Scott NS. Valvular heart disease and pregnancy. Curr Treat Options Cardiovasc Med. 2018;20(6):46.
57. Nanna M, Stergiopoulos K. Pregnancy complicated by valvular heart disease: an update. J Am Heart Assoc. 2014;3(3):e000712.
58. Silversides CK, Colman JM, Sermer M, Siu SC. Cardiac risk in pregnant women with rheumatic mitral stenosis. Am J Cardiol. 2003;91(11):1382–5.
59. Russell EA, Walsh WF, Costello B, McLellan AJ, Brown A, Reid CM, et al. Medical management of rheumatic heart disease: a systematic review of the evidence. Cardiol Rev. 2018;26(4):187–95.
60. Hameed AB, Mehra A, Rahimtoola SH. The role of catheter balloon commissurotomy for severe mitral stenosis in pregnancy. Obstet Gynecol. 2009;114(6):1336–40.
61. Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD, et al. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008;52(13):e1–e142.
62. Yap SC, Drenthen W, Pieper PG, Moons P, Mulder BJ, Mostert B, et al. Risk of complications during pregnancy in women with congenital aortic stenosis. Int J Cardiol. 2008;126(2):240–6.
63. Anthony J, Osman A, Sani MU. Valvular heart disease in pregnancy. Cardiovasc J Afr. 2016;27(2):111–8.
64. Katsi V, Georgiopoulos G, Marketou M, Oikonomou D, Parthenakis F, Makris T, et al. Atrial fibrillation in pregnancy: a growing challenge. Curr Med Res Opin. 2017;33(8):1497–504.
65. Bhargava B, Agarwal R, Yadav R, Bahl VK, Manchanda SC. Percutaneous balloon aortic valvuloplasty during pregnancy: use of the Inoue balloon and the physiologic antegrade approach. Catheter Cardiovasc Diagn. 1998;45(4):422–5.
66. Patel A, Asopa S, Tang AT, Ohri SK. Cardiac surgery during pregnancy. Tex Heart Inst J. 2008;35(3):307–12.

67. Ioscovich AM, Goldszmidt E, Fadeev AV, Grisaru-Granovsky S, Halpern SH. Peripartum anesthetic management of patients with aortic valve stenosis: a retrospective study and literature review. Int J Obstet Anesth. 2009;18(4):379–86.
68. Chandrasekhar S, Cook CR, Collard CD. Cardiac surgery in the parturient. Anesth Analg. 2009;108(3):777–85.
69. Goland S, Elkayam U. Pregnancy and Marfan syndrome. Ann Cardiothorac Surg. 2017;6(6):642–53.
70. Goland S, Barakat M, Khatri N, Elkayam U. Pregnancy in Marfan syndrome: maternal and fetal risk and recommendations for patient assessment and management. Cardiol Rev. 2009;17(6):253–62.
71. Kim SY, Wolfe DS, Taub CC. Cardiovascular outcomes of pregnancy in Marfan's syndrome patients: a literature review. Congenit Heart Dis. 2018;13(2):203–9.
72. Curry RA, Gelson E, Swan L, Dob D, Babu-Narayan SV, Gatzoulis MA, et al. Marfan syndrome and pregnancy: maternal and neonatal outcomes. BJOG. 2014;121(5):610–7.
73. Knotts RJ, Garan H. Cardiac arrhythmias in pregnancy. Semin Perinatol. 2014;38(5):285–8.
74. Adamson DL, Nelson-Piercy C. Managing palpitations and arrhythmias during pregnancy. Heart. 2007;93(12):1630–6.
75. Li JM, Nguyen C, Joglar JA, Hamdan MH, Page RL. Frequency and outcome of arrhythmias complicating admission during pregnancy: experience from a high-volume and ethnically-diverse obstetric service. Clin Cardiol. 2008;31(11):538–41.
76. Cordina R, McGuire MA. Maternal cardiac arrhythmias during pregnancy and lactation. Obstet Med. 2010;3(1):8–16.
77. Salman MM, Kemp HI, Cauldwell MR, Dob DP, Sutton R. Anaesthetic management of pregnant patients with cardiac implantable electronic devices: case reports and review. Int J Obstet Anesth. 2018;33:57–66.
78. Hoeper MM, Granton J. Intensive care unit management of patients with severe pulmonary hypertension and right heart failure. Am J Respir Crit Care Med. 2011;184(10):1114–24.
79. Bhagra CJ, D'Souza R, Silversides CK. Valvular heart disease and pregnancy part II: management of prosthetic valves. Heart. 2017;103(3):244–52.
80. Elkayam U, Bitar F. Valvular heart disease and pregnancy: part II: prosthetic valves. J Am Coll Cardiol. 2005;46(3):403–10.
81. Lawley CM, Algert CS, Ford JB, Nippita TA, Figtree GA, Roberts CL. Heart valve prostheses in pregnancy: outcomes for women and their infants. J Am Heart Assoc. 2014;3(3):e000953.
82. van Hagen IM, Roos-Hesselink JW, Ruys TP, Merz WM, Goland S, Gabriel H, et al. Pregnancy in women with a mechanical heart valve: data of the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC). Circulation. 2015;132(2):132–42.
83. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. J Thorac Cardiovasc Surg. 2014;148(1):e1–e132.
84. Chan WS, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. Arch Intern Med. 2000;160(2):191–6.
85. Steinberg ZL, Dominguez-Islas CP, Otto CM, Stout KK, Krieger EV. Maternal and fetal outcomes of anticoagulation in pregnant women with mechanical heart valves. J Am Coll Cardiol. 2017;69(22):2681–91.
86. McLintock C, McCowan LM, North RA. Maternal complications and pregnancy outcome in women with mechanical prosthetic heart valves treated with enoxaparin. BJOG. 2009;116(12):1585–92.
87. Yinon Y, Siu SC, Warshafsky C, Maxwell C, McLeod A, Colman JM, et al. Use of low molecular weight heparin in pregnant women with mechanical heart valves. Am J Cardiol. 2009;104(9):1259–63.
88. Sirico A, Saccone G, Maruotti GM, Grandone E, Sarno L, Berghella V, et al. Low molecular weight heparin use during pregnancy and risk of postpartum hemorrhage: a systematic review and meta-analysis. J Matern Fetal Neonatal Med. 2019;32(11):1893–900.
89. Goland S, Schwartzenberg S, Fan J, Kozak N, Khatri N, Elkayam U. Monitoring of anti-Xa in pregnant patients with mechanical prosthetic valves receiving low-molecular-weight heparin: peak or trough levels? J Cardiovasc Pharmacol Ther. 2014;19(5):451–6.
90. Tang AW, Greer I. A systematic review on the use of new anticoagulants in pregnancy. Obstet Med. 2013;6(2):64–71.
91. Korkmaz AA, Yuce M, Korkmaz F, Gulcan F, Guden M. Stuck mechanical valve in pregnancy. J Card Surg. 2008;23(6):790–2.
92. Ozkan M, Cakal B, Karakoyun S, Gursoy OM, Cevik C, Kalcik M, et al. Thrombolytic therapy for the treatment of prosthetic heart valve thrombosis in pregnancy with low-dose, slow infusion of tissue-type plasminogen activator. Circulation. 2013;128(5):532–40.
93. Ruys TP, Cornette J, Roos-Hesselink JW. Pregnancy and delivery in cardiac disease. J Cardiol. 2013;61(2):107–12.

Maternal Cardiomyopathy and Critical Care Medicine

11

Benjamin Cobb and Elsje Harker

Bullet Points

- Cardiomyopathy in pregnancy is associated with increased maternal/neonatal morbidity and mortality.
- The symptoms of heart failure that are typical of cardiomyopathy may be masked by the physiologic changes of pregnancy, particularly in the late second and third trimesters.
- Cardiomyopathy may be further categorized into multiple subtypes that may warrant individual treatment modifications.
- A thorough physical examination and echocardiogram are the primary diagnostic modalities in the woman presenting with symptoms suggestive of heart failure during or after pregnancy.
- The treatment goals of congestive heart failure in pregnancy are similar to those of the nonpregnant population.
- In the setting of decompensated maternal heart failure, stabilization of the pregnant/peripartum woman is a priority.
- Careful selection of pharmacologic therapy and titration of heart failure medications may assist in minimizing the risks of fetal teratogenicity while optimizing uterine perfusion. However, the risks and benefits of each medication should primarily take into consideration maternal well-being.
- In the setting of cardiomyopathy with maternal decompensation, the management and timing of delivery should be weighed by a multidisciplinary team.
- Refractory decompensated heart failure may require support with cardiac assist devices and/or cardiac transplantation in severe cases.

11.1 Introduction

Up to 25% of pregnancy-related deaths may be attributed to cardiovascular conditions, and cardiomyopathy may account for 10% of these maternal deaths [1]. In addition to an increased rate of maternal death, women with cardiomyopathy are at risk for an array of complications including dysrhythmia and venous thromboembolism (VTE). Pregnant and peripartum women with cardiomyopathy may require intensive care

B. Cobb (✉) · E. Harker
Department of Anesthesiology, University of North Carolina, Chapel Hill, NC, USA
e-mail: Benjamin_Cobb@med.unc.edu; Elsje_Harker@med.unc.edu

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_11

unit (ICU) admission for monitoring and/or treatment of congestive heart failure as well as for other complications.

11.2 Cardiomyopathy

11.2.1 Definition

Cardiomyopathy is defined as "heart muscle disorders, associated with various degree of anatomic (thickening, dilatation, and stiffness), histological (disarray, fibrosis, fibrofatty dysplasia), and functional (reduced diastolic or systolic function) abnormalities of the myocardium" [2, 3]. Cardiomyopathy in pregnancy may be categorized into subtypes according to these attributes, with both genetic and nongenetic inheritance patterns. The subtypes described in pregnancy include hypertrophic cardiomyopathy, dilated cardiomyopathy, peripartum cardiomyopathy, and other rare types including arrhythmogenic right ventricular cardiomyopathy, left ventricular non-compaction cardiomyopathy, and restrictive cardiomyopathy (Table 11.1). Hypertrophic cardiomyopathy is the most common subtype, followed by dilated cardiomyopathy. In a cross-sectional study of pregnancy hospitalizations in the United States between 2004 and 2006, the rate of cardiomyopathy was 0.46 per 1000 deliveries, 0.18 for apparent peripartum cardiomyopathy, and 0.28 for other cardiomyopathies [4].

Table 11.1 Cardiomyopathy subtypes observed in pregnancy

Type of cardiomyopathy	Pathophysiology	Symptoms
Hypertrophic	Cardiac septal thickening, leading to dynamic left ventricular outflow tract obstruction	Shortness of breath, palpitations, syncope, or sudden death
Dilated	Impaired systolic function from dilated left ventricle	Shortness of breath, fatigue, impaired functional status, palpitations, and generalized edema
Peripartum	"	"
Arrhythmogenic right ventricular	Fibrofatty replacement of myocardium, predisposing to arrhythmias	Palpitations, shortness of breath, chest pain, dizziness, syncope, sudden death
Left ventricular non-compaction	Increased left ventricular myocardial trabeculation	Shortness of breath, fatigue, impaired functional status, palpitations, and generalized edema
Restrictive	Rigid cardiac walls, potentially leading to impaired systolic and diastolic function	"

11.2.2 Subtypes

The most common inherited cardiomyopathy, hypertrophic cardiomyopathy (HCM), has a prevalence as high as 1 in 500 in the general population [5–7]. HCM is distinguished by myocyte disarray and subsequent fibrosis that lead to a characteristic thickening of the septum. This structural abnormality may contribute to noncompliance of the ventricle(s) or "dynamic obstruction of the left ventricular outflow tract" [5]. During pregnancy, cardiac output (CO) increases by an average of 20–40%, but in some cases this increase may actually be higher at term. This increase in CO may compromise flow across a potentially obstructed left heart outflow tract (LVOT). While most women with HCM are asymptomatic, severe cases may present with shortness of breath, palpitations, syncope, or sudden death [5]. In pregnant women with HCM preceding pregnancy, NYHA functional class is related to maternal morbidity. Asymptomatic women and those without LVOT obstruction (i.e., most pregnant women with HCM) tend to have a favorable prognosis and tolerate pregnancy well [8–10].

Dilated cardiomyopathy (DCM) is either primary or secondary. About 50% of cases are classified as idiopathic or primary [11]. Secondary causes may include, but are not limited to, myocarditis, toxins, and autoimmune disorders. The characteristic structural defect is that of a dilated left ventricle, leading to impaired systolic function. Decreased systolic function or heart failure is typically unmasked in the late second trimester when maternal circulating blood volume peaks. When symptomatic, pregnant women present with characteristic symptoms of heart failure such as shortness of breath, fatigue, impaired functional status, palpitations, and generalized edema, this disease process may be subject to rapid deterioration [5]. Pregnancy complicated by DCM is more commonly severe than most other types of cardiomyopathy, affecting both maternal and fetal outcomes. Grewal et al. reported heart failure and dysrhythmia in more than one-third of pregnant women with DCM [5, 12]. The presence and severity of heart failure symptoms are associated with the prevalence of adverse events in pregnancy [12–14].

Peripartum cardiomyopathy (PPCM) is described as "a relatively rare [*idiopathic*] form of heart failure with left ventricular (LV) systolic dysfunction that occurs during the [*peripartum period*]" [15]. While specific diagnostic criteria vary, the 2006 American Heart Association Scientific Statement uses the following definition: "a rare and dilated form associated with [left ventricular] dysfunction and heart failure of unknown cause that manifests clinically in the third trimester of pregnancy or the first 5 months postpartum" [16]. In the developed world, PPCM is diagnosed in approximately 1:3000 pregnancies, but this condition may be much more prevalent in developing countries [5, 17, 18]. The cause and mechanism of PPCM remain unknown. Patten et al. [19] reported cardiac angiogenic imbalances similar to those observed in preeclampsia among women who developed PPCM. However later meta-analyses of the relationship between preeclampsia and peripartum cardiomyopathy found no association between the two [5, 19, 20]. Known risk factors for PPCM include multiparity, multigravidity, advanced maternal age, and prolonged tocolysis [15]. The characteristic signs and symptoms of acute heart failure observed in women with PPCM are similar to those of DCM, which is unsurprising given the similar underlying pathology of dilated congested ventricle(s). Adverse events in PPCM are more likely among women with worse New York Heart Association functional class, reduced ejection fraction (<25%), African-American ethnicity, indigent status, multiparity, and advanced maternal age (>30–35 years of age) [21–26]. Up to 10% of women with PPCM may develop severe heart failure requiring transplantation; however, almost half may recover fully within 6 months of delivery. Recurrence in a subsequent pregnancy has been reported to carry a mortality of up to 19% in women with persistent postpartum systolic dysfunction (LVEF <50%) [2, 27–29].

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is rare in pregnancy. ARVC is characterized by fibrofatty replacement of the myocardium. Pathological coexistence of fibrous and fatty tissues alongside normal myocardium has been suggested to be "a substrate for arrhythmia and sudden death" [5]. Late stages of the disease may include dilatation of the ventricle and/or aneurysmal defects of the myocardium. The stages of this condition include a concealed phase, when the patient is asymptomatic but is still at risk for sudden death, and a more progressed electrical phase, with symptomatic arrhythmias [5]. Although only 11 cases of ARVC in pregnancy have been reported, Krul et al. describe favorable outcomes in asymptomatic women with optimized antiarrhythmic therapy [8].

Another rare subtype of cardiomyopathy seen in pregnant women is left ventricular noncompaction cardiomyopathy (LVNC). This subtype results from abnormal embryonic development, where the trabeculae in the left ventricle fail to recede, leaving an inner lining of increased myocardial trabeculation. In addition to the potential to form thrombi in the trabeculae, pregnant women with LVNC who are symptomatic are likely to present with symptoms of heart failure (e.g., shortness of breath, fatigue, palpita-

tions, edema) [5]. Of note, trabeculation of the myocardium is more frequently being demonstrated as imaging modalities improve. In asymptomatic patients, the clinical significance of this finding remains uncertain.

The final rare subtype of cardiomyopathy seen in pregnant women is restrictive cardiomyopathy (RCM). Underlying etiologies include both infiltrative processes and non-infiltrative processes (i.e., deposition of abnormal material). These cases too present with signs and symptoms characteristic of heart failure (e.g., fatigue, shortness of breath, generalized edema, palpitations) [5]. In restrictive cardiomyopathy, ventricular contractility is preserved, but relaxation is impaired. Restricted ventricular filling and diastolic dysfunction, which are typical of this condition, may be diagnosed using echocardiography. Both ventricles may be affected. The prognosis of both LVNC and RCM is largely unknown, as both are very rare. Therefore it is most logical to assume that the prognosis of pregnant/peripartum women presenting with either condition will mostly depend on the severity of clinical presentation [8].

11.3 Diagnosis

11.3.1 Signs and Symptoms

Heart failure may be masked by symptoms commonly observed in the late second and third trimesters of pregnancy. Shortness of breath, the inability to lie supine, and generalized edema are frequently present in late gestation, even in healthy pregnant women. Further contributing to the diagnostic challenge are the presence of a physiological increase in the resting heart rate (approximately 20%), changes in blood pressure dependent on the week of gestation (see Chap. 9), respiratory alkalosis, and a dilutional anemia from an increase in the circulating blood volume. Palpitations attributed to premature atrial or ventricular beats have also been reported in pregnancy, but in the absence of structural heart disease, these are generally considered benign [30, 31].

Given the overlap between the signs and symptoms of heart failure and the physiology of late pregnancy, clinicians should maintain a high index of suspicion when a pregnant/peripartum woman presents with symptoms reminiscent of heart failure. Furthermore, women of childbearing age who present with symptoms of heart failure should always be screened for pregnancy by history, physical exam, and lab testing. Diagnostic imaging is mostly noninvasive and may be lifesaving in these cases. Timely diagnosis of cardiomyopathy in pregnancy may facilitate early treatment of heart failure and referral to multidisciplinary management, thereby improving both maternal and fetal prognoses [32].

11.3.2 Imaging and Procedural Diagnostic Modalities

Pregnant women who present with nonspecific symptoms such as shortness of breath and fatigue in the second and third trimester of pregnancy should undergo a thorough physical exam, an electrocardiogram (ECG), chest radiography, and an echocardiography.

The presence of a normal ECG is reassuring, as it has a high negative predictive value for severe systolic dysfunction [33]. However, a normal ECG does not counteract the need to perform an echocardiography. Furthermore, if there is an abnormal finding, information regarding the degree and type of myocardial dysfunction is crucial for optimization of management as well as for prognostic insight. Chest radiography may reveal cardiomegaly in women with cardiomyopathy and may also reduce the likelihood of alternative etiologies of clinical decompensation (e.g., pneumonia, pulmonary embolism, or other causes of non-cardiogenic pulmonary edema). Echocardiography confirming any abnormal ventricular function or size should raise a red flag. Left ventricular dysfunction (ejection fraction <50%, fractional shortening <30%, and end diastolic dimension >2.7 cm/m^2 body surface area) confirms the diagnosis of the more common types of cardiomyopathy seen in pregnancy [34–37]. Echocardiography may also determine the

subset and severity of cardiomyopathy, thereby directing management. Additional testing should include 24 h of cardiac telemetry. In the setting of ARVC (concealed phase), telemetry may be the most sensitive diagnostic modality, surpassing imaging techniques [5]. Telemetric identification of underlying arrhythmias may also guide interventions such as anticoagulation and/or antiarrhythmic therapies. Cardiovascular magnetic resonance (CMR) may be useful in characterizing cardiac anatomies but is rarely required in cardiomyopathy, as it is not likely to change treatment [5]. Additional invasive diagnostic tools that should be discussed on a case-by-case basis with an expert cardiologist include coronary catheterization and endomyocardial biopsy (EMB). EMB may be useful in suspected cases of myocarditis or infiltrative cardiomyopathy. However, routine use of EMB as a primary diagnostic modality remains controversial given the invasiveness of the procedure and improvements in noninvasive imaging. In addition, classification of myocarditis in cases of PPCM may remain indeterminate even in cases where EMB is performed [38].

11.3.3 Laboratory Investigations

Serum laboratory testing may be useful in the evaluation of pregnant women with cardiomyopathy-induced heart failure. Electrolyte screening may facilitate early identification of common electrolyte abnormalities accompanying heart failure (e.g., hyponatremia) and may also direct correction of electrolyte abnormalities that could lead to dysrhythmias (e.g., hypokalemia, which is commonly seen during treatment with loop diuretics).

Serum brain natriuretic peptide (BNP) levels may promote identification of cardiac causes of clinical deterioration in pregnancy [39]. In a small study by Hameed et al. (29 pregnant women compared to 25 nonpregnant controls), median BNP levels were approximately twofold higher in pregnant women (10–143 pg/mL) compared with nonpregnant controls (10–37 pg/mL) but remained stable throughout pregnancy [39]. Low BNP levels, below 128 pg/mL [40] or 100 pg/mL [41]), have a very high negative predictive value for cardiac events in pregnant women with structural or congenital cardiac disease. In other words, BNP levels may indicate the potential for cardiac events during pregnancy in these women [40, 41]. Of note, elevated BNP levels have also been found in pregnant women with preeclampsia [2, 42].

11.4 Pharmacologic Considerations

11.4.1 Intravascular Volume Reduction

Salt and water restriction as well as diuretics may be useful in managing intravascular volume in pregnant and peripartum women with cardiomyopathy. Furosemide and hydrochlorothiazide have been safely utilized in pregnancy. However, care must be taken to monitor placental perfusion and amniotic fluid volume, as both may be compromised with dehydration [8, 43].

11.4.2 Afterload-Reducing Medications

Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are widely utilized to reduce afterload in nonpregnant patients with heart failure/cardiomyopathy in both acute and chronic settings (with a mortality benefit) [44–47]. However, thoughtful consideration should be given to treatment with ACE inhibitors during pregnancy given their risk-benefit ratio. While these drugs are normally not considered for use in pregnancy due to concerns over fetal teratogenicity, the balance between maternal well-being and the risk of fetal teratogenicity requires that such decisions be made at an individual level [32, 48]. The European Registry on Pregnancy and Cardiac disease (ROPAC) associated maternal treatment with ACE inhibitors with an 8% rate of fetal malformations [49]. Severe neonatal complications have also been

described in the literature, including anuric renal failure and death [50, 51]. However, others claim that the risk profile of ACE inhibitors is similar to that of other antihypertensives, even when administered during the first trimester, suggesting that any increased risk is likely due to the underlying disease rather than to the treating drugs [52]. Therefore, if a severely ill pregnant woman has not responded to other treatment options, these drugs should be given consideration. Given the low levels found in breast milk, the American Academy of Pediatrics and the NIH do not absolutely contraindicate the use of ACE inhibitors in breastfeeding women [5, 32, 53]. ACE inhibitors may certainly be useful in the postpartum period for afterload reduction.

Spironolactone should also be avoided if possible during pregnancy given its potential antiandrogenic effects [54, 55]. Hydralazine may be a frequently used drug to manage hypertensive emergencies in the setting of preeclampsia with severe features. However, hydralazine use has rarely been described in the published literature for afterload reduction in the setting of heart failure [56, 57]. Similarly, nitrate administration has been described for antihypertensive treatment in the setting of preeclampsia, but its use in the setting of heart failure has not been described [58]. Both hydralazine and nitrate medications should be used with caution in order to avoid hypotension and compromised uteroplacental blood flow [59–61]. Calcium channel blockers are recommended for afterload reduction in heart failure in pregnancy and have been safely utilized in pregnancy [62, 63]. Nitroprusside is best avoided due to the potential for neonatal cyanide poisoning [32, 64].

Beta blockers have been widely utilized in pregnancy as antihypertensives and may be used in heart failure and/or for the management of arrhythmias [65, 66]. Atenolol is generally avoided, as it has been associated with an increased risk of intrauterine growth restriction compared with other selective beta-blocking agents [8]. Of note, in acute symptomatic heart failure, beta blocker therapy may have to be decreased or stopped to maintain hemodynamic stability, particularly in severe cases. In such cases, heart rate should be carefully monitored, as rebound arrhythmias may occur.

11.4.3 Vasopressors and Inotropes

While heart failure is typically accompanied by hypertension, severe cases may present with hemodynamic instability. The choice of vasoactive medications in such cases should be based on the underlying pathology contributing to clinical decompensation. Cardiac output should be optimized while minimizing the risk of dysrhythmia. The safety and efficacy of specific vasoactive medications in pregnancy remain poorly categorized [2]. However, given that these medications are usually administered in extreme maternal decompensation often as a lifesaving measure, the relevance of their effect on the fetus is questionable. For additional information regarding vasoactive drugs during pregnancy, see Chaps. 10 and 38.

11.4.4 Anti-arrhythmic Agents

Severe arrhythmias may occur in the pregnant woman with cardiomyopathy, warranting treatment. Maternal survival should remain a priority when administering any medications during pregnancy; this approach is even more crucial when treating maternal arrhythmias. Unstable arrhythmias should therefore be managed according to advanced cardiac life support guidelines, without concern for teratogenicity. This is also true with regard to direct cardioversion for unstable dysrhythmias. Implantation of an internal cardiac defibrillator (ICD) and/or cardiac catheterization and ablation may be required in severe cases. Both of these are lifesaving procedures and should therefore be performed as indicated regardless of pregnancy [8].

Treatment with some anti-arrhythmic agents is accompanied by more side effects and risk than others. Beta blockers are frequently used for treatment of hypertensive disorders of pregnancy; however, their utilization as anti-arrhythmics are limited to case reports/series in the published literature [67–69]. Beta-1 selective agents such as

metoprolol are preferred over drugs with beta-2 blockade (given the potential deleterious effect on uterine tone). Beta-1 selective agents are generally considered first-line pharmacologic treatment for acute stable arrhythmias in pregnancy [70]. Digoxin has also been widely used in pregnancy for the treatment of fetal arrhythmias in utero [71]. Given its extensive use in pregnancy, digoxin may be a useful adjunct to beta blockers for managing maternal arrhythmias and/or acute symptomatic heart failure (although it is no longer considered the medication of choice for these indications). Calcium channel blockers have been described in pregnancy for treatment of supraventricular tachycardia (SVT) [72–74]. Nicardipine, given by infusion, has also been safely described for treatment of refractory hypertension in the setting of preeclampsia with severe features, with no apparent deleterious maternal or fetal effects [75–77]. Similar to calcium channel blockers, adenosine has been administered to treat maternal SVT refractory to vagal maneuvers, with transient effects on the fetus [74, 78–80]. Amiodarone should be used as a temporizing measure for refractory life-threatening ventricular dysrhythmias. Its effect on fetal thyroid function may be important in longer-term use [70].

11.4.5 Targeted Therapy for Cardiomyopathy

Bromocriptine, a prolactin secretion inhibitor, showed early promise in improving left ventricular function and survival in acute PPCM [81–83]. These preliminary reports were supported by a systematic review by Desplanntie et al. that included two prospective randomized controlled trials evaluating the effects of bromocriptine in PPCM [84]. However, the authors acknowledged that the existing prospective data was limited in size and called for additional multicenter prospective studies [84]. Others have cautioned that postpartum administration of bromocriptine may suppress prolactin, which should be weighed against the potential benefits seen in limited prospective datasets [85]. Recent studies have also attempted to establish the doses required to optimize maternal outcomes in PPCM. One week of therapy has been suggested to equate to an 8-week treatment protocol [86].

11.4.6 Medications for Prevention of Thromboembolism

Pregnancy and heart failure are both risk factors for venous thromboembolism (VTE). The indications for therapeutic anticoagulation in pregnant women with heart failure stemming from cardiomyopathy remain unclear and treatment guidelines are lacking. Therefore, consistent with nonpregnant heart failure guidelines, the indications for therapeutic anticoagulation in the pregnant population with heart failure should probably include the presence of a known systemic/intracardiac thrombus or atrial fibrillation. Usually, therapeutic anticoagulation is not recommended for severely impaired ventricular function alone [87, 88]. However, compared with other cardiomyopathy subtypes, PPCM is associated with an increased risk of VTE (incidence as high as 6.6–6.8%). Therefore, the 2016 American Heart Association guidelines recommend anticoagulation during pregnancy and for 2 months postpartum for this specific type of cardiomyopathy [35, 89–91]. Regardless of cardiomyopathy type, pharmacologic thromboembolism prophylaxis is indicated in hospitalized nonpregnant heart failure patients and should therefore be given to most pregnant women admitted to hospital due to heart failure [87].

The optimal anticoagulant in pregnancy is low-molecular-weight heparin, as it does not cross the placental barrier. Low-molecular-weight heparin also requires less frequent dosing than unfractionated heparin and has a more predictable pharmacodynamic profile [2, 92]. Pregnant women may be transitioned to unfractionated heparin when nearing term in order to minimize the risk of postpartum hemorrhage and/or to enable the use of neuraxial analgesia/anesthesia when appropriate. Intravenous heparin may also be utilized during maternal inpatient admissions (e.g., when surgery may be indicated

and/or there is an increased risk of bleeding), as this mode of therapy allows rapid dosing titration. Vitamin K antagonists (warfarin) are generally contraindicated in the first trimester of pregnancy due to reported fetal anomalies (nasal hypoplasia, fetal bleeding, and more severe abnormalities). However, these too may be utilized when justified for maternal benefit, despite their potential effect on the fetus [8, 93].

11.5 Management of Decompensated Heart Failure

The pregnant woman with decompensated heart failure may require both noninvasive and invasive monitoring to guide treatment. Continuous electrocardiography may be used to monitor for dysrhythmias. Arterial catheterization may also prove helpful for beat-to-beat blood pressure assessment and for intravascular volume assessment. Depending on clinical circumstances, transthoracic/transesophageal echo and catheterization may provide detailed information about cardiac function. Foley catheterization may be indicated to closely monitor urine output in the setting of acute heart failure with ongoing diuresis goals. Central venous access may be required for sampling of mixed venous blood gases and/or administration of vasoactive medications. Although it is used much less frequently today than in the past, pulmonary artery catheterization may also be required in specific cases. Fetal monitoring requirements depend on fetal viability (i.e., gestational age) and the clinical circumstances. Fetal well-being generally reflects maternal well-being.

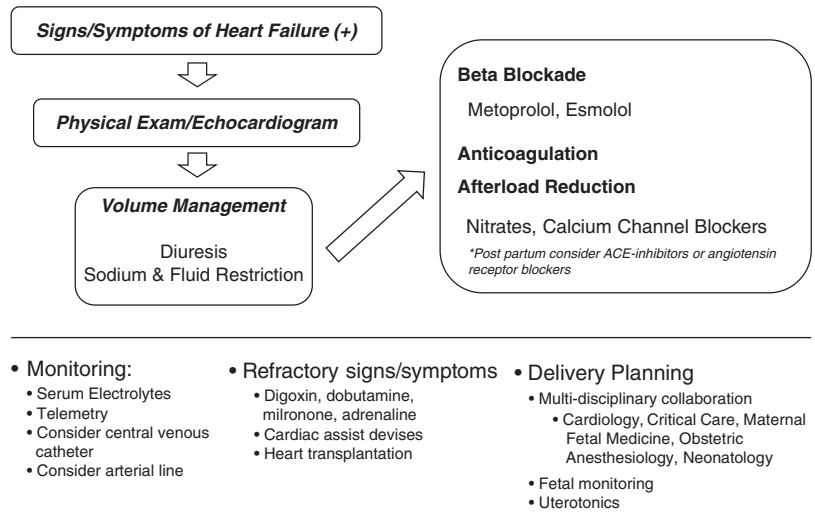
The management goals of acute symptomatic heart failure in the inpatient setting are similar in pregnant and nonpregnant populations. A careful examination of potential triggering factors should be undertaken in any pregnant woman presenting with acute heart failure. Interventions should be guided by intravascular volume assessments and the underlying cause of maternal decompensation. Salt restriction and diuretics are frequently employed to maintain euvolemia in systolic heart failure. Decompensated heart failure may require aggressive diuresis [92] . Cardiac afterload should be reduced, facilitating forward flow, in order to decrease the myocardial workload. Less commonly, heart rate or rhythm control may increase cardiac output in symptomatic heart failure. If maternal arterial saturation is <94%, supplemental oxygen may be administered to facilitate adequate oxygenation. Noninvasive ventilator support or intubation with mechanical ventilation may be warranted in severe heart failure with pulmonary edema. If the acute presentation also manifests with pulmonary hypertension, nitric oxide may be used. Nitric oxide dilates the pulmonary vascular bed in aerated lung zones, thereby reducing ventilation-perfusion mismatch and increasing oxygenation and flow from the right to the left heart.

If hypoxemia and hemodynamic instability persist despite optimization of supportive and medical care, a bridging therapy may be required. There are reports on the use of left ventricular assist devices, extracorporeal membranous oxygenation, and intra-aortic balloon pumps in cases of decompensated maternal heart failure in the literature [2, 94]. For severe cases of maternal cardiomyopathy refractory to conventional care, cardiac transplantation may be the only means of survival. See Fig. 11.1 for an algorithm of symptomatic heart failure management in the parturient with peripartum cardiomyopathy.

11.6 Management of Delivery

When severe hemodynamic compromise occurs during pregnancy, the most complex therapeutic decision that the treating clinician may be required to make is regarding delivery.

Whether the woman presents to labor and delivery, the emergency department, or via the intensive care unit, the first priority is hemodynamic stabilization. Ideally this should take place in the intensive care unit. Following initial stabilization, early delivery or termination of pregnancy should be considered; increased circulating blood volume may be the primary con-



Adapted from Z, Elkayam, Uri. Peripartum Cardiomyopathy. Circulation. 2016;133:1397-1409.

Fig. 11.1 Managment of symptomatic heart failure in the parturient with peripartum cardiomyopathy

tributor to decompensation. Generally, in the setting of maternal cardiomyopathy, the mode (vaginal or cesarean) and timing of delivery are determined primarily by obstetric indications. However, following hemodynamic optimization, these women should be managed by a multidisciplinary team. The 2016 MBRRACE report pointed to disintegration of expertise and services as a major determinant of maternal outcome, particularly in heart disease [95]. The team should consist of obstetricians/maternal fetal medicine, obstetric anesthesiology, cardiac anesthesiology, cardiology, cardiothoracic surgery, intensivists, neonatology, representation from labor and delivery and intensive care nursing, and inpatient pharmacy.

The multidisciplinary team may determine that vaginal delivery or induction of labor is unsafe and that cesarean delivery is preferred after initial maternal stabilization. Such surgery should ideally take place in an operating room and be planned in advance. The choice of operating room (main, labor and delivery, or cardiac) should be tailored to the requirements of the individual woman, as well as to local capabilities and equipment. Individual risk assessment should guide the choice of monitoring. Some cases may benefit from early neuraxial analgesia; this may blunt the sympathetic surge associated with painful contractions and facilitate assisted delivery in cases counseled against valsalva pushing in the second stage of labor.

Delivery (both vaginal and cesarean) may precipitate or worsen heart failure as it is accompanied by substantial fluid shifts and may also involve hemorrhage (see also Chap. 9). In severe cases, extracorporeal membrane oxygenation (ECMO) support may be required to optimize maternal condition (e.g., in persistent maternal hemodynamic compromise or cardiac arrest, see also Chap. 14). In such cases delivery should occur in situ [70]. Admission of a pregnant woman with severe heart failure to the ICU therefore requires that equipment and personnel for both vaginal and cesarean delivery be immediately available on location at all times. If delivery does take place in the ICU, an obstetric anesthesiologist should ideally be present on location to assist with analgesia, anesthesia, and/or peripartum resuscitation.

In the event of cesarean delivery, slow and careful titration of anesthesia is required to maintain maternal preload thus minimizing cardiac stress and/or dysrhythmias. Successful titration may be achieved using incremental epidural, low-dose combined spinal epidural with epidural volume extension or general anesthesia [96]. Pregnant women with cardiomyopathy may be treated with anticoagulants for many reasons. Therefore, if selected, neuraxial anesthesia

should be carefully timed with anticoagulant administration to minimize the risk of spinal hematoma and/or postpartum bleeding. Current recommended intervals for neuraxial anesthesia following anticoagulant dosing include 24 h for therapeutic unfractionated or low-molecular-weight heparin (LMWH) (with a normal PTT for unfractionated). Intravenous (IV) heparin should be held 4–6 h prior to neuraxial block with documented normalization of coagulation studies [97]. Therapeutic anticoagulation may be restarted >1 h after neuraxial block with IV heparin or after 24 h with LMWH, but the time interval should also take into consideration the potential for postpartum hemorrhage [97].

The benefit of uterotonics for treatment of uterine atony must be weighed against the potential for a decrease in preload (oxytocin, dose-dependent) or an increase in afterload (methylergonovine and carboprost) [98]. Careful dosing and/or avoidance may be indicated (in particular with methylergonovine), depending on the clinical circumstances. Oxytocin administration may be concentrated to minimize fluid administration and can be delivered by an infusion to minimize decreases in preload. Nonpharmacologic treatment of uterine atony may be beneficial in this population, as discussed in Chap. 6. Close monitoring in the ICU should be continued for a minimum of 48–72 h given the risk for postpartum heart failure exacerbation and or arrhythmias.

11.7 Conclusion

Cardiomyopathy may lead to decompensated heart failure during or after pregnancy. While intensive care treatment strategies are similar in both the pregnant and nonpregnant parturient, there are important distinctions in the diagnosis, management, and care coordination for the pregnant and postpartum women. A multidisciplinary approach to the critically ill parturient with severe decompensated heart failure may contribute to a decrease in maternal mortality.

Conflicts of Interest None.

References

1. Mhyre JM, Tsen LC, Einav S, Kuklina EV, Leffert LR, Bateman BT. Cardiac arrest during hospitalization for delivery in the United States, 1998-2011. Anesthesiology. 2014;120(4):810–8.
2. Golia E, Gravino R, Rea A, Masarone D, Rubino M, Cirillo A, et al. Management of pregnancy in cardiomyopathies and heart failure. Future Cardiol. 2017;13(1):81–96.
3. Gilson GJ, Samaan S, Crawford MH, Qualls CR, Curet LB. Changes in hemodynamics, ventricular remodeling, and ventricular contractility during normal pregnancy: a longitudinal study. Obstet Gynecol. 1997;89(6):957–62.
4. Kuklina EV, Callaghan WM. Cardiomyopathy and other myocardial disorders among hospitalizations for pregnancy in the United States: 2004-2006. Obstet Gynecol. 2010;115(1):93–100.
5. Herrey AS. Pregnancy in inherited and acquired cardiomyopathies. Best Pract Res Clin Obstet Gynaecol. 2014;28(4):563–77.
6. Watkins H, Ashrafian H, McKenna WJ. The genetics of hypertrophic cardiomyopathy: Teare redux. Heart. 2008;94(10):1264–8.
7. Hershberger RE, Cowan J, Morales A, Siegfried JD. Progress with genetic cardiomyopathies: screening, counseling, and testing in dilated, hypertrophic, and arrhythmogenic right ventricular dysplasia/cardiomyopathy. Circ Heart Fail. 2009;2(3):253–61.
8. Krul SP, van der Smagt JJ, van den Berg MP, Sollie KM, Pieper PG, van Spaendonck-Zwarts KY. Systematic review of pregnancy in women with inherited cardiomyopathies. Eur J Heart Fail. 2011;13(6):584–94.
9. Autore C, Conte MR, Piccininno M, Bernabo P, Bonfiglio G, Bruzzi P, et al. Risk associated with pregnancy in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2002;40(10):1864–9.
10. Avila WS, Amaral FM, Ramires JA, Rossi EG, Grinberg M, Bortolotto MR, et al. Influence of pregnancy on clinical course and fetal outcome of women with hypertrophic cardiomyopathy. Arq Bras Cardiol. 2007;88(4):480–5.
11. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, et al. Classification of the cardiomyopathies: a position statement from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2008;29(2):270–6.
12. Grewal J, Siu SC, Ross HJ, Mason J, Balint OH, Sermer M, et al. Pregnancy outcomes in women with dilated cardiomyopathy. J Am Coll Cardiol. 2009;55(1):45–52.
13. Bernstein PS, Magriples U. Cardiomyopathy in pregnancy: a retrospective study. Am J Perinatol. 2001;18(3):163–8.
14. van Tintelen JP, van Spaendonck-Zwarts KY, van den Berg MP. Lamin A/C-related cardiac disease and pregnancy. Eur J Heart Fail. 2010;12(6):532–4.

15. Blauwet LA, Cooper LT. Diagnosis and management of peripartum cardiomyopathy. Heart. 2011;97(23):1970–81.
16. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association scientific statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation. 2006;113(14):1807–16.
17. Brar SS, Khan SS, Sandhu GK, Jorgensen MB, Parikh N, Hsu JW, et al. Incidence, mortality, and racial differences in peripartum cardiomyopathy. Am J Cardiol. 2007;100(2):302–4.
18. Fett JD, Christie LG, Carraway RD, Murphy JG. Five-year prospective study of the incidence and prognosis of peripartum cardiomyopathy at a single institution. Mayo Clin Proc. 2005;80(12):1602–6.
19. Patten IS, Rana S, Shahul S, Rowe GC, Jang C, Liu L, et al. Cardiac angiogenic imbalance leads to peripartum cardiomyopathy. Nature. 2012;485(7398):333–8.
20. Bello N, Rendon IS, Arany Z. The relationship between pre-eclampsia and peripartum cardiomyopathy: a systematic review and meta-analysis. J Am Coll Cardiol. 2013;62(18):1715–23.
21. Sliwa K, Forster O, Libhaber E, Fett JD, Sundstrom JB, Hilfiker-Kleiner D, et al. Peripartum cardiomyopathy: inflammatory markers as predictors of outcome in 100 prospectively studied patients. Eur Heart J. 2006;27(4):441–6.
22. Haghikia A, Podewski E, Libhaber E, Labidi S, Fischer D, Roentgen P, et al. Phenotyping and outcome on contemporary management in a German cohort of patients with peripartum cardiomyopathy. Basic Res Cardiol. 2013;108(4):366.
23. Murali S, Baldisseri MR. Peripartum cardiomyopathy. Crit Care Med. 2005;33(10 Suppl):S340–6.
24. Sliwa K, Skudicky D, Bergemann A, Candy G, Puren A, Sareli P. Peripartum cardiomyopathy: analysis of clinical outcome, left ventricular function, plasma levels of cytokines and Fas/APO-1. J Am Coll Cardiol. 2000;35(3):701–5.
25. Harper MA, Meyer RE, Berg CJ. Peripartum cardiomyopathy: population-based birth prevalence and 7-year mortality. Obstet Gynecol. 2012;120(5):1013–9.
26. Kao DP, Hsich E, Lindenfeld J. Characteristics, adverse events, and racial differences among delivering mothers with peripartum cardiomyopathy. JACC Heart Fail. 2013;1(5):409–16.
27. Goland S, Modi K, Bitar F, Janmohamed M, Mirocha JM, Czer LS, et al. Clinical profile and predictors of complications in peripartum cardiomyopathy. J Card Fail. 2009;15(8):645–50.
28. Elkayam U, Tummala PP, Rao K, Akhter MW, Karaalp IS, Wani OR, et al. Maternal and fetal outcomes of subsequent pregnancies in women with peripartum cardiomyopathy. N Engl J Med. 2001;344(21):1567–71.
29. Mandal D, Mandal S, Mukherjee D, Biswas SC, Maiti TK, Chattopadhaya N, et al. Pregnancy and subsequent pregnancy outcomes in peripartum cardiomyopathy. J Obstet Gynaecol Res. 2011;37(3):222–7.
30. Adamson DL, Nelson-Piercy C. Managing palpitations and arrhythmias during pregnancy. Heart. 2007;93(12):1630–6.
31. Shotan A, Ostrzega E, Mehra A, Johnson JV, Elkayam U. Incidence of arrhythmias in normal pregnancy and relation to palpitations, dizziness, and syncope. Am J Cardiol. 1997;79(8):1061–4.
32. Pearson GD, Veille JC, Rahimtoola S, Hsia J, Oakley CM, Hosenpud JD, et al. Peripartum cardiomyopathy: National Heart, Lung, and Blood Institute and Office of Rare Diseases (National Institutes of Health) workshop recommendations and review. JAMA. 2000;283(9):1183–8.
33. Davie AP, Francis CM, Love MP, Caruana L, Starkey IR, Shaw TR, et al. Value of the electrocardiogram in identifying heart failure due to left ventricular systolic dysfunction. BMJ. 1996;312(7025):222.
34. Sliwa K, Fett J, Elkayam U. Peripartum cardiomyopathy. Lancet. 2006;368(9536):687–93.
35. Arany Z, Elkayam U. Peripartum cardiomyopathy. Circulation. 2016;133(14):1397–409.
36. Hibbard JU, Lindheimer M, Lang RM. A modified definition for peripartum cardiomyopathy and prognosis based on echocardiography. Obstet Gynecol. 1999;94(2):311–6.
37. Chapa JB, Heiberger HB, Weinert L, Decara J, Lang RM, Hibbard JU. Prognostic value of echocardiography in peripartum cardiomyopathy. Obstet Gynecol. 2005;105(6):1303–8.
38. Bhakta P, Biswas BK, Banerjee B. Peripartum cardiomyopathy: review of the literature. Yonsei Med J. 2007;48(5):731–47.
39. Hameed AB, Chan K, Ghamsary M, Elkayam U. Longitudinal changes in the B-type natriuretic peptide levels in normal pregnancy and postpartum. Clin Cardiol. 2009;32(8):E60–2.
40. Kampman MA, Balci A, van Veldhuisen DJ, van Dijk AP, Roos-Hesselink JW, Sollie-Szarynska KM, et al. N-terminal pro-B-type natriuretic peptide predicts cardiovascular complications in pregnant women with congenital heart disease. Eur Heart J. 2014;35(11):708–15.
41. Tanous D, Siu SC, Mason J, Greutmann M, Wald RM, Parker JD, et al. B-type natriuretic peptide in pregnant women with heart disease. J Am Coll Cardiol. 2010;56(15):1247–53.
42. Resnik JL, Hong C, Resnik R, Kazanegra R, Beede J, Bhalla V, et al. Evaluation of B-type natriuretic peptide (BNP) levels in normal and preeclamptic women. Am J Obstet Gynecol. 2005;193(2):450–4.
43. van Mook WN, Peeters L. Severe cardiac disease in pregnancy, part II: impact of congenital and acquired

cardiac diseases during pregnancy. Curr Opin Crit Care. 2005;11(5):435–48.
44. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med. 1987;316(23):1429–35.
45. SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med. 1991;325(5):293–302.
46. Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med. 1991;325(5):303–10.
47. SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB Jr, Cohn JN. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med. 1992;327(10):685–91.
48. Bullo M, Tschumi S, Bucher BS, Bianchetti MG, Simonetti GD. Pregnancy outcome following exposure to angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists: a systematic review. Hypertension. 2012;60(2):444–50.
49. Ruys TP, Maggioni A, Johnson MR, Sliwa K, Tavazzi L, Schwerzmann M, et al. Cardiac medication during pregnancy, data from the ROPAC. Int J Cardiol. 2014;177(1):124–8.
50. Task Force on the Management of Cardiovascular Diseases During Pregnancy of the European Society of Cardiology. Expert consensus document on management of cardiovascular diseases during pregnancy. Eur Heart J. 2003;24(8):761–81.
51. Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, Dyer S, Gideon PS, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. N Engl J Med. 2006;354(23):2443–51.
52. Li DK, Yang C, Andrade S, Tavares V, Ferber JR. Maternal exposure to angiotensin converting enzyme inhibitors in the first trimester and risk of malformations in offspring: a retrospective cohort study. BMJ. 2011;343:d5931.
53. National Institute for Health and Clinical Excellence: guidance. Hypertension in pregnancy: the management of hypertensive disorders during pregnancy. National Collaborating Centre for Women's and Children's Health (UK). London: RCOG Press; 2010. https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0033454/pdf/PubMedHealth_PMH0033454.pdf. Accessed 15 Aug 2018.
54. Messina M, Biffignandi P, Ghigo E, Jeantet MG, Molinatti GM. Possible contraindication of spironolactone during pregnancy. J Endocrinol Invest. 1979;2(2):222.
55. Hecker A, Hasan SH, Neumann F. Disturbances in sexual differentiation of rat foetuses following spironolactone treatment. Acta Endocrinol. 1980;95(4):540–5.
56. Pritchard JA, Pritchard SA. Standardized treatment of 154 consecutive cases of eclampsia. Am J Obstet Gynecol. 1975;123(5):543–52.
57. Gevaert S, De Pauw M, Tromp F, Ascoop AK, Roelens K, De Backer J. Treatment of pre-existing cardiomyopathy during pregnancy. Acta Cardiol. 2014;69(2):193–6.
58. Snyder SW, Wheeler AS, James FM 3rd. The use of nitroglycerin to control severe hypertension of pregnancy during cesarean section. Anesthesiology. 1979;51(6):563–4.
59. Spinnato JA, Sibai BM, Anderson GD. Fetal distress after hydralazine therapy for severe pregnancy-induced hypertension. South Med J. 1986;79(5):559–62.
60. Kuzniar J, Skret A, Piela A, Szmigiel Z, Zaczek T. Hemodynamic effects of intravenous hydralazine in pregnant women with severe hypertension. Obstet Gynecol. 1985;66(4):453–8.
61. Cotton DB, Longmire S, Jones MM, Dorman KF, Tessem J, Joyce TH 3rd. Cardiovascular alterations in severe pregnancy-induced hypertension: effects of intravenous nitroglycerin coupled with blood volume expansion. Am J Obstet Gynecol. 1986;154(5):1053–9.
62. European Society of Gynecology (ESG); Association for European Paediatric Cardiology (AEPC); German Society for Gender Medicine (DGesGM), Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM, Gibbs JS, Gohlke-Baerwolf C, Gorenek B, Iung B, Kirby M, Maas AH, Morais J, Nihoyannopoulos P, Pieper PG, Presbitero P, Roos-Hesselink JW, Schaufelberger M, Seeland U, Torracca L, ESC Committee for Practice Guidelines. ESC guidelines on the management of cardiovascular diseases during pregnancy: the task force on the management of cardiovascular diseases during pregnancy of the European Society of Cardiology (ESC). Eur Heart J. 2011;32(24):3147–97.
63. Weber-Schoendorfer C, Hannemann D, Meister R, Elefant E, Cuppers-Maarschalkerweerd B, Arnon J, et al. The safety of calcium channel blockers during pregnancy: a prospective, multicenter, observational study. Reprod Toxicol. 2008;26(1):24–30.
64. Palmer RF, Lasseter KC. Drug therapy. Sodium nitroprusside. N Engl J Med. 1975;292(6):294–7.
65. Yakoob MY, Bateman BT, Ho E, Hernandez-Diaz S, Franklin JM, Goodman JE, et al. The risk of congenital malformations associated with exposure to beta-blockers early in pregnancy: a meta-analysis. Hypertension. 2013;62(2):375–81.
66. Nakhai-Pour HR, Rey E, Berard A. Antihypertensive medication use during pregnancy and the risk of major congenital malformations or small-for-gestational-age newborns. Birth Defects Res B Dev Reprod Toxicol. 2010;89(2):147–54.
67. Committee on Obstetric Practice. Committee opinion No. 692: emergent therapy for acute-onset, severe

hypertension during pregnancy and the postpartum period. Obstet Gynecol. 2017;129(4):e90–5.
68. Brodsky M, Doria R, Allen B, Sato D, Thomas G, Sada M. New-onset ventricular tachycardia during pregnancy. Am Heart J. 1992;123(4 Pt 1):933–41.
69. Rotmensch HH, Elkayam U, Frishman W. Antiarrhythmic drug therapy during pregnancy. Ann Intern Med. 1983;98(4):487–97.
70. Jeejeebhoy FM, Zelop CM, Lipman S, Carvalho B, Joglar J, Mhyre JM, et al. Cardiac arrest in pregnancy: a scientific statement from the American Heart Association. Circulation. 2015;132(18):1747–73.
71. Alsaied T, Baskar S, Fares M, Alahdab F, Czosek RJ, Murad MH, et al. First-line antiarrhythmic transplacental treatment for fetal tachyarrhythmia: a systematic review and meta-analysis. J Am Heart Assoc. 2017;6(12):e007164.
72. Klein V, Repke JT. Supraventricular tachycardia in pregnancy: cardioversion with verapamil. Obstet Gynecol. 1984;63(3 Suppl):16S–8S.
73. Byerly WG, Hartmann A, Foster DE, Tannenbaum AK. Verapamil in the treatment of maternal paroxysmal supraventricular tachycardia. Ann Emerg Med. 1991;20(5):552–4.
74. Robins K, Lyons G. Supraventricular tachycardia in pregnancy. Br J Anaesth. 2004;92(1):140–3.
75. Aya AG, Mangin R, Hoffet M, Eledjam JJ. Intravenous nicardipine for severe hypertension in pre-eclampsia—effects of an acute treatment on mother and foetus. Intensive Care Med. 1999;25(11):1277–81.
76. Hanff LM, Vulto AG, Bartels PA, Roofthooft DW, Bijvank BN, Steegers EA, et al. Intravenous use of the calcium-channel blocker nicardipine as second-line treatment in severe, early-onset pre-eclamptic patients. J Hypertens. 2005;23(12):2319–26.
77. Cornette J, Buijs EA, Duvekot JJ, Herzog E, Roos-Hesselink JW, Rizopoulos D, et al. Hemodynamic effects of intravenous nicardipine in severely pre-eclamptic women with a hypertensive crisis. Ultrasound Obstet Gynecol. 2016;47(1):89–95.
78. Harrison JK, Greenfield RA, Wharton JM. Acute termination of supraventricular tachycardia by adenosine during pregnancy. Am Heart J. 1992;123(5):1386–8.
79. Elkayam U, Goodwin TM. Adenosine therapy for supraventricular tachycardia during pregnancy. Am J Cardiol. 1995;75(7):521–3.
80. Dunn JS Jr, Brost BC. Fetal bradycardia after IV adenosine for maternal PSVT. Am J Emerg Med. 2000;18(2):234–5.
81. Jahns BG, Stein W, Hilfiker-Kleiner D, Pieske B, Emons G. Peripartum cardiomyopathy—a new treatment option by inhibition of prolactin secretion. Am J Obstet Gynecol. 2008;199(4):e5–6.
82. Abe T, Amano I, Sawa R, Akira S, Nakai A, Takeshita T. Recovery from peripartum cardiomyopathy in a Japanese woman after administration of bromocriptine as a new treatment option. J Nippon Med Sch. 2010;77(4):226–30.
83. Habedank D, Kuhnle Y, Elgeti T, Dudenhausen JW, Haverkamp W, Dietz R. Recovery from peripartum cardiomyopathy after treatment with bromocriptine. Eur J Heart Fail. 2008;10(11):1149–51.
84. Desplantie O, Tremblay-Gravel M, Avram R, Marquis-Gravel G, Ducharme A, Jolicoeur EM, et al. The medical treatment of new-onset peripartum cardiomyopathy: a systematic review of prospective studies. Can J Cardiol. 2015;31(12):1421–6.
85. Fett JD. Caution in the use of bromocriptine in peripartum cardiomyopathy. J Am Coll Cardiol. 2008;51(21):2083; author reply 2083-4.
86. Hilfiker-Kleiner D, Haghikia A, Berliner D, Vogel-Claussen J, Schwab J, Franke A, et al. Bromocriptine for the treatment of peripartum cardiomyopathy: a multicentre randomized study. Eur Heart J. 2017;38(35):2671–9.
87. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. J Am Coll Cardiol. 2013;62(16):e147–239.
88. Lip GY, Ponikowski P, Andreotti F, Anker SD, Filippatos G, Homma S, et al. Thrombo-embolism and antithrombotic therapy for heart failure in sinus rhythm. A joint consensus document from the ESC Heart Failure Association and the ESC Working Group on Thrombosis. Eur J Heart Fail. 2012;14(7):681–95.
89. Elkayam U. Clinical characteristics of peripartum cardiomyopathy in the United States: diagnosis, prognosis, and management. J Am Coll Cardiol. 2011;58(7):659–70.
90. Sliwa K, Mebazaa A, Hilfiker-Kleiner D, Petrie MC, Maggioni AP, Laroche C, et al. Clinical characteristics of patients from the worldwide registry on peripartum cardiomyopathy (PPCM): EURObservational research Programme in conjunction with the Heart Failure Association of the European Society of Cardiology Study Group on PPCM. Eur J Heart Fail. 2017;19(9):1131–41.
91. Kolte D, Khera S, Aronow WS, Palaniswamy C, Mujib M, Ahn C, et al. Temporal trends in incidence and outcomes of peripartum cardiomyopathy in the United States: a nationwide population-based study. J Am Heart Assoc. 2014;3(3):e001056.
92. Widerhorn J, Rubin JN, Frishman WH, Elkayam U. Cardiovascular drugs in pregnancy. Cardiol Clin. 1987;5(4):651–74.
93. Vitale N, De Feo M, De Santo LS, Pollice A, Tedesco N, Cotrufo M. Dose-dependent fetal complications of warfarin in pregnant women with mechanical heart valves. J Am Coll Cardiol. 1999;33(6):1637–41.
94. Gevaert S, Van Belleghem Y, Bouchez S, Herck I, De Somer F, De Block Y, et al. Acute and critically ill peripartum cardiomyopathy and 'bridge to' therapeutic options: a single center experience with intra-aortic balloon pump, extra corporeal membrane oxygenation and continuous-flow left ventricular assist devices. Crit Care. 2011;15(2):R93.
95. Knight M, Kenyon S, Brocklehurst P, Neilson J, Shakespeare J, Kurinczuk JJ, editors. on behalf of

MBRRACE-UK. Saving lives, improving mothers' care—lessons learned to inform future maternity care from the UK and Ireland confidential enquiries into maternal deaths and morbidity 2009–12. Oxford: National Perinatal Epidemiology Unit, University of Oxford. 2014. https://www.npeu.ox.ac.uk/downloads/files/mbrrace-uk/reports/Saving%20Lives%20Improving%20Mothers%20Care%20report%202014%20Full.pdf. Accessed 15 Aug 2018.

96. Langesaeter E, Dragsund M, Rosseland LA. Regional anaesthesia for a caesarean section in women with cardiac disease: a prospective study. Acta Anaesthesiol Scand. 2010;54(1):46–54.
97. Leffert L, Butwick A, Carvalho B, Arendt K, Bates SM, Friedman A, et al. The Society for Obstetric Anesthesia and Perinatology consensus statement on the anesthetic management of pregnant and postpartum women receiving thromboprophylaxis or higher dose anticoagulants. Anesth Analg. 2018;126(3):928–44.
98. Committee on Practice Bulletins-Obstetrics. Practice Bulletin No. 183: postpartum hemorrhage. Obstet Gynecol. 2017;130(4):e168–86.

Pulmonary Hypertension

12

Marie-Louise Meng and Elena Reitman

Bullet Points

- Women with severe PH, and particularly those with pulmonary arterial hypertension (PAH) and Eisenmenger syndrome, should be counseled to avoid pregnancy (or consider termination). Although more recent studies suggest improved outcomes, maternal morbidity and mortality remain very high despite advanced therapies.
- The medical management for chronic and acute management of PH during pregnancy is targeted toward vasodilation of the maternal pulmonary circulation. Treatment includes (1) parenteral and inhaled prostacyclin, as well as phosphodiesterase inhibitors, (2) continuous supplemental oxygen, (3) inhaled nitric oxide around the time of delivery, and (4) inotropes such as dobutamine, milrinone, and epinephrine, to improve maternal cardiac output.
- Since PH causes a hypercoagulable state, compounded with the hypercoagulable state of pregnancy, women with PH should receive pharmacological thromboembolic prophylaxis throughout pregnancy and the postpartum period.
- Thrombocytopenia is often present in these patients; therefore, thrombocytopenia monitoring is needed.
- Balancing adequate anticoagulation and possible thrombocytopenia poses a real challenge in terms of weighing the benefits versus risks associated with neuraxial labor analgesia or anesthesia for cesarean delivery.
- The available literature does not currently support one mode of delivery over the other. The choice of vaginal versus cesarean delivery should be based on a case-by-case multidisciplinary discussion.
- Neuraxial labor analgesia is highly recommended for an attempted trial of labor with vaginal delivery. Neuraxial analgesia modulates the excess catecholamine release seen with prolonged maternal labor pain and enables vaginal-assisted delivery or an intrapartum cesarean delivery if a vaginal delivery is not achieved. Forceps or vacuum may be used to reduce bearing down and Vlasalva manuevers during vaginal-assisted delivery.

M.-L. Meng · E. Reitman (✉)
Department of Anesthesiology, Columbia University Medical Center, New York, NY, USA
e-mail: er2323@cumc.columbia.edu

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_12

- Urgent cesarean delivery should absolutely be avoided whenever possible.
- For a planned cesarean delivery, neuraxial (epidural or combined spinal-epidural) anesthesia is recommended over general anesthesia. General anesthesia is known to depress cardiac contractility and increase pulmonary vascular resistance via positive pressure ventilation.
- The periods of highest risk for maternal mortality are the peripartum period and immediate postpartum period (up to 2 months). This is probably due to the rapid fluid shifts during these periods and peak hypercoagulable state.

12.1 Overview of the Disease

Pulmonary hypertension (PH) is a condition characterized by chronic elevation of mean pulmonary arterial pressure > 25 mmHg at rest [1]. PH may be idiopathic, familial, or associated with multiple other diseases. The revised World Health Organization (WHO) classification system describes five categories of PH [2]. Patients in the first group are considered to have pulmonary *arterial* hypertension (PAH), whereas patients in the remaining four groups are considered to have pulmonary hypertension (PH) (Table 12.1). When all five groups are discussed collectively, the term PH is generally used.

Historically, high rates of maternal and fetal death have been reported for pregnant women with PH (30–56% and 11–28%, respectively) [3, 4]. The causes of poor maternal outcomes are varied and include right heart failure, arrhythmia, and/or stroke from intracardiac shunting [5]. Furthermore, the prevalence of maternal peri- and postpartum right heart failure is high, probably due to both hemodynamic stress and bleeding complications [6, 7]. The most common risk to the fetus is death; however, premature birth and growth restriction are also common [8, 9].

Table 12.1 World Health Organization (WHO) classification of pulmonary hypertension [2]

Group	Etiology of pulmonary hypertension	Example
1	Pulmonary arterial hypertension	Idiopathic Heritable Drug and toxin induced Congenital heart disease Connective tissue diseases
2	Left heart disease	Systolic or diastolic failure Valvular disease
3	Chronic lung disease or hypoxemia	Chronic obstructive pulmonary disease (COPD) Interstitial lung disease Obstructive sleep apnea
4	Chronic thrombotic disease	Chronic thromboembolic pulmonary hypertension (CTEPH)
5	Unclear multifactorial mechanisms	Hematologic disorders Systemic disorders Metabolic disorders Tumor obstruction

Current guidelines unequivocally recommend avoidance of pregnancy in women with PH, and termination when pregnancy does occur [10]. However, if a woman is already pregnant and chooses to continue her pregnancy, she should be informed by a multidisciplinary team including her obstetrician and cardiologist of the estimated risk of continuing this pregnancy. These discussions should be tailored to each woman's specific etiology and severity of PH, as both maternal and fetal risks vary from case to case [9]. Women should be referred to specialized PH centers with cardiologists trained in treatment of PH, maternal fetal medicine specialists, and cardiothoracic and obstetric anesthesiologists familiar with the management of PH in pregnancy, neonatal and maternal ICUs, and extracorporeal membrane oxygenation (ECMO) capabilities as both termination and continuation of pregnancy require advanced cardiopulmonary care [11].

12.2 Pulmonary Arterial Hypertension (WHO Classification Group 1)

The estimated incidence of PAH in pregnancy is 1.1 per 100,000 pregnancies [12]. For reasons still unknown, PAH affects women 3–4 times more than men [2, 13, 14].

PAH is characterized by a primary elevation in pulmonary vascular resistance (PVR) accompanied by an increase pulmonary arterial pressure (PAP) leading to right ventricular failure. With this type of pathology, pulmonary artery occlusion (or wedge) pressure typically remains normal throughout pregnancy and in the postpartum.

The pathologic appearance of the small pulmonary arteries and arterioles is qualitatively similar in all patients with PAH. PAH typically involves worsening structural changes in the pulmonary vasculature, including intimal proliferation, smooth muscle hypertrophy, atheromatous changes, narrowing of the arterial bed, and in situ thrombosis [15]. The process may also involve increased endothelin levels (endothelin is a vasoconstrictor and mitogen), estrogen-induced growth, decreased nitric oxide levels (nitric oxide is a vasodilator and is antiproliferative), and/or decreased prostacyclin levels (prostacyclin is a vasodilator, is antiproliferative, and inhibits platelet function) [11].

The small vessel arteriopathy in PAH leads to a progressive rise in RV afterload and PVR. As a result, the RV undergoes stereotypical changes including hypertrophy, dilatation, and ultimately dysfunction. If PAH is left untreated, RV failure will ensue.

The development of PAH has been associated with multiple factors including human immunodeficiency virus infection, liver disease, sickle cell disease, connective tissue disorders, congenital heart disease, and drugs or toxins [16]. Rarely, there is no identifiable cause or associated underlying disease. In such cases, PAH is referred to as idiopathic (IPAH) or primary PAH (PPH). A familial form of IPAH (FPAH) accounts for about 6% of cases [2]. The proliferative nature of PAH has led some to consider it analogous to cancer leading to emergence of a multiple hit theory for explaining the development of the disease [11]. In other words, patients with PAH are thought to have an underlying genetic predisposition to pulmonary vascular disease, and a superimposed "second hit" or modifying factor then activates the disease process [17–19].

12.3 Pulmonary Hypertension (WHO Classification Groups 2–5)

The pathophysiology of all other PH classification (WHO Group 2–5) is less understood than PAH (WHO Group 1). However, it is clear that some overlap exists since vascular remodeling and increased PVR are present in all groups.

- Group 2 includes PH with conditions that affect the left side of the heart, such as mitral valve disease [20].
- Group 3 includes PH associated with lung diseases, such as chronic obstructive pulmonary disease (COPD), interstitial lung diseases, and sleep apnea. This group is very uncommon in young women [9].
- Group 4 includes PH caused by blood clots in the lungs or blood clotting disorders in women with a venous thromboembolic (VTE) disease. This cause of PH is of particular importance in pregnant woman since the hypercoagulable status of pregnancy increases the risk of pulmonary emboli and pulmonary arterial thrombosis [4, 7].
- Group 5 includes PH caused by various other diseases or conditions such as blood disorders (e.g., polycythemia vera, essential thrombocythemia), systemic disorders, (e.g., sarcoidosis, vasculitis), metabolic disorders (e.g., thyroid disease, glycogen storage disease), renal disease, and other conditions (tumors that press on the pulmonary arteries) [21].

12.4 Failure of the Physiologic Adaptation to Pregnancy in Women with Pulmonary Hypertension

Pregnancy is associated with an increase in blood volume. In the healthy pregnant woman, the pulmonary vasculature adapts to this increase in volume by vasodilation, thereby preventing increases in pulmonary pressure [11]. In women with PH, the pulmonary vasculature is unable to adapt to the increase in flow and volume, leading to an acute increase in pulmonary pressure [11]. This rapid increase in flow and volume can precipitate right heart failure. As right ventricular function deteriorates, the preload of the left heart is compromised and cardiac output decreases.

Specifically in women with shunt lesions (intra or extracardiac defects), PH may also cause right to left shunting resulting in Eisenmenger syndrome. The combination of pregnancy-induced systemic vascular resistance (SVR) reduction and increasing pulmonary pressures will cause blood to flow preferentially through a shunt bypassing the lungs (Eisenmenger syndrome) [22]. Right to left shunting may therefore increase during pregnancy resulting in increased systemic hypoxia.

12.5 Clinical Presentation of PH During Pregnancy

Fatigue and exertional dyspnea are the most frequent presenting symptoms of PH. Both of these symptoms indicate reduced cardiac output and impaired oxygen transport. However, since these symptoms are nonspecific and commonly occur in healthy pregnant women, this may result in a critical delay in diagnosis of PH or right heart failure.

In women with undiagnosed PH, the expectation is that these symptoms will dramatically worsen during the course of pregnancy with dyspnea eventually occurring even at rest. During second trimester particularly, increases in plasma volume are a common trigger for maternal decompensation in the context of known or undiagnosed PH. Therefore with a medical history indicating precipitous and consistent deterioration in a previously healthy woman, the diagnosis of PH should be strongly considered.

Most signs of right heart failure, such as hepatomegaly, ascites, and ankle edema, result from poor right heart forward flow. These signs are often difficult to identify during pregnancy or resemble normal pregnancy. On physical exam, elevated jugular venous pressure and a loud pulmonary component of the second heart sound are useful signs that point to the diagnosis.

If the condition of the woman enables this at the time of presentation, functional capacity needs to be evaluated (New York Heart Association or World Health Organization functional class) [1]. Although assessment of exercise capacity with a 6-min walking test is recommended [10], this should not be performed during acute deterioration.

Right ventricular failure is the most common cause of death in patients with PAH [23]. Typical clinical manifestations of severe RV failure include syncope, angina, edema, and abdominal distention. Syncope can result from low cardiac output. Chest pain is a late sign and may reflect right ventricular ischemia. Right ventricular ischemia results from mild reduction in right heart function leading to decreased left-sided filling and decreased cardiac output which can result in decreased coronary perfusion and further right heart failure. As coronary perfusion is compromised (especially to the subendocardium in the hypertrophied right ventricle), cardiac output falls and end-diastolic pressures increase. With higher filling pressures, coronary perfusion continues to decrease, and pulmonary congestion and edema develop, further increasing pulmonary pressures and right heart afterload.

12.6 Diagnosis and Assessment

12.6.1 Transthoracic Echocardiography

In a woman with unexplained dyspnea during pregnancy, transthoracic echocardiography

(TTE) should be performed. TTE is noninvasive and allows assessment of myocardial function, valves, and estimated pulmonary pressures. TTE usually reveals PH and right heart strain if such exist. The tricuspid regurgitation jet observed in TTE can be used to estimate disease severity [24]. In women with PH, TTE is also the ideal tool for repeated assessments of pulmonary artery pressures and cardiac heart function during pregnancy; serial TTE exams can identify early signs of right heart strain and guide escalation in management of PH and myocardial function.

12.6.2 Right Heart Catheterization

Right heart catheterization is usually required to confirm the diagnosis of PH and provides useful additional information on pulmonary vascular resistance and cardiac output. In the pregnant woman, cardiac catheterization should only be performed if TTE is unavailable or unable to provide information about pulmonary pressures or the degree of pulmonary vascular response to therapy. It should also be reserved for women in whom the results have therapeutic consequences to assess the maternal response to pulmonary vasodilator therapy. Catheterization can be performed with relatively low fetal risk since radiation can be avoided.

12.7 Management of PH During Pregnancy

Women with known PH who become pregnant should have monthly obstetrical and cardiology follow-up during the first trimester. As pregnancy symptoms such as dyspnea and edema develop, aggravation of PH and right heart failure should be assessed clinically and with TTE [11, 25]. As pregnancy progresses, these women will require more frequent monitoring. Hospital admission may be indicated from the second trimester until delivery. The mainstay of early therapy is diuresis, which is intended to manage the increase in plasma volume.

Prevention of venous thromboembolism must be addressed as women with PH may have cumulative pro-thrombotic risk factors. The hypercoagulability of pregnancy combined with the specific thrombogenic underlying characteristics of PH, occurring in women with decreased physical activity in the context of reduced heart function, results in a significant risk of pulmonary emboli and pulmonary arterial thrombosis. Women who are admitted to the hospital for management of PH or who are on bed rest should be at the least receiving pharmacological thromboprophylaxis, and with more significant risk factors (low flow states, shunt lesions), higher anticoagulation goals may be indicated (LMWH 1 mg/kg subcutaneously twice daily) [24, 26]. Paradoxical emboli are a risk in women with a patent foramen ovale, Eisenmenger syndrome, or any shunt lesion. According to the statement on pregnancy in pulmonary hypertension from the Pulmonary Vascular Research Institute guidelines, anticoagulant treatment is recommended in any patient with idiopathic PAH although no prospective studies have proved the efficacy of this treatment [11, 27]. Additionally, all hospitalized patients should have mechanical compression stockings [28].

Options for anticoagulation in pregnancy include unfractionated heparin (UFH), low-molecular- weight heparin (LMWH), and coumadin. In patients receiving anticoagulation before pregnancy, the risk and benefits of this therapy should be re-evaluated. Both UFH and LMWH do not cross the placenta so teratogenicity is not a concern as it is with coumadin. LMWH provides optimal VTE prophylaxis in pregnancy. The pharmacokinetics/dynamics of UFH are less reliable in pregnancy. New evidence suggests that common dosing of UFH in pregnancy (5000 units subcutaneously twice daily) is likely not sufficient to achieve the targeted goal of reducing the likelihood of a thromboembolic event and compensate for the pregnancy-related changes that affect anticoagulant pharmacokinetics (increased plasma volume, renal blood flow and glomerular filtration rate, and lower albumin concentrations). Warfarin should be stopped due to its teratoge-

nicity and unfractionated or low-molecular-weight heparin should be used if anticoagulation is to be continued [11].

With the recent consensus statement of the Society for Obstetric Anesthesia and Perinatology (SOAP) proposing how to best mitigate the risks of thromboprophylaxis and anticoagulants dosing versus the risks of a neuraxial procedure in this setting (low risk of spinal epidural hematoma), versus the risk of having to perform a general anesthetic in this high-risk population, the optimal time interval between the last UFH or LMWH dose and a neuraxial procedure for delivery will need to be addressed case by case [29]. Individualized plans considering risks and benefits of holding, reducing doses, or changing anticoagulants (UFH/LMWH) should be made as delivery approaches [29]. Laboratory tests of coagulation and monitoring of platelet count should be done as necessary prior to initiation of neuraxial anesthesia [29].

12.8 Pharmacological Therapies for Pulmonary Vasodilation

Oxygen is key in the management of PH as it is a potent vasodilator reducing hypoxic vasoconstriction.

Inhaled nitric oxide delivered via high flow nasal cannula at 5–20 parts per million is a useful, rapid pulmonary vasodilator [30]. Patients on high flow nasal cannula should be observed closely when not kept fasting as aspiration can happen when flow settings are high.

The 2015 consensus statement from the Pulmonary Vascular Research Institute provides a useful guide as to which patients may benefit from each type of pulmonary vasodilator [11]. There are five classes of specific pulmonary vasodilator drugs (Table 12.2).

Table 12.2 Medications used for pulmonary hypertension management

Medication class	Examples	FDA category in pregnancy
Phosphodiesterase-5 inhibitors (PDE-5 inhibitors)	Sildenafil, tadalafil	B
Endothelin receptor antagonists	Bosentan, ambrisentan, macitentan	Contraindicated unless critical for maternal survival
Prostacyclins	Iloprost, epoprostenol, treprostinil	C
Calcium channel blockers	Nicardipine, nifedipine	C
Nitric oxide		C

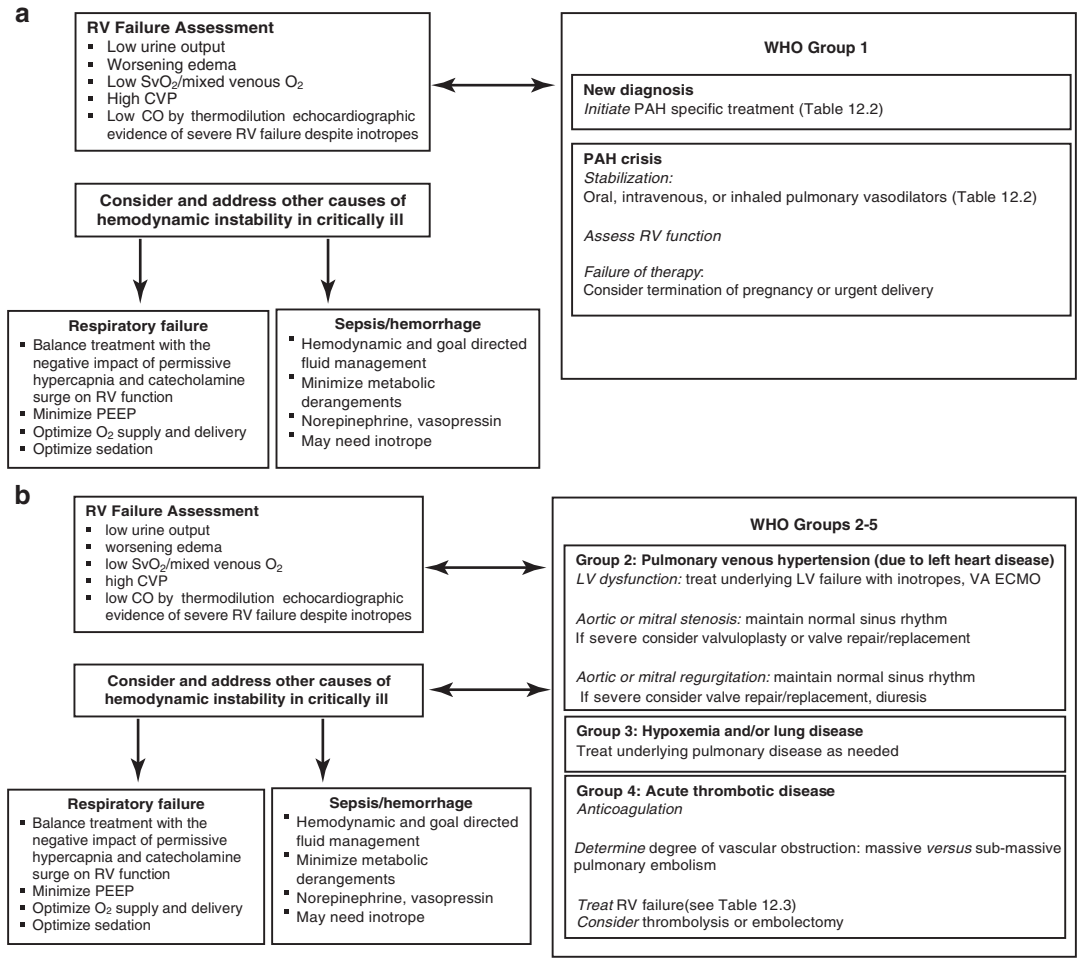
12.9 Management of Right Ventricular Failure in Women with PH

There are very few studies evaluating or even reporting on the management of patients with PAH in the ICU, and none of the studies report on management and outcomes in obstetric patients.

Nonetheless, a comprehensive treatment algorithm for pregnant patients with PH has been proposed over a decade ago and remains appropriate (Fig. 12.1, b) [31].

Treatment of right ventricular failure should include [30, 32]:

1. Fluid restriction, a low sodium diet, and the use of diuretics, in order to maintain optimal preload and cardiac output, reduce RV distension and minimize the risk of acute decompensation
2. Management of arrhythmias, with maintenance of sinus rhythm and atrioventricular synchrony
3. Inotropic support
4. Selective pulmonary vasodilators



WHO: World Health Organization; RV: right ventricular; LV: left ventricular; BNP: brain natriuretic peptide; iNO: inhaled nitric oxide; PEEP: positive end-expiratory pressure; CVP: central venous pressure; Sv,O2: mixed venous oxygen saturation; PAH: pulmonary arterial hypertension; CO: cardiac output; SVR: systemic vascular resistance.

Modified from: Zamanian RT, Haddad F, Doyle RL, et al. Management strategies for patients with pulmonary hypertension in the intensive care unit. Crit Care Med 2007; 35: 2037–2050.

Fig. 12.1 (**a**) Algorithm for management in the intensive care unit (ICU) of pregnant patients with pulmonary hypertension with WHO classification Group 1. (**b**) Algorithm for management in the intensive care unit (ICU) of pregnant patients with pulmonary hypertension with WHO classification Groups 2–5

TTE is useful for assessing volume status. Decisions about fluid requirements should be made with TTE and the usual measures of fluid status such as blood pressure, urine output, and thirst. If a central venous line is placed, central venous pressure can be followed as a trend, but the utility of central venous pressure as a guide to assessing volume status in pregnancy has not been established. Central venous pressure should only be used along with other clinical indicators to determine fluid status.

It is recommended that patients without right ventricular failure benefit from oral calcium channel blockers or oral phosphodiesterase-5 inhibitors as monotherapy [11]. Patients with heart failure or decreased functional status may need the addition of intravenous or inhaled prostacyclins [11].

Severe PH and RV failure are particularly challenging to manage during acute exacerbations (Table 12.3). However, **management of RV dysfunction and failure is critical** because of its association with increased mortality. Patients with RV failure have tenuous volume status and are prone to kidney injury from renal venous congestion and decreased cardiac output, right ventricular ischemia, and arrhythmias. If right ventricular ischemia is present (likely due to increased RV diastolic pressure threatening the coronary perfusion pressure gradient), increased diuresis or alternative methods of fluid removal (e.g., hemofiltration) may be warranted possibly in conjunction with inotropic support. Inotropic support is required if cardiac output is not adequate to perfuse vital organs including the fetal placental unit. Decreased urine output, worsening edema, decline in functional status, diminished RV function on TTE, or issues with the fetal heart tracing can be used as signs suggestive of the need for an inotrope or, if considered life-saving for the mother, phosphodiastase inhibitors. The effects of each inotrope are best guided by echocardiography and arterial pressure monitoring.

Doses for inotropes are the same as in the non-pregnant patient. Dobutamine (2.5–20 mcg/kg/min) is recommended as the first-line inotrope, but milrinone is also an option for improving right ventricular function without increases in PVR [10, 11]. Dobutamine can precipitate arrhythmias which may preclude its use. Milrinone (0.125–0.375 mcg/kg/min, with or without a load of 25–50 mcg/kg over 30 min) may decrease SVR necessitating vasopressor therapy in conjunction with its use.

Table 12.3 Practical approach for right ventricular failure management

Diuretics:
Monitor daily weight, patient intake, and output and electrolytes closely.
Some volume unloading is likely required in all patients with PH:
1. IV furosemide
2. Sodium and fluid restriction
3. Hemofiltration
4. Hemofiltration
Inotropes:
Consider inotropes if right ventricular function worsens, with low urine output, or worsening edema.
1. Dobutamine 2.5–20 mcg/kg/min, start at 2.5 and increase by 2.5 as needed
2. Milrinone 0.125–0.375 mcg/kg/min, with or without an initial loading dose 25–50 mcg/kg over 30 min
3. Dopamine 1–20 mcg/kg/min
4. Epinephrine 1–3 mcg/min
Monitor for arrhythmias
Assess systemic vascular resistance and volume status before initiation
If low systemic vascular resistance: Norepinephrine 1–8 mcg/min or vasopressin 1–6 units/h
Pulmonary vasodilators (guided by echocardiography)
1. Inhaled iloprost 150 mcg per day (every 2–3 h or even continuously)
2. Inhaled NO 10–20 ppm

12.10 Extracorporeal Membrane Oxygenator

Experience with the use of extracorporeal membrane oxygenator (ECMO) for right heart failure in patients with pulmonary hypertension is growing [33]. Case reports and case series are beginning to illuminate the management of such patients and suggest that ECMO in this setting may be beneficial to reduce mortality of the mother and the fetus [9, 34]. There has been at least one reported case of a patient with PH in pregnancy laboring while on ECMO support [9, 34].

In women with severe PH, Eisenmenger's syndrome, and severe right heart failure, peri-delivery placement of femoral wires to facilitate urgent use of veno-venous or venoarterial ECMO may be considered. There are reports of women with PH laboring and delivering while on ECMO [9, 34]. Since rapid decompensation of the right ventricle may occur in the peripartum period, preemptive establishment of vascular access may benefit the most critically ill women.

12.11 Mode of Delivery

The mode of delivery and anesthetic management of pregnant PH patients remain a source of debate. While a vaginal delivery, if achievable, is

probably the safest mode of delivery, as it minimizes the risks of surgical stress and inflammation, it is difficult to predict if a woman will achieve a trial of labor and proceed with an uncomplicated vaginal delivery. The highest morbidity and mortality seem to occur among women with unsuccessful trials of labor requiring intrapartum cesarean deliveries whether urgent or semi-urgent, with a mortality of up to 33% in such situations [9]. A planned cesarean delivery has the advantage of occurring during the day with experts in high-risk maternal care available and avoids the risk of an urgent intrapartum cesarean delivery during labor. Therefore, in certain circumstances, a scheduled cesarean delivery may be chosen or indicated.

While challenging to predict, obstetricians should attempt to forecast which women have a high likelihood of successful vaginal delivery. Clues such as previous vaginal delivery, favorable cervical exam, and reassuring fetal tracing may be useful for predicting likelihood of successful vaginal delivery. The indication for delivery should guide mode of delivery, for example, a woman who is being delivered of the fetus early because of maternal or fetal indications may not tolerate induction of labor without maternal or fetal decompensation, and a scheduled cesarean delivery should be considered. A woman who is being induced at term with stable cardiopulmonary function is one who warrants an attempt at vaginal delivery. Cardiologists and anesthesiologists should contribute information about anticipated likelihood of maternal tolerance to prolonged induction of labor.

12.12 Management of Delivery

12.12.1 Hemodynamic Monitoring

During delivery, monitoring with electrocardiography, pulse oximetry, and invasive arterial blood pressure monitoring are recommended. Central venous access should be established in women with reduced myocardial function who may benefit from inotropic agents or in women with cardiac disease that requires maintenance of systemic vascular resistance with vasopressors to prevent right to left shunting and systemic hypoxia (e.g., Eisenmenger syndrome, shunt lesions).

The use of a pulmonary artery catheter is debatable. Pulmonary artery catheters can cause arrhythmias and in rare events have caused pulmonary artery rupture and thrombosis in PH [35, 36]. If a right heart catheterization is being performed around the time of delivery, it is reasonable to leave a pulmonary artery catheter in place to guide management through delivery. At the time of central line placement peri-delivery, the anesthesiologist who is comfortable utilizing the measurements afforded by a pulmonary artery catheter may choose to place a pulmonary artery catheter, but placement should be aborted if significant arrhythmias occur during placement.

Echocardiography offers more instantaneous and comprehensive information than any other hemodynamic monitor, enabling identification of the cause of hemodynamic instability and guidance of hemodynamic therapy. The only real debate surrounds the degree of accuracy of TTE for measured pulmonary arterial pressures. Some authors have shown that measurements obtained by TTE during pregnancy may overestimate the severity of PH [37, 38]. Still, the risk-benefit ratio justifies preferring TTE in these circumstances, and once the clinician is aware of the potential for overestimation, management may be modified accordingly. It is therefore advisable that clinicians managing these parturients should have at least basic knowledge of point-of-care TTE [39].

12.12.2 Hematologic Monitoring

Specific considerations in PH women include hematologic monitoring. The mechanisms for and implications of alterations in platelet function and number in PH are not yet completely understood [40]. Platelet consumption and shearing have been reported in patients with PH resulting in thrombocytopenia [40, 41]. Pulmonary vasodilators such as prostacyclins and nitric oxide have been associated with platelet dysfunction, activation, and thrombocytopenia [40].

Anecdotally, thrombocytopenia can occur during a PH crisis and especially when patient blood is exposed to extracorporeal circulation or endothelial injury [40]. It may therefore be prudent to establish preemptive neuraxial analgesia or anesthesia as a preparation for likely delivery.

Anesthesiologists may even choose to place neuraxial anesthesia at lower platelet counts than usual if the risk of general anesthesia outweighs the risk of epidural hematoma. The authors of this chapter have placed neuraxial anesthesia in a few patients with PH and platelets in the 60–90,000/μL range.

12.12.3 Anesthesia Considerations

If a trial of labor for a vaginal delivery is attempted, neuraxial labor analgesia, epidural, or combined-spinal epidural (CSE) with low concentration local anesthetics is considered of greatest importance. Epidural anesthesia may even considerably decrease the adverse hemodynamic consequences of labor [4]. When a cesarean delivery is indicated, the urgency of the procedure, indication for the surgery, and maternal or fetal condition may dictate whether neuraxial anesthesia is possible or if general anesthesia is necessary. There may be times where preventing further maternal decompensation necessitates slow and careful establishment of anesthesia and monitoring, precluding emergency cesarean delivery for fetal indications.

Neuraxial anesthesia is believed to have better outcomes than general anesthesia in patients with PH; therefore, the time needed to establish neuraxial anesthesia may come at the cost of fetal well-being as medical providers should not make management decisions that compromise the well-being of the mother for the sake of the fetus. Epidural anesthesia, when performed under appropriate monitoring and with caution, has no significant deleterious hemodynamic effect by itself and has been used safely in women with cardiac disease [42]. However, specifically for surgery, CSE anesthesia is preferred because it provides a better sensory block than epidural anesthesia alone, and no additional risk of hypotension when a low spinal dose is used. With CSE, anesthesia should be achieved with an initial low dose of intrathecal opioid alone (fentanyl 10mcg) or in combination with low-dose local anesthetic (bupivacaine 2.5–5 mg) followed by slow incremental doses of epidural local anesthetic (lidocaine 2% in 3–5 mL doses to a total of 15–20 mL over 20 min until desired T4 level is achieved) and while monitoring and supporting maternal blood pressure. Intrathecal morphine in the usual or enhanced dose (150–300 mg) or epidural morphine (1.5–3 mg) should be given for postoperative analgesia. Single-shot spinal anesthesia is considered contraindicated in these patients and does not afford prolonged post-cesarean pain management therapies [43].

With general anesthesia, there is concern with increased pulmonary arterial pressure during laryngoscopy and tracheal intubation; moreover, adverse effects of positive-pressure ventilation on venous return may ultimately lead to cardiac failure [43, 44]. In a systematic review of 48 case reports or case series, 73 parturients from 1997 to 2007 were identified PH patients receiving general anesthesia had a four times higher mortality risk than patients having neuraxial anesthesia [7]. In a more recent prospective observational study of 26 pregnancies, it was noted that mortality in pregnant PH patients was associated with general anesthesia for dilation and curettage for spontaneous abortion or general anesthesia for cesarean delivery [6]. However, several groups have reported the successful use of general anesthesia in pregnant PH patients with good maternal outcomes [9, 32, 45, 46]. Likely patients with more severe disease require emergent procedures and general anesthesia, so the nature of the disease, rather than the use of general anesthesia may be the driver for adverse outcomes, such as thrombotic complications, pulmonary edema, stroke, organ failure, arrhythmias, worsening heart failure or functional status, and maternal mortality.

For the more critically ill patients, a coordinated team of both obstetric and cardiac anesthe-

Table 12.4 Mechanisms, effects, and side effects of commonly used uterotonics

Medication	Mechanisms and effects	Side effects related to pulmonary hypertension
Oxytocin	Activation of uterine G protein-coupled receptors Increases uterine intracellular calcium and stimulates uterine contractions	Decrease in systemic vascular resistance Tachycardia Coronary vasospasm Arrhythmia
Prostaglandins E1 (misoprostol) E2 (dinoprostone)	Synthetic prostaglandin E1/E2 analog that stimulates prostaglandin E1/E2 receptors Bind to myometrial cells, causing strong myometrial contractions leading to expulsion of tissue These agents also cause cervical ripening with softening and dilation of the cervix	Rare cardiovascular adverse reactions
Carboprost tromethamine, prostaglandin F2 alpha (hemabate)	Synthetic prostaglandin analogue of PGF2α with oxytocic properties Stimulates myometrial contractions in the gravid uterus similar to the contractions of term labor (exact mechanism of action unknown, possibly by direct stimulation, regulation of cellular calcium transport, or regulation of intracellular levels of cAMP)	Bronchospasm Hypertension
Methylergonovine	Semisynthetic ergot alkaloid Acts directly on the smooth muscle of the uterus and increases the tone, rate, and amplitude of rhythmic contractions	Hypertension Tachycardia Arrhythmia Coronary vasospasm

siologists may be required. The obstetric anesthesiologist is skilled in placing neuraxial anesthesia in the most challenging patients and knows best all the obstetric procedures and medications (in particular uterotonics, Table 12.4) and can provide a communication bridge between teams and the patient; indeed, the obstetric anesthesiologist is well versed in caring for the anxious awake obstetric patient. The cardiac anesthesiologists are familiar with bedside echocardiography and titration of inotropes, vasopressors, and pulmonary vasodilators and can readily identify when patients may require ECMO.

12.13 Termination of Pregnancy

Women with PH who require termination of pregnancy are often critically ill and require a coordinated multidisciplinary team including maternal fetal medicine specialists, cardiologists specializing in PH, ECMO surgeons and perfusionists, anesthesiologists, neonatologist, and intensive care physicians. Both obstetric and cardiac anesthesiologists may be involved in these procedures. Laminaria insertion can be uncomfortable, and pulmonary pressures can rise with the painful stimuli. Women should remain in monitored settings after laminaria placement while awaiting dilation and evacuation procedures as contractions will be accompanied by both pain and fluid shifts.

Slow initiation of neuraxial anesthesia with arterial pressure monitoring is usually the safest anesthetic approach for the dilation and evacuation procedures. It is recommended to keep these women in the intensive care unit until the immediate peri-procedure fluid shifts have resolved which may be days to weeks depending on the cardiopulmonary functional status of the patient.

12.14 Postpartum Considerations

In the immediate post-delivery period, as the uterus contracts back to prepregnancy size, acute increases in plasma volume can precipitate right heart failure and increased pulmonary pressures due to increased flow to the right heart and the pulmonary vasculature. Pregnancy physiology

also continues into the postpartum period. Increases in plasma volume can continue in to the post-delivery and post-termination period as edema is mobilized into the vasculature.

12.14.1 Uterotonic Medications

After a vaginal delivery, management of the third stage of labor is crucial to prevent postpartum hemorrhage. Uterotonics are routinely administered after delivery to decrease the risk of uterine atony and postpartum hemorrhage. It has been established that when dosing of uterotonics is decreased or uterotonics are not given due to concern for effects on cardiopulmonary status, higher rates of postpartum hemorrhage result.

A prospective, cohort study compared low-dose oxytocin infusion (10 units of oxytocin in 500 mL of normal saline given intravenously at 36 mL/h for 4 h (12 mUnits/min)) to the same infusion plus 2 units of oxytocin given over 10 min after delivery and demonstrated lower blood loss in the group that received the extra oxytocin and no change in cardiac parameters or adverse event [47]. Uterotonics should therefore be given with appropriate knowledge of side effect profiles and optimal delivery strategies (Table 12.3).

12.14.1.1 Oxytocin

Oxytocin is the first-line uterotonic in obstetric practice. Oxytocin typically causes tachycardia, a decrease in systemic vascular resistance, an increase in cardiac output, and a rise in pulmonary vascular resistance. If oxytocin is administered, the lowest effective dose administered as an infusion rather than a bolus dose is the safest plan [48].

12.14.1.2 Second-Line Uterotonics (Prostaglandins, Ergot Alkaloid Derivatives)

Second-line uterotonics include prostaglandins (PG). Since they each have a differential smooth muscle effect, selection of the PG with no bronchoconstrictive effect is key.

Misoprostol (PGE1) should have minimal effect on the pulmonary vasculature and can be administered vaginally, orally rectally, or sublingually (misoprostol 800 mcg vaginally, 600–1000 mcg oral or rectal, 400–800 mcg sublingual).

Carboprost tromethamine, PGF2 alpha can cause bronchospasm and is contraindicated in patients with reactive airway disease and PH as small increases in PVR from increased airway pressure may not be tolerated.

Methylergonovine, an ergot alkaloid derivative, can cause pulmonary vasoconstriction and therefore is relatively contraindicated in PH [49]. Personal communication with experts in the field provides some rare experiences with giving methylergonovine via very slow intravenous titration (10mcg IV at a time), with frank awareness of the fact that pulmonary resistance may increase with its administration. Methergine should only be used in this manner if the risk of bronchospasm from PGF2 alpha is unacceptable, and uterine atony is so profound that additional uterotonic medication is required.

The usual options for surgical management of PPH should also be considered, such as Bakri Balloon, B-Lynch suture, and hysterectomy.

12.14.2 Postpartum Monitoring

The first postpartum week has been recognized as particularly vulnerable period for patients with PAH [6, 32]. Mortality is associated with heart failure, sudden death, and thromboembolism [3, 7]. Postpartum monitoring in an intensive care unit in the first few days to a week after delivery is recommended until it is clear that the major fluid shifts have decreased, arrhythmias have subsided, and maternal function has improved. This is especially pertinent to the highest-risk patients such as women with right heart failure, hemodynamic instability, or arrhythmias during delivery. There will be some patients who require more than a week of ICU management during this time.

Prophylactic anticoagulation is important in this period and needs to be restarted, if it had

been held for delivery or neuraxial anesthesia, as soon as possible [29].

12.15 Long-Term Considerations

12.15.1 Maternal Outcomes

In a recent series of 49 pregnant patients with PH managed in academic medical centers in the United States, overall mortality was 16%, despite advanced cardiopulmonary therapies and targeted management [9]. Of note, 7 of 8 deaths reported in the cohort were in women with WHO Group 1 PH [9]. There were no deaths in women with WHO Group 2 PH. When patients were divided based on severity of PH, there was a trend suggestive of worse outcomes in women with more severe disease [9]. It may be useful to use severity of PH, degree of right heart function, and etiology of PH as a guide when counseling patients with PH about outcomes of pregnancy. In the modern era of anti-pulmonary hypertensive medications and ECMO outcomes are slowly improving, large cohorts of women with PH in pregnancy are necessary to further delineate maternal outcomes.

12.15.2 Fetal and Neonatal Outcomes

Maternal PH is associated with an increased risk of fetal and neonatal complications, including stillbirth and neonatal death, fetal growth restriction, and preterm delivery. Some series describe a complication rate as high as 100% [7]. Fetal intrauterine growth retardation and prematurity are the main neonatal complications [50, 51]. The risk is highest in women with prepregnancy poor functional class (New York Heart Association functional class III or IV), cyanosis, or left heart obstruction. The increased risk may be a result of the direct effects of the underlying cardiac disease, compounded by the complications of preterm delivery when it is indicated for maternal reasons [50]. Despite this, the improved neonatal care and survival of preterm infants over the past decade have led to an increased willingness to undertake the challenge of pregnancy despite the presence of PH.

12.16 Conclusion

PH in pregnancy carries significant risk of both maternal and fetal mortality [7]. Patients with Group 1 PH and Eisenmenger syndrome have the highest 1-year mortality (50%) [9].

Women with PH are considered WHO classification of maternal cardiovascular risk level IV and are advised to avoid pregnancy altogether or terminate pregnancy should it occur [11].

Once pregnant, the severity of prepregnancy PH and right heart failure may be used to guide risk assessment. These women should be cared for at centers with anesthesiologists, cardiologists, obstetricians, and intensivists who are comfortable managing pregnant women with PH. While there is still no clear evidence that ECMO improves immediate or long-term maternal outcomes, advanced interventional therapies have been used and should be available in women with PAH with Eisenmenger syndrome.

Management during pregnancy, delivery and post-delivery or post-termination requires close follow-up. Of note, there is to date no evidence that one mode of delivery is preferable over the other, but intrapartum urgent cesarean delivery should be avoided at all cost, as any precipitous anesthetic (particularly general anesthesia) may result in irreversible cardiovascular collapse. Both delivery and termination are high-risk procedures and multidisciplinary collaboration is essential to ensure optimization of maternal care.

12.17 Addendum

Despite major advances in the care of PH patients and the advent of several classes of medications to treat this condition, PH in general and PAH in particular remain highly lethal, and pregnancy is poorly tolerated. This chapter summarizes the current ICU treatment knowledge on pregnancy in PH, with a focus on PAH, as the greatest

amount of literature is available for this disease state. Most of the management of unstable pregnant patients with PAH should be guided by clinical experience and pathophysiological reasoning, since, it is unlikely that randomized controlled trials will be possible in unstable PAH patients to improve current treatment algorithms.

References

1. Badesch DB, Champion HC, Sanchez MA, Hoeper MM, Loyd JE, Manes A, et al. Diagnosis and assessment of pulmonary arterial hypertension. J Am Coll Cardiol. 2009;54(1 Suppl):S55–66.
2. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013;62(25). Suppl:D34–41.
3. Weiss BM, Zemp L, Seifert B, Hess OM. Outcome of pulmonary vascular disease in pregnancy: a systematic overview from 1978 through 1996. J Am Coll Cardiol. 1998;31(7):1650–7.
4. Bonnin M, Mercier FJ, Sitbon O, Roger-Christoph S, Jaïs X, Humbert M, et al. Severe pulmonary hypertension during pregnancy. Anesthesiology. 2005;102(6):1133–7.
5. Hsu CH, Gomberg-Maitland M, Glassner C, Chen JH. The management of pregnancy and pregnancy-related medical conditions in pulmonary arterial hypertension patients. Int J Clin Pract Suppl. 2011(172):6–14.
6. Jaïs X, Olsson KM, Barbera JA, Blanco I, Torbicki A, Peacock A, et al. Pregnancy outcomes in pulmonary arterial hypertension in the modern management era. Eur Respir J. 2012;40(4):881–5.
7. Bédard E, Dimopoulos K, Gatzoulis MA. Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? Eur Heart J. 2009;30(3):256–65.
8. Gleicher N, Midwall J, Hochberger D, Jaffin H. Eisenmenger's syndrome and pregnancy. Obstet Gynecol Surv. 1979;34(10):721–41.
9. Meng ML, Landau R, Viktorsdottir O, Banayan J, Grant T, Bateman B, et al. Pulmonary hypertension in pregnancy: a report of 49 cases at four tertiary North American sites. Obstet Gynecol. 2017;129(3):511–20.
10. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37(1):67–119.
11. Hemnes AR, Kiely DG, Cockrill BA, Safdar Z, Wilson VJ, Al Hazmi M, et al. Statement on pregnancy in pulmonary hypertension from the Pulmonary Vascular Research Institute. Pulm Circ. 2015;5(3):435–65.
12. Knight MKJ, Spark P, Brocklehurst P. United Kingdom Obstetric Surveillance System (UKOSS) annual report 2007. Oxford: National Perinatal Epidemiology Unit; 2007.
13. Badesch DB, Raskob GE, Elliott CG, Krichman AM, Farber HW, Frost AE, et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL registry. Chest. 2010;137(2):376–87.
14. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med. 2006;173(9):1023–30.
15. McLaughlin VV, Shah SJ, Souza R, Humbert M. Management of pulmonary arterial hypertension. J Am Coll Cardiol. 2015;65(18):1976–97.
16. Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2015;46:903–75.
17. Yuan JX, Rubin LJ. Pathogenesis of pulmonary arterial hypertension: the need for multiple hits. Circulation. 2005;111(5):534–8.
18. Machado RD, James V, Southwood M, Harrison RE, Atkinson C, Stewart S, et al. Investigation of second genetic hits at the BMPR2 locus as a modulator of disease progression in familial pulmonary arterial hypertension. Circulation. 2005;111(5):607–13.
19. Austin ED, Loyd JE. Genetics and mediators in pulmonary arterial hypertension. Clin Chest Med. 2007;28(1):43–57, vii–viii
20. Ma L, Liu W, Huang Y. Perioperative management for parturients with pulmonary hypertension: experience with 30 consecutive cases. Front Med. 2012;6(3):307–10.
21. Toro K, Herjavecz I, Vereckei E, Kovacs M. Fatal idiopathic pulmonary haemosiderosis in association with pregnancy - medico-legal evaluation. J Forensic Legal Med. 2012;19(2):101–4.
22. Ouzounian JG, Elkayam U. Physiologic changes during normal pregnancy and delivery. Cardiol Clin. 2012;30(3):317–29.
23. Chin KM, Kim NH, Rubin LJ. The right ventricle in pulmonary hypertension. Coron Artery Dis. 2005;16(1):13–8.
24. European Society of Group, Association for European Paediatric Committee, German Society for Gender M, Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, et al. ESC guidelines on the management of cardiovascular diseases during pregnancy: the task force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J. 2011;32(24):3147–97.

25. Pieper PG, Lameijer H, Hoendermis ES. Pregnancy and pulmonary hypertension. Best Pract Res Clin Obstet Gynaecol. 2014;28(4):579–91.
26. Bates SM, Middeldorp S, Rodger M, James AH, Greer I. Guidance for the treatment and prevention of obstetric-associated venous thromboembolism. J Thromb Thrombolysis. 2016;41(1):92–128.
27. Rosengarten D, Kramer MR. Pregnancy in pulmonary arterial hypertension patients. Harefuah. 2013;152(9):547–51, 63, 62.
28. D'Alton ME, Friedman AM, Smiley RM, Montgomery DM, Paidas MJ, D'Oria R, et al. National Partnership for Maternal Safety: consensus bundle on venous thromboembolism. Anesth Analg. 2016;123(4):942–9.
29. Leffert L, Butwick A, Carvalho B, Arendt K, Bates SM, Friedman A, et al. The Society for Obstetric Anesthesia and Perinatology consensus statement on the anesthetic management of pregnant and postpartum women receiving thromboprophylaxis or higher dose anticoagulants. Anesth Analg. 2018;126(3):928–44.
30. Tremblay JA, Couture EJ, Albert M, Beaubien-Souligny W, Elmi-Sarabi M, Lamarche Y, et al. Noninvasive administration of inhaled nitric oxide and its hemodynamic effects in patients with acute right ventricular dysfunction. J Cardiothorac Vasc Anesth. 2019;33(3):642–7.
31. Zamanian RT, Haddad F, Doyle RL, Weinacker AB. Management strategies for patients with pulmonary hypertension in the intensive care unit. Crit Care Med. 2007;35(9):2037–50.
32. Duarte AG, Thomas S, Safdar Z, Torres F, Pacheco LD, Feldman J. Management of pulmonary arterial hypertension during pregnancy: a retrospective, multicenter experience. Chest J. 2013;143(5):1330–6.
33. Rosenzweig EB, Brodie D, Abrams DC, Agerstrand CL, Bacchetta M. Extracorporeal membrane oxygenation as a novel bridging strategy for acute right heart failure in group 1 pulmonary arterial hypertension. ASAIO J. 2014;60(1):129–33.
34. Agerstrand C, Abrams D, Biscotti M, Moroz L, Rosenzweig EB, D'Alton M, et al. Extracorporeal membrane oxygenation for cardiopulmonary failure during pregnancy and postpartum. Ann Thorac Surg. 2016;102(3):774–9.
35. Weeks SK, Smith JB. Obstetric anaesthesia in patients with primary pulmonary hypertension. Can J Anaesth. 1991;38(7):814–6.
36. Barash PG, Nardi D, Hammond G, Walker-Smith G, Capuano D, Laks H, et al. Catheter-induced pulmonary artery perforation. Mechanisms, management, and modifications. J Thorac Cardiovasc Surg. 1981;82(1):5–12.
37. Cowie B, Kluger R, Rex S, Missant C. The utility of transoesophageal echocardiography for estimating right ventricular systolic pressure. Anaesthesia. 2015;70(3):258–63.
38. Penning S, Robinson KD, Major CA, Garite TJ. A comparison of echocardiography and pulmonary artery catheterization for evaluation of pulmonary artery pressures in pregnant patients with suspected pulmonary hypertension. Am J Obstet Gynecol. 2001;184(7):1568–70.
39. Dennis AT, Dyer RA. Cardiac output monitoring in obstetric anaesthesia. Int J Obstet Anesth. 2014;23(1):1–3.
40. Zanjani KS. Platelets in pulmonary hypertension: a causative role or a simple association? Iran J Pediatr. 2012;22(2):145–57.
41. Herve P, Humbert M, Sitbon O, Parent F, Nunes H, Legal C, et al. Pathobiology of pulmonary hypertension. The role of platelets and thrombosis. Clin Chest Med. 2001;22(3):451–8.
42. Gomar C, Errando CL. Neuroaxial anaesthesia in obstetrical patients with cardiac disease. Curr Opin Anaesthesiol. 2005;18(5):507–12.
43. Blaise G, Langleben D, Hubert B. Pulmonary arterial hypertension: pathophysiology and anesthetic approach. Anesthesiology. 2003;99(6):1415–32.
44. Jenkins J, Lynn A, Edmonds J, Barker G. Effects of mechanical ventilation on cardiopulmonary function in children after open-heart surgery. Crit Care Med. 1985;13(2):77–80.
45. Monnery L, Nanson J, Charlton G. Primary pulmonary hypertension in pregnancy; a role for novel vasodilators. Br J Anaesth. 2001;87(2):295–8.
46. O'Hare R, McLoughlin C, Milligan K, McNamee D, Sidhu H. Anaesthesia for caesarean section in the presence of severe primary pulmonary hypertension. Br J Anaesth. 1998;81(5):790–2.
47. Cauldwell M, Steer PJ, Swan L, Uebing A, Gatzoulis MA, Johnson MR. The management of the third stage of labour in women with heart disease. Heart. 2017;103(12):945–51.
48. Curry R, Fletcher C, Gelson E, Gatzoulis M, Woolnough M, Richards N, et al. Pulmonary hypertension and pregnancy—a review of 12 pregnancies in nine women. BJOG Int J Obstet Gynaecol. 2012;119(6):752–61.
49. Roberts NV, Keast PJ. Pulmonary hypertension and pregnancy—a lethal combination. Anaesth Intensive Care. 1990;18(3):366–74.
50. Siu SC, Sermer M, Colman JM, Alvarez AN, Mercier LA, Morton BC, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. Circulation. 2001;104(5):515–21.
51. Presbitero P, Somerville J, Stone S, Aruta E, Spiegelhalter D, Rabajoli F. Pregnancy in cyanotic congenital heart disease. Outcome of mother and fetus. Circulation. 1994;89(6):2673–6.

13 Point-of-Care Ultrasound in the Critically Ill Pregnant Woman

Laurent Zieleskiewicz, Gary Duclos, Malik Haddam, and Marc Leone

Bullet Points

- Point-of-care ultrasound (POCUS) is defined as ultrasonography performed at the bedside by the physician in charge of the patient.
- There are currently no recommendations for the use of ultrasound in pregnant women who are critically ill.
- POCUS algorithms suggest fast and simple cardiac and pulmonary evaluations to determine patient diagnosis and optimize patient management.
- Emergency transthoracic echocardiography (TTE) is the most rapid way to diagnose aortic dissection.
- Pericardial effusion and cardiac tamponade are simple to diagnose using TTE with subcostal or parasternal long axis views.
- POCUS can provide definitive diagnosis when an embolic event is suspected if cardiac and lung ultrasound are combined.
- POCUS can identify many causes of maternal cardiac arrest, enabling adaptation of treatment in real time.
- Abdominal ultrasound examination provides a great deal of information to physicians treating the critically ill pregnant or postpartum woman.
- Clinicians treating pregnant women should be encouraged to acquire the POCUS skills required to optimize treatment.

13.1 Definition and Applications

Point-of-care ultrasound (POCUS) is defined as ultrasonography performed at the bedside by the physician in charge of the patient [1]. POCUS can be used for procedural, diagnostic, or screening applications. Over the last 20 years, ultrasound devices have increased in quality, while both their size and cost decreased. At the same time, several guidelines have recommended using ultrasound in different clinical situations [2–6]. Consequently POCUS is now used in more than 20 specialties [1].

Surprisingly, there are currently no recommendations for the use of ultrasound in pregnant

L. Zieleskiewicz (✉) · G. Duclos · M. Haddam
M. Leone
Department of Anesthesiology and Intensive Care Medicine, Aix Marseille Université, Assistance Publique Hôpitaux de Marseille, North Hospital, Marseille, France
e-mail: Laurent.ZIELESKIEWICZ@ap-hm.fr

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_13

women who are critically ill, and it seems POCUS may be insufficiently used, despite its many advantages for obstetrical anesthesia and maternal critical care [7–9]. In 2012, a survey found that transthoracic echocardiography was only used for 13% of pregnant women admitted to four tertiary referral obstetric units [10]. Nonetheless, the pregnant woman represents a perfect field of application for POCUS for several reasons:

Firstly ultrasound is a noninvasive, nonionizing, and popular technology particularly for obstetric workup. In critically ill patients, several studies have shown than the use of POCUS may decrease exposure to ionizing radiation [11–13].

Secondly, POCUS can provide information regarding the physiological alterations typical of pregnancy, thereby enabling an individualized approach to care.

Finally, pregnant women are at risk of acute respiratory failure, bleeding, and infections – all clinical situations where POCUS has a high diagnostic and therapeutic impact [7]. The aim of this chapter is therefore to discuss several potential applications of POCUS for critically ill pregnant women. Lung ultrasound is discussed in detail in Chap. 22.

13.2 Point-of-Care Transthoracic Echocardiography During Pregnancy

In some industrialized countries, heart disease is the leading cause of death during pregnancy [14, 15]. Most preexisting or newly acquired cardiovascular diseases may be diagnosed at the bedside, using a systematic heart and lung ultrasound assessment. A large survey in 142 European intensive care units (ICU) demonstrated that POCUS assessment had a large impact on diagnostic (84%) and therapeutic (64%) procedures [7]. POCUS algorithms focus on fast and simple cardiac and pulmonary evaluations to determine the diagnosis and optimize the management of patients. This systematic approach is well documented in the ICU and emergency departments where diagnostic algorithms are available for specific clinical conditions. For example, the focus-assessed transthoracic echocardiography (FATE) and the focused-echocardiographic evaluation in life support (FEEL) protocols are used to guide diagnosis in patients with severe hemodynamic compromise or cardiac arrest, respectively [16–18]. Furthermore, a detailed POCUS evaluation is strongly recommended by several guidelines for guiding fluid management during shock states [19–21]. While there is no validated algorithm for pregnant women presenting with critical illness, Dennis has described the rapid obstetric screening echography (ROSE) scan. This includes hemodynamic and embolism key views and a fetal heart assessment [22, 23]. Of note, fetal assessment should probably not comprise a part of the maternal screening algorithm; alerting to the presence of fetal compromise will divert attention away from the mother. Fetal distress may alert to compensated maternal compromise when there is no overt maternal hemodynamic instability. However, once maternal compromise has been established, the focus of treatment should remain the mother. Maternal stabilization will also improve fetal condition.

13.3 Cardiovascular POCUS During Pregnancy

The normal cardiovascular changes of pregnancy are described in detail in Chap. 9. Normal pregnancy is accompanied by significant changes to the diastolic phase of the cardiac cycle. There is a tendency toward reduced diastolic reserve and impaired chamber diastolic function at term. In echocardiographic imaging, this manifests as a decreased E wave (peak velocity flow in early diastole), a decreased E/A ratio [ratio of peak velocity flow in early diastole (E wave) to peak velocity flow in late diastole caused by atrial contraction of the mitral inflow (A wave)], and a slight increase of E/Ea ratio caused by decreased early diastolic mitral annular velocity. These may all be measured using tissue Doppler [24, 25].

Heart failure: Diverse clinical entities may manifest as cardiac dysfunction. Management of heart failure depends on its etiology and is

described in specific guidelines [26, 27]. These are discussed in detail in Chaps. 10–12. In pregnant women, heart failure typically occurs around 28 weeks gestation when cardiovascular adaptations to pregnancy peak, including increased CO and volemia.

Heart failure is commonly classified into two major groups depending on the presence of echocardiographic evidence of left ventricle ejection fraction (LVEF) compromise or lack thereof (the accepted cut-off is 40%). These two types of heart failure present with typical features that assist in diagnosis. Heart failure with preserved LVEF is usually associated with diastolic dysfunction. Although pulmonary edema can be seen, cardiac output (CO) is usually normal. Heart failure due to reduced LVEF is accompanied by a decrease in CO. This is typically associated with an increase in capillary lung pressure and activation of the renin-angiotensin system, resulting in fluid retention. CO can be calculated using two echocardiographic variables: (1) the velocity time integral (VTI) and (2) the cross-sectional area of the left outflow tract [28]. Measurement of CO with transthoracic echocardiography has been validated against pulmonary artery catheter measurements in critically ill parturients [29]. The authors of this comparative study promoted cardiac ultrasound as a noninvasive gold standard for measurement of CO in pregnant and postpartum critically ill women.

Peripartum cardiomyopathy: Peripartum cardiomyopathy presents as a systolic myocardial dysfunction with reduced LVEF. It is associated with breathlessness, fatigue, and tachycardia and is accompanied by normal or reduced blood pressure. Echocardiographic imaging of global reduction of left ventricle function and a low CO establish the diagnosis [30, 31].

Global left ventricle dysfunction can be assessed using different transthoracic echocardiography methods. Visual semiquantitative estimation discriminates between low, altered, or normal systolic function with excellent precision (7% deviation from ventriculographic measurement). Visual semiquantitative estimations can be performed from a parasternal view, a short axis view, or an apical four-chamber view [28, 32, 33]. However, 30–50% of visual estimations of LVEF are imprecise. Therefore, three other methods may be used to improve assessment accuracy: the Teichholz method, the Simpson biplane method, and speckle tracking echocardiography.

The Teichholz method estimates LVEF by using M-Mode recordings of cardiac structure motions achieved by positioning the cursors at the level of mitral leaflet tips in the parasternal long-axis view. This method is accurate as long as the cursors of the M-Mode are relatively perpendicular to the septal wall, provided the left ventricle has no marked difference in regional function. The Simpson biplane method of discs is the recommended method for LVEF measurement. This method requires volumetric measurement of end-diastole and end-systole using 2D echocardiography from apical four-chamber and two-chamber views [28, 34]. Recently, speckle tracking echocardiography has been used to provide information regarding myocardial function in its longitudinal, radial, and circumferential components. This semiautomated measurement method provides both global and regional evaluation of left ventricle function with low inter- and intra-operator variability [35, 36].

Preeeclampsia: Preeclampsia is a common cause of heart failure during pregnancy. Clinically, the pregnant woman may exhibit breathlessness, fatigue, and tachycardia associated with hypertension. Heart failure is a very late feature of preeclampsia and is often associated with proteinuria and edema accompanied by severe hepatic and hematological abnormalities. Classically, the heart failure of preeclampsia presents with diastolic dysfunction and preserved systolic function [30, 31]. Diastolic function worsening is particularly significant in preeclampsia with a higher incidence of complications (acute pulmonary edema or severe eclampsia) [30].

Left ventricular diastolic relaxation is impaired in preeclampsia because of cardiac structural changes secondary to hypertension (hypertrophy, interstitial fibrosis). The diastolic function of the left ventricle may be investigated using transthoracic echocardiography Döppler measurement of mitral inflow and tissue velocity

of the annular mitral ring. Measurement of the E/A ratio is critical as it reflects left ventricle filling pressure which is elevated in case of impaired left ventricular systolic function. Severe diastolic dysfunction causing elevated left ventricle filling pressures should be suspected in women presenting with an with E/A ratio >2 [i.e., high velocity of the early diastolic mitral inflow wave (E wave) and low velocity of the atrial diastolic mitral inflow wave (A wave)] (Fig. 13.1a). Demonstration of a preserved ejection fraction requires measurement of the early diastolic velocity of the mitral annulus (Ea) at the septal or lateral part of mitral ring using tissue Doppler. An average E/Ea ratio >13 indicates severe diastolic dysfunction [37] (Fig. 13.1b). Dyspnea accompanied by chest radiography opacities, lung ultrasonography demonstrating B-lines, and severe myocardial diastolic dysfunction in echocardiography cinch the diagnosis of acute cardiogenic pulmonary edema.

Myocardial infarction: Acute myocardial infarction (AMI) is an important cause of maternal morbidity. AMI occurs in 1:17000 pregnancies and has a mortality rate of 5–7%. Most pregnancy-associated AMIs occur in the 6 weeks postpartum. The risk of AMI in the peripartum period is three times higher than seen among nonpregnant women of the same age. Increased age, cardiovascular risk factors (smoking or diabetes), and a history of preeclampsia increase the risk of peripartum AMI. Most pregnancy-associated AMIs are related to acute coronary dissection (a hormone-associated connective tissue abnormality), rather than coronary occlusive disease [38]. There are no specific diagnostic tests for AMI during pregnancy and the postpartum period.

Pregnancy does not influence the electrocardiogram, nor does it affect troponin I levels. Therefore interpretation of these tests should remain unaffected by the presence of a fetus. Similarly, the echocardiogram remains the cornerstone of diagnosis in pregnant women presenting with chest pain (whether typical or atypical); ECG findings may assist in ruling out much of the relevant differential diagnosis [39]. Transthoracic echocardiography typically shows regional wall motion abnormalities (hypo or akinesis) with impaired thickening of the affected myocardium. The distribution of wall motion abnormalities depends on the area perfused by the affected coronary vessel/s. A full echocardiography should therefore explore all of the 17 myocardial segments from the apical four-chamber and two-chamber views, the parasternal long axis view, and the parasternal short axis view from base to apex. Visual assessment of regional wall motion is the most common method but is highly dependent on operator expertise. Assessment of LV regional motion can be considerably improved using an automatized speckle tracking echocardiography which explores myocardial deformation in three dimensions and decreases reproducibility issues [28, 35].

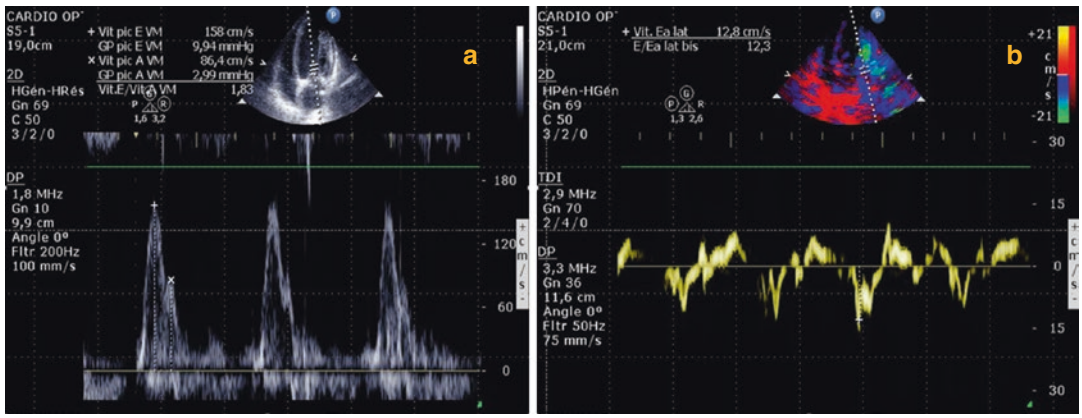


Fig. 13.1 (**a**, **b**) Elevated left filling pressure in a woman with preeclampsia

Aortic dissection, regurgitation, and cardiac tamponade: Aortic dissection is another cause of maternal death that typically occurs secondary to connective tissue abnormalities. Hormonal changes occurring during pregnancy induce structural aortic wall vulnerability to dissection. Hemodynamic stress is at its peak during the third trimester and the postpartum period; therefore, most dissections occur at this time [40, 41]. Aortic dissection is often accompanied by typical chest pain and electrocardiogram changes (repolarization abnormalities) and is the cause of nearly half of the cases of pregnancy-associated AMIs and severe aortic regurgitations. Cardiac tamponade is the most common cause of cardiac arrest in the case of Type A dissection [42, 43].

Emergency transthoracic echocardiography (TTE) is the most rapid way to diagnose aortic dissection. TTE may also diagnose the more common and serious complications of aortic dissection such as acute aortic regurgitation or pericardial effusion. TTE visualization of a dilated aortic root, a dilated ascending aorta, or a dissection flap in the parasternal long axis view should lead to more advanced imaging (transesophageal echocardiography, computed tomography, or magnetic resonance imaging of the chest).

Aortic regurgitation: Transthoracic echocardiography serves to diagnose aortic regurgitation (AR), to assess its severity, and to identify its etiology [44]. Severe AR is diagnosed when an abnormal or flail motion of the aortic leaflets associated with a wide coaptation defect is seen in the parasternal long axis view. Color flow Doppler shows a large central retrograde diastolic flow or variable eccentric flows. Chronic AR is associated with a dilated left ventricle. Acute AR is characterized by abrupt overload seen as a left ventricle with a normal size but high filling pressure.

Pericardial effusion and cardiac tamponade are simple to diagnose using TTE with subcostal or parasternal long axis views (Fig. 13.2). Pericardial effusion is typically seen as echolucence between the parietal myocardium and pericardial membranes (both of which are echodense). Pericardial effusions vary in echogenicity depending on the presence of blood, clot, bacteria, and more. One of the main differential diagnoses for such an echo-lucent finding is a left-sided pleural effusion. The characteristic differentiating between the two is their relationship with the descending thoracic aorta. A left-sided pleural effusion is seen posterior to the aorta, while pericardial effusion is anterior to it.

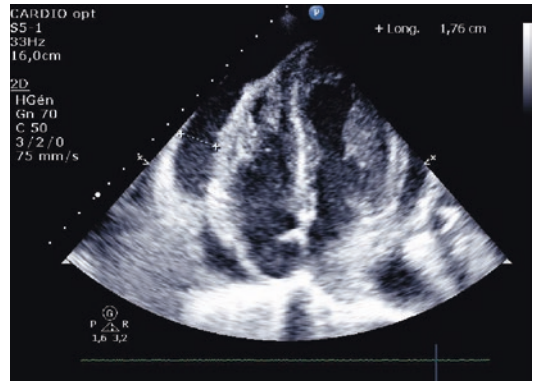


Fig. 13.2 Pericardial effusion subcostal view

Cardiac tamponade is defined as an accumulation of pericardial fluid that compresses the cardiac chambers. This compression inhibits chamber filling, leading to a reduction in CO [45]. Cardiac tamponade may occur with a relatively small pericardial collection. Echocardiographically the presentation is a circumferential pericardial effusion >1 cm with hemodynamic effects. Typical findings include right atrial and ventricular collapse caused by the pericardial effusion. Collapse first occurs during diastole (mild tamponade) and only later occurs during systole (severe tamponade). A diagnosis of collapse also requires the presence of a dilated inferior vena cava (>2.1 cm) and minimal respiratory changes). In case of severe tamponade, Doppler examination shows respiratory variations of mitral flow decrease by more than 30% between expiration and inspiration time (Fig. 13.3) [46, 47].

Thromboembolic phenomena: Pulmonary embolism (PE) may occur at any time during pregnancy and the postpartum period. The incidence of PE increases with the presence of several risk factors (e.g., body mass index>30 kg/m^2, parity>3, previous thromboembolism or throm-

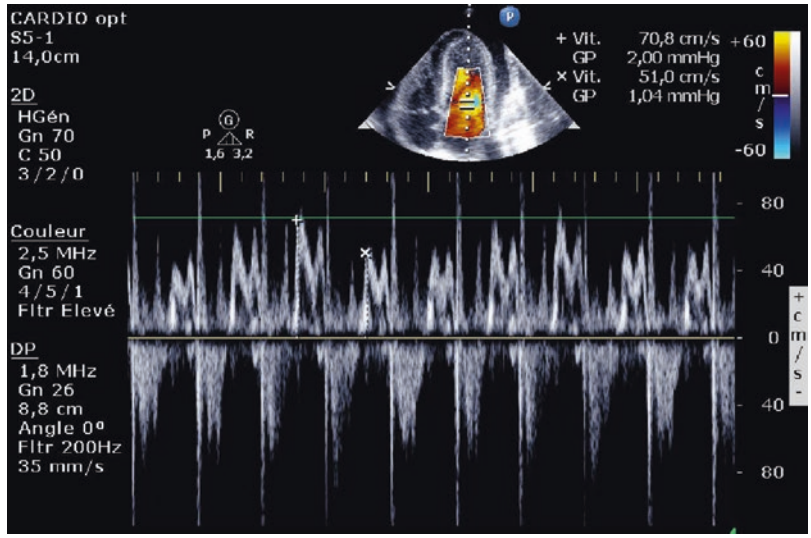


Fig. 13.3 Tamponade mitral inflow variation

bophilia, surgical procedures as cesarean section, infection, or immobility) [14, 48]. The incidence of amniotic fluid embolism (AFE) is very low (2–8:100,000 deliveries), and it mainly occurs during labor and immediately postpartum [49, 50]. AFE causes progressive pulmonary vasospasm and hypertension. These lead to right heart failure followed by global cardiogenic shock. Circulatory failure is often associated with an early change in mental status or seizures and disseminated intravascular coagulopathy.

When circulatory failure occurs, echocardiography typically demonstrates signs of acute cor pulmonale and right-sided cardiac overload. Common signs include conserved left ventricular function accompanied by right ventricular dilation and dysfunction, flattening of the ventricular septum or paradoxical septal motion, and an increase in pulmonary artery pressure with secondary tricuspid regurgitation (Figs. 13.4 and 13.5). Of note, previous chronic obstructive pulmonary disease or chronic pulmonary hypertension undermines the significance of these findings as they may have developed as a consequence of these conditions. Rarely, a thrombus may be observed in the right heart cavity or in the pulmonary artery.

POCUS can provide a definite diagnosis when an embolic event is suspected, combining cardiac

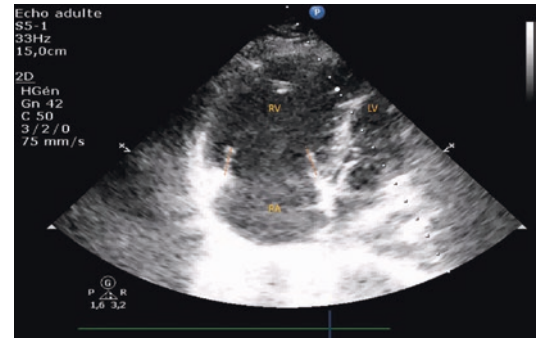


Fig. 13.4 Right ventricle dilatation during pulmonary embolus in apical four-chamber view

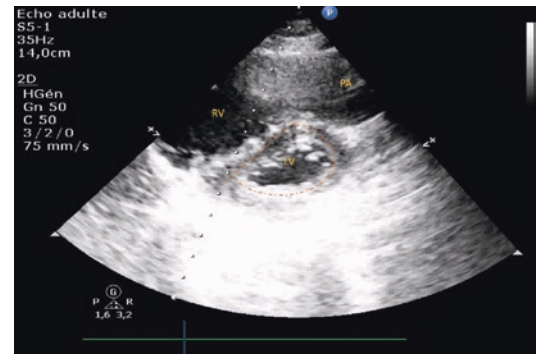


Fig. 13.5 Right ventricle dilatation during major pulmonary embolus with D sign in parasternal short axis

and lung ultrasound (Chap. 22), with an assessment for deep vein ultrasound [51, 52]. A POCUS technique to identify two compression points of the deep vein is validated for the diagnosis of deep venous thrombosis and PE [53–55]. The probability of diagnosis is high in the case of thrombus in the vein or vein incompressibility (Figs. 13.6 and 13.7). This is a simple technique to learn after 2 h training [56]. A single complete compression can exclude deep venous thrombosis in the postpartum period [57]. The absence of acute cor pulmonale or deep venous thrombosis and an alternative diagnosis suggested by lung ultrasound effectively rule out the diagnosis of pulmonary embolism with a negative predictive value of almost 100%. The presence of acute cor pulmonale with a deep venous thrombosis confirms the diagnosis of pulmonary embolism [51, 52]. This facilitates early treatment, even before computed tomography scan is performed.

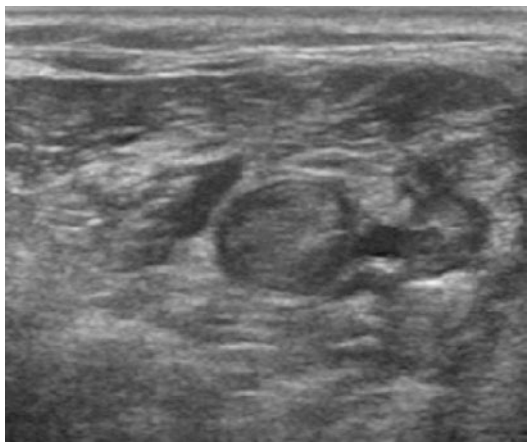


Fig. 13.6 Deep venous thrombosis transversal scan

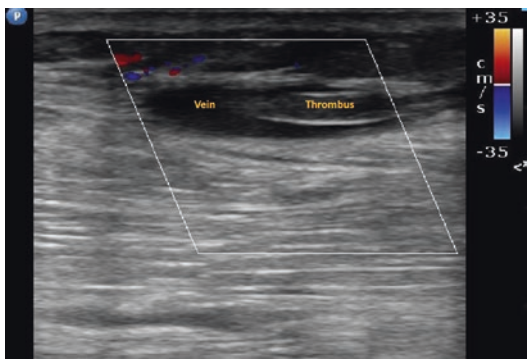


Fig. 13.7 Venous thrombosis long axis view

Hypovolemia: Acute circulatory failure due to hypovolemia is most common during the peripartum period and is usually related to severe bleeding or may be due to sepsis. POCUS is useful for diagnosing occult abdominal bleeding in pregnant or postpartum women and for guiding volume replacement. The echocardiographic features typical of severe hypovolemia include decreased left ventricular diastolic volume, with a direct contact between the mitral pillars at the end of the systole, also called "kissing heart." Diagnosis is simple using a parasternal small axis view. Severe hypovolemia may also be associated with a decreased afterload if intense vasoplegia occurs [28].

The left ventricular outflow tract (LVOT) velocity time integral (VTI) is the systolic velocity of the blood exiting the heart. LVOT VTI may be traced in real time or offline on the parasternal long axis view of the LVOT during systole. VTI dynamics can predict fluid responsiveness in acute circulatory failure. Several guidelines suggest that CO increase or VTI increase >12% during passive leg raising indicates the likelihood of fluid responsiveness. Importantly, this finding has also been validated in spontaneously breathing pregnant women [58–60].

13.4 Maternal Cardiac Arrest

Management of maternal cardiac arrest is dictated in specific guidelines [61]; see Chap. 27. These guidelines recommend identification and treatment of reversible causes of arrest. POCUS can identify many of these causes, enabling adaptation of treatment in real time. The FEEL protocol (focused echocardiography evaluation in life support) has been proposed for critical emergencies such as during patient collapse and advanced life support. The protocol was constructed to systematically seek some of the potentially treatable causes of cardiac arrest, including tamponade, massive pulmonary embolism, severe ventricular dysfunction, pneumothorax, and hypovolemia. Papers describing use of the FEEL protocol noted

that images were obtained in 96% of cases, and management was adapted to these images in 78% of cases. Regardless of the cause of cardiac arrest, interruptions to chest compression should not exceed 10 s, even in order to perform POCUS. Ideally, POCUS may be performed between chest compression cycles [17, 18].

13.5 Point-of-Care Abdominal Ultrasonography During Pregnancy

Pregnancy is accompanied by multiple anatomic and physiologic changes to the abdominal organs [62, 63]. The enlarged gravid uterus compresses and/or displaces the surrounding viscera. The anterior abdominal wall becomes relaxed. Atypical anatomical location of intra-abdominal structures and delayed signs of peritonitis hinder clinical diagnosis of intra-abdominal abnormalities. Bile concentration is increased during pregnancy. This causes biliary stasis, increasing the risk of cholelithiasis and biliary colic [64] (Figs. 13.8 and 13.9). Higher concentrations of progesterone reduce lower esophageal sphincter pressure and small and large bowel motility. These changes may lead to gastroesophageal reflux and constipation [65]. Ureteric dilatation occurs secondary to compression of the lower ureter by the gravid uterus and to decreased ureter peristalsis resulting from progesterone-induced smooth muscle relaxation. These factors increase the risk of stone formation and infection in the urinary tract [66]. Increased progesterone levels also promote thrombosis. Uterine compression of the inferior vena cava leads to a reduction in venous return. This combination is associated with an increased rate of venous thrombosis in the extremities and, rarely, development of Budd-Chiari syndrome [67].

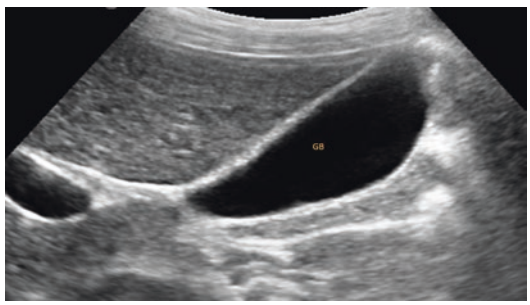


Fig. 13.8 Normal gallbladder

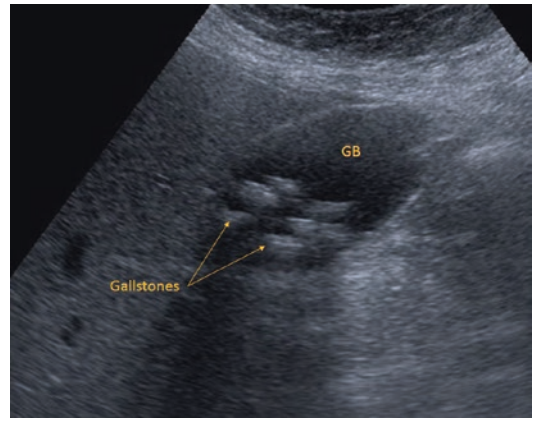


Fig. 13.9 Lithiasic gallbladder

This section will discuss abdominal POCUS assessment of pregnant women with non-pregnancy-related conditions and those with obstetrical complications. Abdominal ultrasound examination provides a great deal of information to the physician treating the critically ill pregnant or postpartum woman. Shock states are a leading cause of intensive care admission. In pregnant women, multiple causes may lead to hemodynamic compromise. POCUS can be useful for diagnosing the cause of shock [68] but needs to be integrated into a global imaging strategy which includes magnetic resonance and/or computed tomography. This is particularly true for critically ill pregnant women where it is essential to seek both obstetrical and non-obstetrical etiologies for shock.

13.5.1 POCUS Assessment of Pregnant Women with Non-pregnancy-Related Conditions

Focused Abdominal Sonography for Trauma (FAST) during pregnancy: Trauma is one of the leading causes of death in pregnant women. Between 5 and 8% of all pregnancies are com-

plicated by trauma, and 0.4% require hospitalization for the management of traumatic injuries [69]. Fildes et al. reported that nearly 50% of maternal deaths are caused by trauma [70]. The incidence of trauma in pregnant women remains underestimated. Many cases remain unreported, especially if due to domestic violence [63]. During management of a pregnant trauma victim, the mother should be prioritized; maternal death is associated with fetal loss [71].

The pregnant woman with an abdominal trauma represents a diagnostic challenge. In the first trimester of pregnancy, about 7% of women may have a small quantity of anechoic fluid (<0.4 cm maximum measured in the anteroposterior dimension of the pelvis) [72, 73]. Other than this, during pregnancy, the prevalence of free pelvic fluid without trauma is very low. Therefore, ultrasound identification of free fluid in the pelvis of a pregnant woman following blunt abdominal trauma should prompt further investigation. The likelihood of a pathological finding is particularly high if there is >2–4 mm of free fluid with no history of ovarian hyperstimulation or other condition known to be associated with pelvic fluid. Ormsby et al. demonstrated that detection of free fluid in the abdomen and/or the pelvis by ultrasound is significantly associated with abdominal trauma for both pregnant and nonpregnant patients [74].

The definition of positive abdominal US examination could be an intraperitoneal free fluid >0.4 cm or parenchymal abnormality, regardless of gestational age [69, 73]. One retrospective study described the results of FAST examination (including screening of parenchymal organs) in 19,128 trauma patients among which 2% were pregnant, and all but two of the pregnant women suffered blunt trauma [75]. Seven abdominal regions were assessed including the right and left upper quadrants, the epigastrium, the pelvis, the paracolic gutters, and the retroperitoneum. The most common findings in pregnant patients were massive amounts of free intraperitoneal fluid, placental abruption or subchorionic hematoma, and liver, kidney, and spleen laceration (Figs. 13.10, 13.11, and 13.12).

The specificity of FAST in pregnant women is similar to that in nonpregnant patients. The sensitivity and positive predictive value of abdominal ultrasound exam in pregnancy are at least 85 and 99.5%, but sensitivity may decrease to 60% with increasing gestational age [75] Moreover, the accuracy of FAST for detecting abdominal injury has been reported to be similar to that of computed tomography. Ultrasound also facilitates detection of placental injury and the rare fetal injury. No less importantly, integration of FAST into the initial trauma assessment does not delay diagnosis. Finally, if hemodynamic instability is ongoing and/or new symptoms appear, it may necessary to repeat imaging. Although radiographic examinations may be performed in pregnant women, use of POCUS may reduce fetal exposure to the damaging effects of radiation.

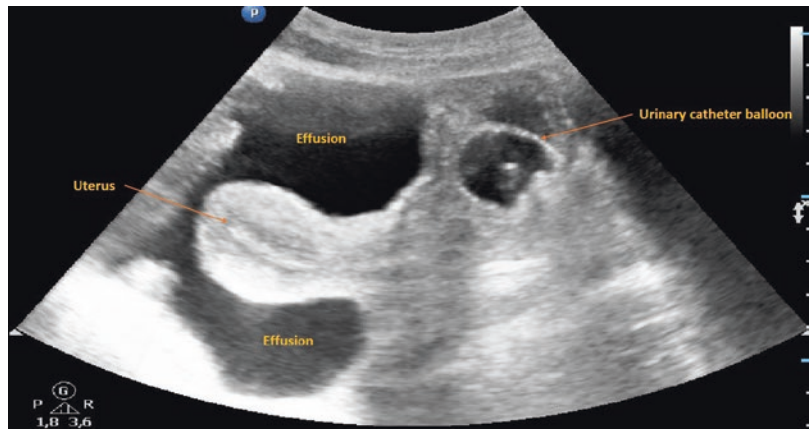


Fig. 13.10 Pelvic cul de sac effusion longitudinal view

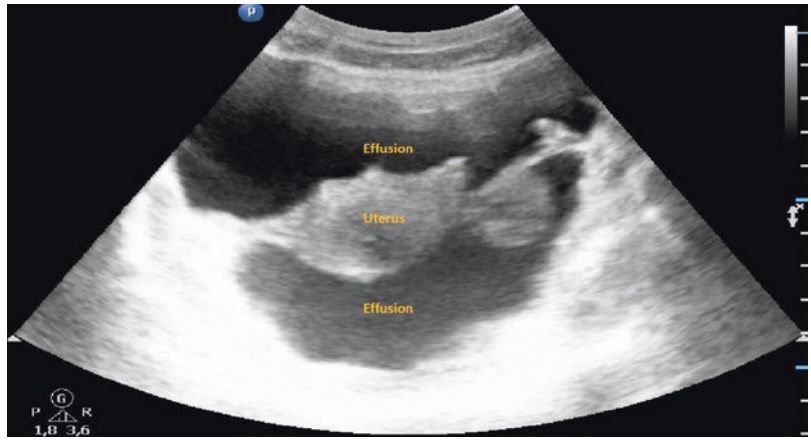


Fig. 13.11 Pelvic cul de sac effusion short axis view

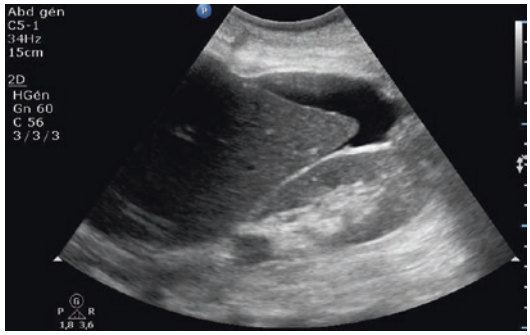


Fig. 13.12 Morison's pouch effusion

Ultrasound examination may be repeated multiple times if required, with far less concerns regarding potential fetal damage.

Urinary tract infections: Urinary tract infections are the most common bacterial infections in pregnant women. Compared to the general population, the incidence of acute pyelonephritis is increased in pregnant women, ranging from 0.5 to 2% and is higher during the second half of pregnancy [76]. Pyelonephritis also represents a risk for preterm delivery. Thus diagnosing this condition is important for both the mother and the unborn child.

In case of suspected urinary tract infection, POCUS should be considered the imaging modality of choice for initial urinary tract investigation although no recommendation suggesting so have been published to date [71]. A retrospective study showed that 14.3% of the pregnant women assessed urinary tract infection had no abnormal sonographic findings. Hydronephrosis, defined as dilatation of pyelocalicious cavities, was found in more than 50% of pregnant women with pyelonephritis [77]. There is a physiological dilation of the pyelocalicious cavities. The right kidney is more frequently involved than the left one when the obstruction is caused by an enlarged gravid uterus [78]. Perinephretic fluid could be observed in 10% of healthy pregnant women. Abdominal ultrasound may also be used to seek other causes of obstruction (i.e., stones, ureteral stricture, pelvic tumor, congenital abnormalities) as well as intra-abdominal infection.

Ultrasound evaluation of the abdominal vessels (thromboses, aneurisms): Pregnancy is accompanied by a hypercoagulable state which leads to an increased risk of thrombotic intravascular pathology (i.e., venous thrombosis of the lower extremities, pelvis, liver, mesenteric, or gonadal veins). Acute thrombosis typically causes expansion of the lumen of the involved vessel, and an echogenic thrombus may also usually be identified [68]. Pregnancy is also accompanied by an increased risk of rupture of arterial aneurysms. As previously noted hormonal changes incur structural arterial wall changes.

Splenic artery aneurysms (SAAs) are the most common among visceral artery aneurysms. SAAs are commonly associated with pregnancy, portal hypertension, atherosclerosis, and various congenital diseases. Most cases of ruptured SAA in pregnant women are initially misdiagnosed as

uterine rupture. The mortality rate of pregnant women with a ruptured SAA is very high (65–75%). Computed tomography, magnetic resonance imaging, and angiography have limited roles in the diagnostic evaluation of unstable patients primarily because of time constraints. However, POCUS does not necessitate patient relocation, and it can rapidly detect intra-abdominal free fluids and demonstrate less common causes of bleeding (e.g., rupture of an hepatic or splenic artery aneurysm) [79–81].

Intra-abdominal gastrointestinal tract pathologies: Gallbladder disease is a frequent complication of pregnancy. Cholelithiasis occurs in up to 12% of pregnant women and may be symptomatic in 0.1–0.3% [21]. Ultrasound remains the best modality for initial evaluation of the liver and biliary system. An ultrasound finding of cholelithiasis with either gallbladder wall thickening (>3 mm) or a sonographic Murphy sign has a high positive predictive value for diagnosing cholecystitis (92.2% and 95.2% sensitivity and specificity, respectively) [79] (Fig. 13.13).

Conversely, ultrasound is not the best modality to evaluate other causes of disease stemming from the gastrointestinal tract. Pancreatitis may occur during pregnancy, most often in the third trimester. Such cases require evaluation with computed tomography or magnetic resonance imaging. Ultrasound also has limited utility for diagnosing appendicitis; the appendix is infrequently visualized. Similarly, diseases of the hollow organs (e.g., bowel obstruction, diverticulitis, inflammatory bowel disease) are best investigated with modalities other than ultrasound. However, ultrasound detection of free fluid in the peritoneum suggests the presence of secondary complications of these diseases (e.g., perforation, leak, infection).

13.6 POCUS to Identify Obstetrical Complications

This section is divided into the POCUS strategies for women with severe acute hemodynamic compromise for suspected obstetrical causes and for those with obstetric diseases that may lead to critical illness more slowly. This includes all women of childbearing age who may be pregnant and women with a known pregnancy. Regardless of the population, the most important sign of a potential obstetric crisis is intraperitoneal free fluid. Severe hemorrhage constitutes one of the lead causes of ICU admission and death during pregnancy and the peripartum period [82–84].

13.6.1 Emergency Screening of Women of Childbearing Age (Possible or Confirmed Pregnancies) for Severe Acute Causes of Hemodynamic Compromise

Transabdominal ultrasound is useful for emergency department screening of women of child-

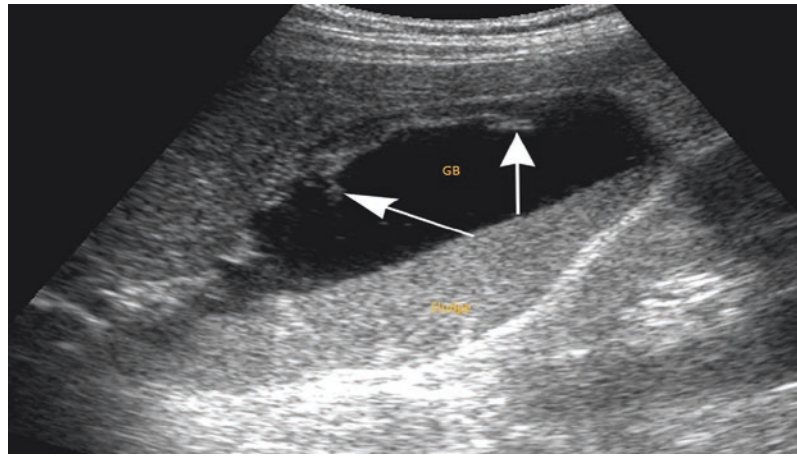


Fig. 13.13 Gangrenous cholecystitis

bearing age (whether pregnant or not) especially if hemodynamic collapse is present. Abnormal ultrasound finding combined with unfavorable clinical presentation in a woman of childbearing age requires involvement of a senior obstetrician capable of making rapid decisions. One strategy to identify potential obstetrical causes of abdominal symptoms using POCUS in women of childbearing age has been proposed based on a case series. The authors suggested that an initial pelvic view be followed by right and left upper quadrant views and a pericardial view to evaluate right heart strain [80]. Although further studies are needed to evaluate the value of this protocol, it is probably the best protocol date for this population.

The pelvic view can quickly establish the presence or lack of an intrauterine pregnancy or an ectopic pregnancy. Transvaginal ultrasonography has a 90% sensitivity and a 99% specificity for diagnosing ectopic pregnancy which is generally superior to that of transabdominal ultrasound and should therefore be considered the imaging modality of choice for this diagnosis [85].

However, the studies on transvaginal ultrasonography were not performed in patients with hemodynamic compromise [86]. The use of transabdominal ultrasound in emergency departments confirmed the presence or absence of an intrauterine pregnancy with a sensitivity of 82% and a specificity of 92% [87]. In pregnant women with hemodynamic compromise, the use of transabdominal ultrasound to establish intrauterine pregnancy is likely the most time-efficient diagnostic study to perform.

If b-HCG indicates the presence of a pregnancy and ultrasound has detected intraperitoneal fluid but no intrauterine pregnancy, ectopic pregnancy should be suspected. If an intrauterine pregnancy has been detected, the complications of intrauterine pregnancy should be sought—pelvic POCUS examination may serve to detect uterine rupture, placenta previa, or abruption. Uterine rupture may diagnosed on ultrasound by detection of a uterine wall defect (i.e., a large hypoechoic lesion between the uterus and the bladder) or by amniotic sac or fetal parts protruding beyond the uterine margin [88].

Both intrauterine pregnancy and ectopic pregnancy presenting with free abdominal fluid raise the suspicion of hemorrhage. Such women should be transferred immediately to a location with full emergency support facilities, such as an operating room or the labor and delivery department. Such cases require a suitable management strategy, including immediate delivery and expert transfusion management. The mortality rate associated with ectopic pregnancy is decreasing but still remains approximately 0.2:1000 ectopic pregnancies [85]. Uterine rupture is rare (incidence<0.1% of deliveries) but is more likely to occur in women with history of prior uterine surgery (e.g., cesarean delivery).

If pelvic ultrasound has detected intraperitoneal fluid but no intrauterine pregnancy and if b-HCG is negative and there is no evidence of ectopic pregnancy, right and left upper quadrant views of the hepatorenal and splenorenal recesses should be obtained. The likelihood of detecting a hepatic or splenic etiology for the free peritoneal fluid is high with either view. Such women should be referred to surgical consultation immediately and prepared for the operating room.

13.6.2 Use of POCUS to Screen Pregnant Woman for Obstetric Diseases that Cause Gradual Maternal Deterioration

If these views yield no pathological findings, a pericardial view should be obtained in order to evaluate the right heart for the presence of strain as a sign of PE or peripartum cardiomyopathy. If these are identified, the patient should be referred to the ICU, interventional radiology, or even cardiac surgery depending on the severity and the location of the emboli.

13.7 Pregnant Women: *The HELLP Syndrome*

The obstetrical complications described above are accompanied by acute hemodynamic decompensation and are pertinent for women with a

known pregnancy. However, pregnant women may also suffer from the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) which may lead to critical illness but does not necessarily manifest with hemodynamic decompensation (albeit it may).

HELLP syndrome occurs in 4–12% of pregnant women with severe preeclampsia. POCUS can contribute important information with regard to clinically significant abdominal findings in women with preeclampsia and the HELLP syndrome. HELLP syndrome can be associated with hepatic subcapsular or intraparenchymal hemorrhage, hepatic rupture, hepatic parenchymal infarction, placental disruption, and retroplacental hematoma. One case report even described diagnosis of a rare cause of hemodynamic compromise in a pregnant woman with HELLP; the woman had no external evidence of uterine hemorrhage, but pelvic ultrasound detected a large uterine hematoma [89].

Several POCUS findings are typically associated with the HELLP syndrome, and if discovered incidentally in a pregnant woman, should lead to specific investigations to diagnose HELLP syndrome before its complications become life-threatening. These findings include a hypoechoic lentil posterior to the placenta, hypoechoic free fluid between the right kidney and the liver, or a unilateral cystic or abnormal area in the liver (reflecting intrahepatic hematoma secondary to hepatic rupture) [90]. Diagnosis of an intrahepatic hematoma during pregnancy should also prompt immediate further imaging as the differential diagnosis of such a finding includes adenoma, trauma, and rupture of an hepatic artery pseudoaneurysm [90].

Postpartum hemodynamic instability: Abdominal ultrasound is a useful diagnostic tool for women who are hemodynamically unstable or whose hematocrit is decreasing postpartum with no evident cause of hemorrhage [91]. Apart from detection of free fluid in this situation, POCUS may locate atypical causes of bleeding. Case reports of such findings include a pulsed color or Doppler signal within a hematoma suggesting rupture of a uterine artery pseudoaneurysm [92], new subcapsular hemorrhage from the liver, and spontaneous rupture of utero-ovarian vessels. Women suffering postpartum hemorrhage who have an intrauterine mass or an intra-abdominal effusion (indicating greater blood loss) identified by POCUS have poorer outcomes [93].

13.8 Conclusion

POCUS contributes relevant information for managing pregnant and postpartum women in critical condition. The efficiency of this noninvasive imaging technique, which involves no exposure to radiation, makes it perfectly suitable for this population. Recent studies suggest that associating different POCUS views and examinations increases its diagnostic impact. Clinicians treating this population should be encouraged to acquire the POCUS skills required to optimize treatment of this population.

References

1. Moore CL, Copel JA. Point-of-care ultrasonography. N Engl J Med. 2011;364(8):749–57.
2. Volpicelli G, Elbarbary M, Blaivas M, Lichtenstein DA, Mathis G, Kirkpatrick AW, et al. International evidence-based recommendations for point-of-care lung ultrasound. Intensive Care Med. 2012;38(4):577–91.
3. Troianos CA, Hartman GS, Glas KE, Skubas NJ, Eberhardt RT, Walker JD, et al. Guidelines for performing ultrasound guided vascular cannulation: recommendations of the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists. J Am Soc Echocardiogr. 2011;24(12):1291–318.
4. American College of Emergency Physicians. Emergency ultrasound guidelines. Ann Emerg Med. 2009;53(4):550–70.
5. Mayo PH, Beaulieu Y, Doelken P, Feller-Kopman D, Harrod C, Kaplan A, et al. American College of Chest Physicians/La Société de Réanimation de Langue Française statement on competence in critical care ultrasonography. Chest. 2009;135(4):1050–60.
6. Vieira RL, Hsu D, Nagler J, Chen L, Gallagher R, Levy JA, et al. Pediatric emergency medicine fellow training in ultrasound: consensus educational guidelines. Acad Emerg Med. 2013;20(3):300–6.
7. Zieleskiewicz L, Muller L, Lakhal K, Meresse Z, Arbelot C, Bertrand P-M, et al. Point-of-care ultrasound in intensive care units: assessment of 1073 pro-

cedures in a multicentric, prospective, observational study. Intensive Care Med. 2015;41(9):1638–47.
8. Bobbia X, Zieleskiewicz L, Pradeilles C, Hudson C, Muller L, Claret PG, et al. The clinical impact and prevalence of emergency point-of-care ultrasound: a prospective multicentre study. Anaesth Crit Care Pain Med. 2017;36(6):383–9.
9. Bernier-Jean A, Albert M, Shiloh AL, Eisen LA, Williamson D, Beaulieu Y. The diagnostic and therapeutic impact of point-of-care ultrasonography in the intensive care unit. J Intensive Care Med. 2017;32(3):197–203.
10. Paech MJ, Hillyard SG. New techniques and technologies for obstetric anaesthesia. Int J Obstet Anesth. 2012;21(1):101–2.
11. Oks M, Cleven KL, Cardenas-Garcia J, Schaub JA, Koenig S, Cohen RI, et al. The effect of point-of-care ultrasonography on imaging studies in the medical ICU: a comparative study. Chest. 2014;146(6):1574–7.
12. Zieleskiewicz L, Cornesse A, Hammad E, Haddam M, Brun C, Vigne C, et al. Implementation of lung ultrasound in polyvalent intensive care unit: impact on irradiation and medical cost. Anaesth Crit Care Pain Med. 2015;34(1):41–4.
13. Peris A, Tutino L, Zagli G, Batacchi S, Cianchi G, Spina R, et al. The use of point-of-care bedside lung ultrasound significantly reduces the number of radiographs and computed tomography scans in critically ill patients. Anesth Analg. 2010;111(3):687–92.
14. Cantwell R, Clutton-Brock T, Cooper G, Dawson A, Drife J, Garrod D, et al. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. BJOG Int J Obstet Gynaecol. 2011;118(Suppl 1):1–203.
15. Kassebaum NJ, Bertozzi-Villa A, Coggeshall MS, Shackelford KA, Steiner C, Heuton KR, et al. Global, regional, and national levels and causes of maternal mortality during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet Lond Engl. 2014;384(9947):980–1004.
16. Jensen MB, Sloth E, Larsen KM, Schmidt MB. Transthoracic echocardiography for cardiopulmonary monitoring in intensive care. Eur J Anaesthesiol. 2004;21(9):700–7.
17. Breitkreutz R, Walcher F, Seeger FH. Focused echocardiographic evaluation in resuscitation management: concept of an advanced life support-conformed algorithm. Crit Care Med. 2007;35(5 Suppl):S150–61.
18. Breitkreutz R, Price S, Steiger HV, Seeger FH, Ilper H, Ackermann H, et al. Focused echocardiographic evaluation in life support and peri-resuscitation of emergency patients: a prospective trial. Resuscitation. 2010;81(11):1527–33.
19. Cecconi M, De Backer D, Antonelli M, Beale R, Bakker J, Hofer C, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. Intensive Care Med. 2014;40(12):1795–815.
20. Intravascular volume therapy in adults: guidelines from the Association of the Scientific Medical Societies in Germany. [Internet]. [cited 2017 Aug 7]. https://www.ncbi.nlm.nih.gov/pubmed/?term=27043493.
21. Bentzer P, Griesdale DE, Boyd J, MacLean K, Sirounis D, Ayas NT. Will this hemodynamically unstable patient respond to a bolus of intravenous fluids? JAMA. 2016;316(12):1298–309.
22. Dennis AT. Transthoracic echocardiography in obstetric anaesthesia and obstetric critical illness. Int J Obstet Anesth. 2011;20(2):160–8.
23. Dennis A. The rapid obstetric sreenning echocardiography examination. Australian and New zealand College of Anaesthetists (ANZCA). http://anzca.edu.au/events/asm/asm2010/abstracts/staturday/the-rapid-obstetric-screening-echocardiography.htlm.
24. Bamfo JEAK, Kametas NA, Nicolaides KH, Chambers JB. Reference ranges for tissue Doppler measures of maternal systolic and diastolic left ventricular function. Ultrasound Obstet Gynecol. 2007;29(4):414–20.
25. Melchiorre K, Sharma R, Khalil A, Thilaganathan B. Maternal cardiovascular function in normal pregnancy: evidence of maladaptation to chronic volume overload. Hypertension. 2016;67(4):754–62.
26. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129–200.
27. van Hagen IM, Cornette J, Johnson MR, Roos-Hesselink JW. Managing cardiac emergencies in pregnancy. Heart. 2017;103(2):159–73.
28. Porter TR, Shillcutt SK, Adams MS, Desjardins G, Glas KE, Olson JJ, et al. Guidelines for the use of echocardiography as a monitor for therapeutic intervention in adults: a report from the American Society of Echocardiography. J Am Soc Echocardiogr. 2015;28(1):40–56.
29. Cornette J, Laker S, Jeffery B, Lombaard H, Alberts A, Rizopoulos D, et al. Validation of maternal cardiac output assessed by transthoracic echocardiography against pulmonary artery catheterization in severely ill pregnant women: prospective comparative study and systematic review. Ultrasound Obstet Gynecol. 2017;49(1):25–31.
30. Castleman JS, Ganapathy R, Taki F, Lip GYH, Steeds RP, Kotecha D. Echocardiographic structure and function in hypertensive disorders of pregnancy: a systematic review. Circ Cardiovasc Imaging. 2016;9(9):e004888.
31. Dennis AT, Castro JM. Echocardiographic differences between preeclampsia and peripartum cardiomyopathy. Int J Obstet Anesth. 2014;23(3):260–6.

32. Amico AF, Lichtenberg GS, Reisner SA, Stone CK, Schwartz RG, Meltzer RS. Superiority of visual versus computerized echocardiographic estimation of radionuclide left ventricular ejection fraction. Am Heart J. 1989;118(6):1259–65.
33. Van Camp G, Franken RR, Schoors D, Hagers Y, Koole M, Demoor D, et al. Impact of second harmonic imaging on the determination of the global and regional left ventricular function by 2D echocardiography: a comparison with MIBI gated SPECT. Eur J Echocardiogr. 2000;1(2):122–9.
34. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16(3):233–70.
35. Sun JP, Lee AP-W, Wu C, Lam Y-Y, Hung M-J, Chen L, et al. Quantification of left ventricular regional myocardial function using two-dimensional speckle tracking echocardiography in healthy volunteers—a multi-center study. Int J Cardiol. 2013;167(2):495–501.
36. Echocardiographic Normal Ranges Meta-Analysis of the Left heart (EchoNoRMAL) Collaboration. A meta-analysis of echocardiographic measurements of the left heart for the development of normative reference ranges in a large international cohort: the EchoNoRMAL study. Eur Heart J Cardiovasc Imaging. 2014;15(3):341–8.
37. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016;29(4):277–314.
38. James AH, Jamison MG, Biswas MS, Brancazio LR, Swamy GK, Myers ER. Acute myocardial infarction in pregnancy: a United States population-based study. Circulation. 2006;113(12):1564–71.
39. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;64(24):e139–228.
40. European Society of Gynecology (ESG), Association for European Paediatric Cardiology (AEPC), German Society for Gender Medicine (DGesGM), Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, et al. ESC guidelines on the management of cardiovascular diseases during pregnancy: the task force on the management of cardiovascular diseases during pregnancy of the European Society of Cardiology (ESC). Eur Heart J. 2011;32(24):3147–97.
41. Immer FF, Bansi AG, Immer-Bansi AS, McDougall J, Zehr KJ, Schaff HV, et al. Aortic dissection in pregnancy: analysis of risk factors and outcome. Ann Thorac Surg. 2003;76(1):309–14.
42. Clough RE, Nienaber CA. Management of acute aortic syndrome. Nat Rev Cardiol. 2015;12(2):103–14.
43. Vignon P, Spencer KT, Rambaud G, Preux PM, Krauss D, Balasia B, et al. Differential transesophageal echocardiographic diagnosis between linear artifacts and intraluminal flap of aortic dissection or disruption. Chest. 2001;119(6):1778–90.
44. Bonow RO, Carabello BA, Chatterjee K, de Leon AC, Faxon DP, Freed MD, et al. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2008;118(15):e523–661.
45. Klein AL, Abbara S, Agler DA, Appleton CP, Asher CR, Hoit B, et al. American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with pericardial disease: endorsed by the Society for Cardiovascular Magnetic Resonance and Society of Cardiovascular Computed Tomography. J Am Soc Echocardiogr. 2013;26(9):965–1012.e15.
46. Mercé J, Sagristà-Sauleda J, Permanyer-Miralda G, Evangelista A, Soler-Soler J. Correlation between clinical and Doppler echocardiographic findings in patients with moderate and large pericardial effusion: implications for the diagnosis of cardiac tamponade. Am Heart J. 1999;138(4 Pt 1):759–64.
47. Faehnrich JA, Noone RB, White WD, Leone BJ, Hilton AK, Sreeram GM, et al. Effects of positive-pressure ventilation, pericardial effusion, and cardiac tamponade on respiratory variation in transmitral flow velocities. J Cardiothorac Vasc Anesth. 2003;17(1):45–50.
48. Kane EV, Calderwood C, Dobbie R, Morris C, Roman E, Greer IA. A population-based study of venous thrombosis in pregnancy in Scotland 1980-2005. Eur J Obstet Gynecol Reprod Biol. 2013;169(2):223–9.
49. Abenhaim HA, Azoulay L, Kramer MS, Leduc L. Incidence and risk factors of amniotic fluid embolisms: a population-based study on 3 million births in the United States. Am J Obstet Gynecol. 2008;199(1):49.e1–8.
50. Knight M, Berg C, Brocklehurst P, Kramer M, Lewis G, Oats J, et al. Amniotic fluid embolism incidence, risk factors and outcomes: a review and recommendations. BMC Pregnancy Childbirth. 2012;12:7.
51. Nazerian P, Vanni S, Volpicelli G, Gigli C, Zanobetti M, Bartolucci M, et al. Accuracy of point-of-care multiorgan ultrasonography for the diagnosis of pulmonary embolism. Chest. 2014;145(5):950–7.

52. Koenig S, Chandra S, Alaverdian A, Dibello C, Mayo PH, Narasimhan M. Ultrasound assessment of pulmonary embolism in patients receiving CT pulmonary angiography. Chest. 2014;145(4):818–23.
53. Bernardi E, Camporese G, Büller HR, Siragusa S, Imberti D, Berchio A, et al. Serial 2-point ultrasonography plus D-dimer vs whole-leg color-coded Doppler ultrasonography for diagnosing suspected symptomatic deep vein thrombosis: a randomized controlled trial. JAMA. 2008;300(14):1653–9.
54. Cogo A, Lensing AW, Koopman MM, Piovella F, Siragusa S, Wells PS, et al. Compression ultrasonography for diagnostic management of patients with clinically suspected deep vein thrombosis: prospective cohort study. BMJ. 1998;316(7124):17–20.
55. Le Gal G, Righini M, Sanchez O, Roy P-M, Baba-Ahmed M, Perrier A, et al. A positive compression ultrasonography of the lower limb veins is highly predictive of pulmonary embolism on computed tomography in suspected patients. Thromb Haemost. 2006;95(6):963–6.
56. Jang T, Docherty M, Aubin C, Polites G. Resident-performed compression ultrasonography for the detection of proximal deep vein thrombosis: fast and accurate. Acad Emerg Med. 2004;11(3): 319–22.
57. Le Gal G, Kercret G, Ben Yahmed K, Bressollette L, Robert-Ebadi H, Riberdy L, et al. Diagnostic value of single complete compression ultrasonography in pregnant and postpartum women with suspected deep vein thrombosis: prospective study. BMJ. 2012;344:e2635.
58. Guy GP, Ling HZ, Machuca M, Poon LC, Nicolaides KH. Effect of change in posture on maternal functional hemodynamics at 35-37 weeks' gestation. Ultrasound Obstet Gynecol. 2018;51(3):368–74.
59. Zieleskiewicz L, Contargyris C, Brun C, Touret M, Vellin A, Antonini F, et al. Lung ultrasound predicts interstitial syndrome and hemodynamic profile in parturients with severe preeclampsia. Anesthesiology. 2014;120(4):906–14.
60. Brun C, Zieleskiewicz L, Textoris J, Muller L, Bellefleur J-P, Antonini F, et al. Prediction of fluid responsiveness in severe preeclamptic patients with oliguria. Intensive Care Med. 2013;39(4):593–600.
61. Jeejeebhoy FM, Zelop CM, Lipman S, Carvalho B, Joglar J, Mhyre JM, et al. Cardiac arrest in pregnancy: a scientific statement from the American Heart Association. Circulation. 2015;132(18):1747–73.
62. Petrone P, Asensio JA. Trauma in pregnancy: assessment and treatment. Scand J Surg. 2006;95(1):4–10.
63. Petrone P, Marini CP. Trauma in pregnant patients. Curr Probl Surg. 2015;52(8):330–51.
64. Ko CW. Risk factors for gallstone-related hospitalization during pregnancy and the postpartum. Am J Gastroenterol. 2006;101(10):2263–8.
65. Baron TH, Ramirez B, Richter JE. Gastrointestinal motility disorders during pregnancy. Ann Intern Med. 1993;118(5):366–75.
66. Fiadjoe P, Kannan K, Rane A. Maternal urological problems in pregnancy. Eur J Obstet Gynecol Reprod Biol. 2010;152(1):13–7.
67. Hepburn IS, Schade RR. Pregnancy-associated liver disorders. Dig Dis Sci. 2008;53(9):2334–58.
68. Khandelwal A, Fasih N, Kielar A. Imaging of acute abdomen in pregnancy. Radiol Clin North Am. 2013;51(6):1005–22.
69. Lavery JP, Staten-McCormick M. Management of moderate to severe trauma in pregnancy. Obstet Gynecol Clin North Am. 1995;22(1):69–90.
70. Fildes J, Reed L, Jones N, Martin M, Barrett J. Trauma: the leading cause of maternal death. J Trauma. 1992;32(5):643–5.
71. Seidman DS, Soriano D, Dulitzki M, Heyman Z, Mashiach S, Barkai G. Role of renal ultrasonography in the management of pyelonephritis in pregnant women. J Perinatol. 1998;18(2):98–101.
72. Sirlin CB, Casola G, Brown MA, Patel N, Bendavid EJ, Deutsch R, et al. Us of blunt abdominal trauma: importance of free pelvic fluid in women of reproductive age. Radiology. 2001;219(1):229–35.
73. Hussain ZJ, Figueroa R, Budorick NE. How much free fluid can a pregnant patient have? Assessment of pelvic free fluid in pregnant patients without antecedent trauma. J Trauma. 2011;70(6):1420–3.
74. Ormsby EL, Geng J, McGahan JP, Richards JR. Pelvic free fluid: clinical importance for reproductive age women with blunt abdominal trauma. Ultrasound Obstet Gynecol. 2005;26(3):271–8.
75. Meisinger QC, Brown MA, Dehqanzada ZA, Doucet J, Coimbra R, Casola G. A 10-year restrospective evaluation of ultrasound in pregnant abdominal trauma patients. Emerg Radiol. 2016;23(2):105–9.
76. Schnarr J, Smaill F. Asymptomatic bacteriuria and symptomatic urinary tract infections in pregnancy. Eur J Clin Invest. 2008;38(Suppl 2):50–7.
77. Farkash E, Weintraub AY, Sergienko R, Wiznitzer A, Zlotnik A, Sheiner E. Acute antepartum pyelonephritis in pregnancy: a critical analysis of risk factors and outcomes. Eur J Obstet Gynecol Reprod Biol. 2012;162(1):24–7.
78. vanSonnenberg E, Casola G, Talner LB, Wittich GR, Varney RR, D'Agostino HB. Symptomatic renal obstruction or urosepsis during pregnancy: treatment by sonographically guided percutaneous nephrostomy. AJR Am J Roentgenol. 1992;158(1):91–4.
79. Ralls PW, Colletti PM, Lapin SA, Chandrasoma P, Boswell WD, Ngo C, et al. Real-time sonography in suspected acute cholecystitis. Prospective evaluation of primary and secondary signs. Radiology. 1985;155(3):767–71.
80. Jackson HT, Diaconu SC, Maluso PJ, Abell B, Lee J. Ruptured splenic artery aneurysms and the use of an adapted fast protocol in reproductive age women with hemodynamic collapse: case series. Case Rep Emerg Med. 2014;2014:454923.
81. Sarikaya S, Ekci B, Aktas C, Cetin A, Ay D, Demirag A. A rare clinic presentation of abdominal pain: rup-

ture of splenic artery aneurysm: a case report. Cases J. 2009;2:148.
82. Hazelgrove JF, Price C, Pappachan VJ, Smith GB. Multicenter study of obstetric admissions to 14 intensive care units in southern England. Crit Care Med. 2001;29(4):770–5.
83. Sriram S, Robertson MS. Critically ill obstetric patients in Australia: a retrospective audit of 8 years' experience in a tertiary intensive care unit. Crit Care Resusc. 2008;10(2):124.
84. Tang LC, Kwok AC, Wong AY, Lee YY, Sun KO, So AP. Critical care in obstetrical patients: an eight-year review. Chin Med J. 1997;110(12):936–41.
85. Newbatt E, Beckles Z, Ullman R, Lumsden MA, Guideline Development Group. Ectopic pregnancy and miscarriage: summary of NICE guidance. BMJ. 2012;345:e8136.
86. Condous G, Okaro E, Khalid A, Lu C, Van Huffel S, Timmerman D, et al. The accuracy of transvaginal ultrasonography for the diagnosis of ectopic pregnancy prior to surgery. Hum Reprod. 2005;20(5):1404–9.
87. Wong TW, Lau CC, Yeung A, Lo L, Tai CM. Efficacy of transabdominal ultrasound examination in the diagnosis of early pregnancy complications in an emergency department. J Accid Emerg Med. 1998;15(3):155–8.
88. Mizutamari E, Honda T, Ohba T, Katabuchi H. Spontaneous rupture of an unscarred gravid uterus in a primigravid woman at 32 weeks of gestation. Case Rep Obstet Gynecol. 2014;2014:209585.
89. Zieleskiewicz L, Pierrou C, Ragonnet B, Tourret M, Chau C, Craighero F, et al. [Role of whole-body ultrasound in severe pre-eclampsia and post-partum hemorrhage]. Can J Anaesth. 2013;60(8):796–802.
90. Heller MT, Tublin ME, Hosseinzadeh K, Fargiano A. Imaging of hepatobiliary disorders complicating pregnancy. AJR Am J Roentgenol. 2011;197(3):W528–36.
91. Sentilhes L, Vayssière C, Deneux-Tharaux C, Aya AG, Bayoumeu F, Bonnet M-P, et al. Postpartum hemorrhage: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF): in collaboration with the French Society of Anesthesiology and Intensive Care (SFAR). Eur J Obstet Gynecol Reprod Biol. 2016;198:12–21.
92. McGonegle SJ, Dziedzic TS, Thomas J, Hertzberg BS. Pseudoaneurysm of the uterine artery after an uncomplicated spontaneous vaginal delivery. J Ultrasound Med. 2006;25(12):1593–7.
93. Lousquy R, Morel O, Soyer P, Malartic C, Gayat E, Barranger E. Routine use of abdominopelvic ultrasonography in severe postpartum hemorrhage: retrospective evaluation in 125 patients. Am J Obstet Gynecol. 2011;204(3):232.e1–6.

14 Extracorporeal Membrane Oxygenation During Pregnancy and the Peripartum Period

Romain Rambaud, Christophe Guervilly, and Laurent Papazian

Bullet Points

- At this time, there are reports of more than 100 women who have been supported by ECMO during pregnancy and/or the postpartum period.
- The indications for the use of ECMO as well as for ECMO configuration for the pregnant and postpartum population are similar to those of the general population.
- Deterioration to cardiac arrest during pregnancy or the peripartum period rarely occurs due to irreversible background disease.
- Women requiring ECMO support should be managed in a high-volume referral ECMO center if possible.
- The survival rates following ECMO therapy in pregnancy and the peripartum period are 81% for the mother and 63.2% for the fetus.
- Positioning the pregnant woman in a left lateral tilt position may facilitate cannulation of the femoral vessels.
- Cannula positions must be verified as in the non-pregnant patient despite the presence of the pregnancy.
- High pump flows may be required to maintain reasonable perfusion pressures in this specific population. Flow may be augmented by the use of a second drainage cannula. Induction of moderate hypothermia (if not contraindicated) and intravenous beta-blockers may also be useful.
- A small series of cases suggests that women presenting with DIC following massive hemorrhage may initially be managed without anticoagulation, provided that heparin-coated circuits and high flows are used.
- Severe bleeding complications are frequently reported irrespective of the method of delivery.
- There is currently no evidence to support early induction of delivery to improve either maternal or neonatal outcomes during maternal ECMO therapy.

R. Rambaud · C. Guervilly (✉) · L. Papazian
Aix-Marseille Univ, APHM, URMITE UMR CNRS 7278, Hôpital Nord, Réanimation des Détresses Respiratoires et Infections sévères, Marseille, France
e-mail: Christophe.GUERVILLY@ap-hm.fr

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_14

14.1 Introduction

Extracorporeal life support (ECLS) refers to the use of extracorporeal cardiopulmonary bypass in patients with cardiac or respiratory failure when other treatment options fail. The term extracorporeal membrane oxygenation (ECMO) is preferred for patients who require only respiratory support. However, both terms can be used interchangeably [1]. In this chapter, the term "ECMO" will be used for both ECMO and ECLS.

During the 2009 influenza A (H1N1) pandemic, the use of ECMO for treatment of acute respiratory disease (ARDS) came to the fore [2, 3]. Technical advances, improved biocompatibility, and the publication of the CESAR trial have all contributed to the worldwide increase in ECMO use since then [4–6]. However, this increased ECMO use has not been accompanied by a parallel growth in information regarding the outcomes of specific patient populations. Among the populations still lacking clear outcome data are women managed with ECMO while pregnant or in their postpartum period. At the current time, the published experience with ECMO during pregnancy and the peripartum period remains limited to case reports and small cohort studies.

As pregnant women are at increased risk to develop severe ARDS during influenza infections [7–13], information regarding the use of ECMO is essential in this population. Furthermore, management of ECMO in the pregnant population is uniquely challenging. Not only are two lives at stake; when treating such women with ECMO, the clinician must balance two major risks, hypercoagulability and hemorrhage, take into consideration the physiological changes of pregnancy, and deal with both fetal monitoring and delivery—neither of which have clear timing or management strategies.

14.2 Literature Review

In order to write this chapter, a comprehensive literature search of the MEDLINE database was performed (January 1991–October 2017). The terms used were "Pregnancy" AND ("ECMO" or ECLS") and "Post-Partum" AND ("ECMO or ECLS"). The search was limited to articles published in the English language. At the time, this search revealed a total of 100 women supported by ECMO during pregnancy and/or the postpartum period [14–58]. Statistical analysis was performed on the search data after extraction of individual case variables. The median age of the 89 women was 30 years (IQR, 25–33). Among them, 54 (60.7%) were pregnant and 35 (39.3%) were in the postpartum period. The gestational age of the pregnant women at the ECMO initiation was 29 weeks (IQR, 23–33). Postpartum patients had delivered a median of 3 days (IQR, 1–3) prior to cannulation. The ECMO configuration was veno-venous (VV) in 65 patients and venoarterial (VA) in 24 patients. The indications for initiating ECMO therapy were mainly ARDS (73%), followed by cardiogenic shock (18%) and cardiopulmonary resuscitation (CPR) (9%). The main risk factor for ARDS was H1N1 (73.8%). The survival rate was 81%, which is better than the outcomes of the overall ECMO cohort in the ELSO registry [59]. The survival rate of the fetuses of pregnant women who were supported by ECMO was 63.8% (Table 14.1). Since then, there have been additional reports.

Table 14.1 Characteristics and outcomes of pregnant and postpartum women who have undergone ECMO (systematic review of the literature Jan 1991-October 2017)

Variable	Value
Age, years	31 (25–33)
Pregnant	57 (57%)
Gestational age, weeks	29 (23–33)
Postpartum	43 (43%)
Cannulation days after delivery	3 (1–3)
Maternal survival	81 (81%)
Fetal survival	36 (63.2%)
Venovenous ECMO	69 (69%)
H1N1	49 (49%)
Pneumoniae	13 (13%)
Other	7 (7%)
Venoarterial ECMO	24 (27%)
Cardiogenic shock	18 (18%)
ECPR	13 (13%)
ECMO duration, days	7 (5–13)
ICU length of stay, days	24 (15,5–35)
Mechanical ventilation duration, days	18 (10–31)

Data are median (interquartile range) or number (%)
ECMO extracorporeal membrane oxygenation, *ICU* intensive care unit, *ECPR* early cardio pulmonary resuscitation

There may be overestimation of survival in the pregnant and postpartum population due to publication bias stemming from the reporting of mostly positive outcomes. However, such favorable outcomes can also be explained by the young age of this patient population, by the fact that many of them were suffering from H1N1 which has been associated with better ECMO outcomes [60] and by an earlier ECMO initiation after a median duration of mechanical ventilation of 1 day [61].

14.3 Technical Aspects of ECMO Management

14.3.1 ECMO Circuit

In a typical ECMO circuit, venous blood is drained from the right atrium via a large cannula through a major vein (usually femoral). A centrifugal pump revolving at the desired rate per minute generates blood flow by vortex effect, thereby routing it through the membrane lung. This allows diffusion of oxygen from the blender and extracorporeal CO_2 removal from the venous blood of the patient. Blood oxygenated to 100% saturation and warmed to a preset temperature is then drawn back into the circulation through either a major artery (usually femoral) (VA-ECMO) or a vein (jugular or femoral) (VV-ECMO) (Fig. 14.1) [62].

14.3.2 Pump

Most ECMO centers have abandoned roller pumps (which often cause hemolysis and may damage the tubing in long-term use) in favor of

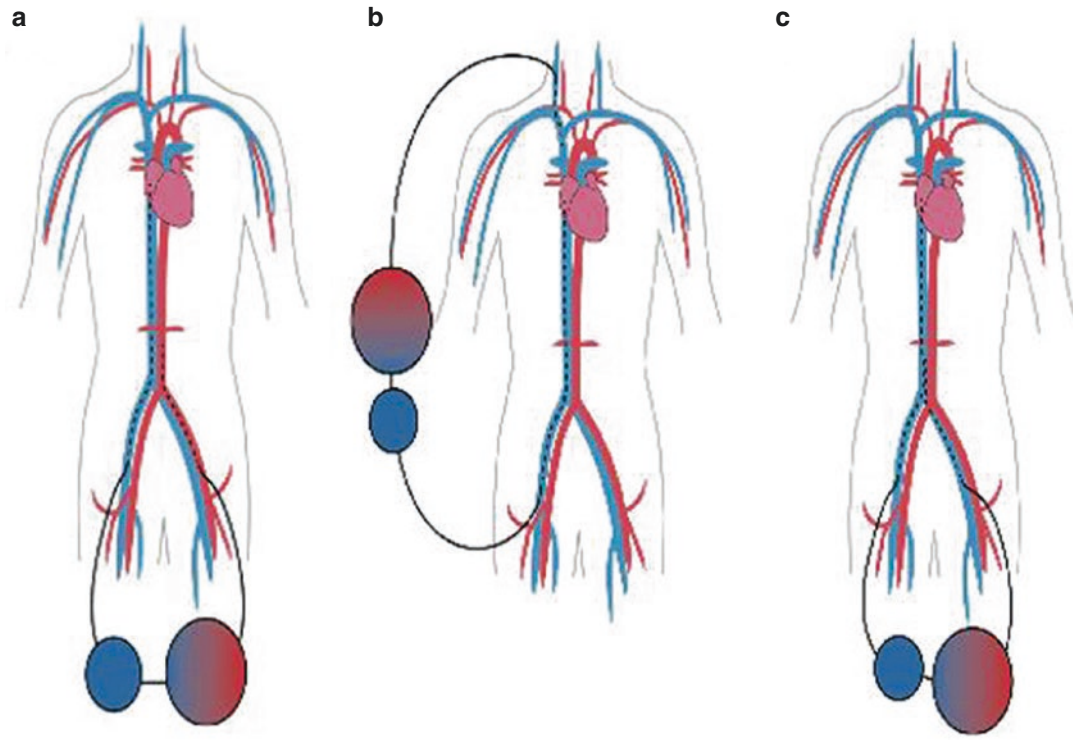


Fig. 14.1 Extra corporeal membrane oxygenation (ECMO) configurations: (**a**) veno-arterial ECMO with femoral vein for drainage and femoral artery for perfusion; (**b**) veno-venous ECMO with femoral vein for drainage and right internal jugular vein for infusion; (**c**) veno-venous ECMO where both femoral veins are used, one for drainage and the other for perfusion. (Adapted from Makdisi G, Wang I-W. Extra Corporeal Membrane Oxygenation (ECMO) review of a lifesaving technology. J Thorac Dis. 2015 Jul;7(7):E166–176.)

centrifugal pumps. Centrifugal pumps use magnetic impellers to generate blood flow while minimizing blood stasis and hemolysis [63]. An additional benefit of centrifugal pumps is the low fluid volume required for priming, which decreases the need for transfusion. The ECMO blood flow, which is determined by pump's revolutions per minute (RPM), establishes the degree of extracorporeal oxygenation and CO_2 removal.

14.3.3 Oxygenator or Membrane Lung

The membrane lung is responsible for gas exchange. The lung is comprised of hollow fiber membranes and compressed micropores which allow diffusion of O_2 and CO_2. The diffusion coefficient of CO_2 is 20 times greater than that of O_2. This discrepancy requires that diffusion of O_2 and removal of CO_2 be controlled by two different mechanisms. Oxygen tension is controlled by a gas blender which adjusts the fraction of oxygen delivered by the extracorporeal circuit ($F_{EC}O_2$ from 21 to 100%). CO_2 removal is adjusted by the rate of sweep gas flow. Sweep gas is introduced into the gas phase of the membrane, and its flow is controlled by flow meters (L/min).

14.3.4 Cannulation

Vascular access is usually obtained percutaneously. It is recommended to perform cannulations under ultrasound guidance. In very low-flow or no-flow states, Doppler may be noninformative. Therefore, in particularly difficult cases (e.g., cardiac arrest), direct visualization of the vessels by cut-down may be necessary. Cannulations are performed using the Seldinger technique [64, 65]. Because potentially lethal complications may occur during cannulation (e.g., major vessel dissection or perforation), a vascular surgeon should always be available [66].

Adult-size cannulas range from 23 to 29F for venous drainage and from 21 to 23F (VV) and from 17 to 19F (VA) for blood reinjection [67]. Blood flow, and therefore oxygenation, is highly dependent on the diameter of the drainage cannula [68]. The presence of the fetus causes an increase in intra-abdominal pressure during pregnancy. Ngatchou et al. [41] have also shown that aortocaval compression may occur in the supine position during late pregnancy. The decrease in blood flow resulting from these two issues may lead to difficulties in cannulating the femoral vein and to low-flow drainage. Positioning the pregnant woman in a left lateral tilt position may alleviate inferior vena cava compression, thereby facilitating cannulation of the femoral vessels. One paper describing maternal ECMO suggested that insertion of a second drainage cannula may augment flow, thus establishing adequate overall ECMO blood flow [49].

Even in the presence of pregnancy, the position of the cannula tip must always be verified either by US or X-ray (with minimal penetration and specific protection of the pelvis). Drainage cannulas placed via the femoral vein should be located 5–10 cm from the junction of the inferior vena cava and the right atrium. With regard to return lines, when the return cannula is inserted via the right internal jugular, the tip of the line should be located at the junction between the superior vena cava and the right atrium. When the return line is inserted through the femoral vein, the tip of the line should be located in the lower part of the right atrium. A minimal distance $\geq$10 cm between the tips of the cannulas usually prevents excessive recirculation in VV ECMO. This is true of both femoral-jugular and femoral-femoral configurations [69]. In VA ECMO, the tip of the return line in the femoral artery should be positioned in the middle part of the descending aorta. As the cannulated limb may suffer downstream ischemia due to obstruction of the common femoral artery, an additional reperfusion line is mandated through cannulation of the superficial femoral artery [70, 71].

14.4 Which Configuration for Which Patients?

The indications for ECMO configuration in the general population hold true for the pregnant and postpartum population as well. The major-

ity of patients with acute respiratory failure require only pulmonary support. For such patients, VV ECMO is the preferred configuration. During ECMO support, FiO_2 should be decreased to the minimum level required to ensure that the SpO_2 remains above 92%. At the same time, mechanical ventilation should be decreased to the minimum required to prevent lung collapse in order to allow the lungs to heal from the injurious effects of both mechanical stress and strain and high oxygen concentrations [72]. Ventilator-induced lung injuries (VILI) may exacerbate the release of inflammatory mediators and worsen the endothelial-epithelial barrier dysfunction and edema of the injured lung [73].

The femoral-jugular configuration offers the best compromise between high ECMO flow to RPM ratio and maximal oxygen delivery by limiting recirculation [74]. The femoro-femoral configuration is less effective [75] and should therefore be reserved for emergency situations which require rapid cannulation [69].

Acute cor pulmonale can occur in up to 50% of patients with severe ARDS (defined as a PaO_2/FiO_2 ratio of <100 mmHg) [76]. Hypercapnia is also a potent pulmonary vasoconstrictor and can further increase right ventricular afterload [77]. VV ECMO offers gas exchange without direct hemodynamic support. However, VV ECMO is accompanied by a decrease in ventilator support and an improvement in gas exchange, both of which may reduce RV afterload. Therefore, VA ECMO should not be considered for acute cor pulmonale occurring during ARDS [78].

VV ECMO does not provide hemodynamic support and therefore is not indicated in case of acute circulatory failure (e.g., refractory cardiogenic shock, ongoing cardiac arrest). VA ECMO is mandated in such cases. Drainage of blood from the right atrium decreases right ventricular afterload. Organ perfusion is ensured by arterial line through retrograde aortic perfusion in case of peripheral VA ECMO. In case of severe left ventricular failure with pulseless contraction, mean arterial pressure is ensured at 100% by ECMO flow targeting at least 65 mmHg. The differences between VA ECMO and VV ECMO are summarized in Table 14.2.

Table 14.2 Differences between venoarterial and venovenous extracorporeal membrane oxygenation

	VA-ECMO	VV-ECMO
Left ventricle effect	Decreased preload	None
	Increased afterload	
Right ventricle effect	Decreased preload	Indirect effect[a]
	Decreased afterload	
Perfusion rate	Lower perfusion rates are needed	Higher perfusion rates are needed
Pulmonary blood flow	Bypass pulmonary circulation	Maintains pulmonary blood flow
ECMO circuit	Connected in parallel to the heart and lungs	Connected in series to the heart and lungs

VA venoarterial, *VV* venovenous, *ECMO* extracorporeal membrane oxygenation

[a]May have indirect effect by reversing hypoxemic pulmonary vasoconstriction, decreasing hypercapnia and limiting positive intrathoracic pressure

14.5 ECMO Indications and Contraindications

The indication for ECMO use should always be discussed on a case-by-case basis, taking into account the benefit-risk ratio of the individual situation. ECMO is an invasive support tool that carries inherent risks and should therefore be considered only after failure of standard management, including the use of protective ventilation strategies and hemodynamic optimization with monitoring. More importantly, ECMO is a bridging tool that provides time to achieve recovery but does not cure the cause of either respiratory or cardiac failure. Therefore, having a reversible cause of pulmonary or cardiac dysfunction is an indispensable prerequisite for the use of ECMO.

14.5.1 Contraindications

There is no absolute contraindication to the use of ECMO. However, most ECMO circuits are heparin-coated. In the presence of known or suspected heparin-induced thrombocytopenia, the use of such a circuit is contraindicated, and an alternative should be sought (see "Bleeding Complications" below).

The risk-benefit ratio of ECMO should be considered unfavorable in cases of coma following cardiac arrest, hemorrhagic intracranial lesions, prolonged mechanical ventilation, and multi-organ failure [78].

14.5.2 Indications

The indications for VV ECMO for ARDS, VA ECMO for cardiogenic shock, and VA ECMO for ECLS will be discussed separately as they are all distinct.

14.5.2.1 VV ECMO for ARDS

As per the ELSO guidelines [59], VV ECMO should be considered in cases of:

- Hypoxic respiratory failure when the risk of mortality is 50% or greater. VV ECMO is indicated when the risk of mortality is 80% or greater (Table 14.3) despite the use of protective ventilation strategies.
- CO_2 retention on mechanical ventilation despite high Pplat (>30 cm H_2O).
- Severe air leak syndromes.

14.5.2.2 VA ECMO for Cardiogenic Failure

Women with cardiogenic shock (cardiac index <2 L/min/m^2 with systolic blood pressure <90 mmHg) and inadequate tissue perfusion (persistent lactic acidosis despite adequate volume resuscitation, high-dose inotropes and vasopressors) are eligible for VA ECMO [59]. In our literature review, main causes of maternal cardiogenic failure were peripartum cardiomyopathy, embolism (pulmonary or fluid amniotic embolism), and septic shock. Regardless of indication, the use of VA ECMO should be envisaged early in the course of cardiogenic shock in order to avoid multiple organ failure.

14.5.2.3 VA ECMO for Refractory Cardiac Arrest

ECMO should be considered for women with cardiac arrest if they have a reasonable chance of recovery. Women who deteriorate to cardiac arrest during pregnancy or the peripartum period rarely

Table 14.3 Mortality risk in hypoxemic respiratory failure

50% mortality risk is associated with:	PaO_2/FiO_2 < 150 on FiO_2 > 90%
	And/or Murray score 2–3[a]
	And/or AOI score 60[b]
	And/or APSS score[c]
80% mortality risk is associated with:	PaO_2/FiO_2 < 100 on FiO_2 > 90%
	And/or Murray score 3–4[a]
	And/or A01 > 80[b]
	And/or APSS 8[c]

AOI age-adjusted oxygenation index, *APPS* Age, PaO_2/FiO_2, and Plateau Pressure Score

[a]Murray JF, Matthay MA, Luce JM, Flick MR: An expanded definition of the adult respiratory distress syndrome. American Review of Respiratory Disease 1988, 138:720–723

[b]Dechert RE, Park PK, Barlett RH: Evaluation of the oxygenation index in adult respiratory failure. J Trauma Acute Care Surg 2014; 76:469–473

[c]Villar J, Ambrós A, Soler JA, et al; Stratification and Outcome of Acute Respiratory Distress Syndrome (STANDARDS) Network: Age, PaO_2/FiO_2, and Plateau Pressure Score: A Proposal for a Simple Outcome Score in Patients with the Acute Respiratory Distress Syndrome. Crit Care Med 2016; 44:1361–1369

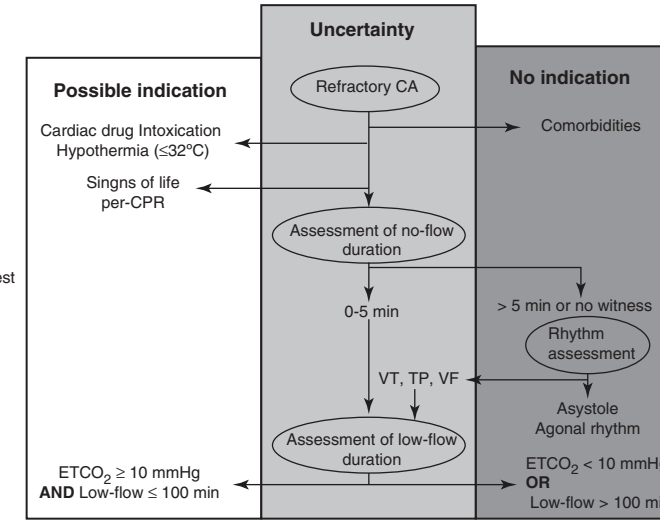


Fig. 14.2 French Ministry of Health guideline indications for the use of extracorporeal life support for refractory cardiac arrest. (Adapted from Guidelines for Indications for the use of extracorporeal life support for refractory cardiac arrest)

CA = cardiac arrest

reach this condition due to irreversible background disease [52, 58]. Therefore, two pertinent issues impact the decision to initiate ECLS in this population: the duration of no-flow time (the time in full arrest before initiation of chest compression) and the duration of low-flow time (the duration of full arrest with chest compression). In order to determine no-flow time, cardiac arrest must be witnessed. Therefore, cases with unwitnessed arrest are automatically excluded from ECMO treatment. Figure 14.2 details the decision support algorithm for selecting patients in cardiac arrest that may benefit from ECMO treatment as proposed by the French medical scientific societies under the auspices of the French Ministry of Health [79].

14.6 Referral ECMO Centers and Mobile ECMO Teams

ECMO support is both technically and conceptually challenging. It therefore requires provision of care by an organized and experienced medical team. ECMO during pregnancy requires multidisciplinary management, involving intensivists, surgeons (vascular, cardiac, obstetric), cardiologists, neonatologists (once the age of neonatal viability has been reached), and a specialized ECMO nursing team available 24/7. A recent international study demonstrated that higher annual ECMO volume is associated with lower hospital mortality [80]. Women requiring ECMO support are therefore best referred to a high-volume referral ECMO center, if such exists.

Following the 2009 H1N1 influenza pandemic, mobile ECMO units were developed to transport patients on ECMO to an ECMO referral center [58, 81, 82]. A recent review of the literature has shown the safety and efficacy of such transfers [83]. An ECMO referral center, which is usually regional, may establish a protocol for ECMO patient selection, transfers, and admissions. This may include a mobile unit capable of initiating ECMO in the referring hospitals themselves prior to patient transfer. The mobile ECMO team must include at least one cardiac surgeon, one perfusionist, the prehospital medical service team, and intensivists from the referral ECMO center. In case of refractory cardiopulmonary failure, physicians from various institutions could then directly contact the ECMO referral center. Once approved for ECMO care, patients should undergo initial stabilization by the mobile ECMO transport unit that will also undertake their transfer to the ECMO center [78].

14.7 ECMO Management

14.7.1 Anticoagulation

Most ECMO centers use heparin-coated circuits. This provides better hemocompatibility and

reduces the required level of anticoagulation, thereby theoretically reducing the risk of bleeding. A small series of cases suggests that women presenting with DIC following massive hemorrhage may initially be managed without anticoagulation (with no undue side effects), provided that heparin-coated circuits and high flows are used [58]. However, such cases require close follow-up of both coagulation profile and complete blood counts to determine the optimal time for initiating anticoagulant therapy. Even VA ECMO is feasible in the absence of anticoagulation [84]. Once anticoagulation is provided, the targeted PTT or anti-Xa levels depend on the indication for ECMO support. Sharma et al. describe the use of similar anticoagulation targets for VV ECMO and VA ECMO (0.2–0.5 IU/mL) in a series of cases involving women with coagulation disorders during pregnancy. Despite this "unorthodox" approach, there were no thrombotic or major bleeding complications [52]. However, decisions regarding ECMO initiation in women with suspected amniotic fluid embolism require careful consideration; one case reported oxygenator blockage by amniotic fluid debris, ultimately leading to maternal death [58].

14.7.2 ECMO Settings

At this time, there is no data suggesting that pregnant women differ from other patients with regard to the amount of fluids required at the onset of ECMO therapy. Nor is there evidence that their transfusion requirements differ from those of other patients during ECMO therapy. The ideal pump speed to mitigate the risks of hemolysis versus thrombotic complications is 3000–3500 RPM [78]. In practice, the optimal setting will depend on the type of pump, the inflow cannula (position, diameter), and the volume status. Clinicians should target the best ratio between the highest ECMO flow achieved for the minimal pump speed rotation. However, pregnant women at term have a significant increase in cardiac output and are relatively anemic. One case series suggested that high pump flows may be required to maintain reasonable perfusion pressures in this specific population [60]. Agerstrand et al. describe median pump flows of 3.9 L/min (IQR 3.2 and 4.8 L/min) 24 h after ECMO initiation [55]. Biderman et al. describe median pump flows of 5.40 L/min on VA ECMO and 4.10 L/min on VV ECMO [58]. In the latter series, mild hypothermia and beta-blockers were also used to decrease the flow rates required [58].

14.7.2.1 VV ECMO

During VV ECMO, blood flow should be maintained at >60% of the cardiac output in order to obtain a minimal arterial oxygen saturation of 90%. During ECMO, dilution techniques according to the Stewart-Hamilton principle may be inaccurate (pulmonary arterial catheter, pulse index cardiac contour output) and cardiac output measurements by Doppler technique may be preferred. The oxygen fraction delivered by ECMO should be set at 100%. Arterial target arterial oxygen saturation >92% should allow adequate maternal and fetal oxygenation. Agerstrand et al. describe a median sweep gas flow of 3.8 L/min (3.0–5.3), which is the same as in the general population [55]. As there is currently no evidence to support adjustment to the somewhat lower CO_2 levels of pregnancy, sweep gas flow should be set to provide normocapnia, thereby maintaining normal blood pH values [85–87].

14.7.2.2 VA ECMO

In case of circulatory support, pump flows must suffice to ensure organ perfusion. Flow should therefore be started at 4–5 L/min and then titrated to maintain a mean blood pressure greater than 65 mmHg [59].

14.8 Respiratory Management

14.8.1 Ventilator Setting for ARDS

During ECMO treatment for ARDS, the patient's oxygenation and CO_2 elimination are determined by the ECMO settings. Mechanical ventilation is intended only to prevent pulmonary complications while allowing the lungs to recuperate. Mechanical ventilation should therefore

be adjusted to protective ventilation settings. The positive end expiratory pressure should be maintained relatively high, between 10 and 15 cm H_2O, to limit atelectrauma [88–90]. The tidal volume used should be ultra-protective, below 4 mL/kg predicted body weight [91]. Airway pressures should be similarly reduced, and plateau pressure should be set to less than 25 cm H_2O [92] and the driving pressure to less than 15 m H_2O [93]. The respiratory rate should be relatively low (6–10 breaths/min) in order to limit alveolar strain [94, 95]. FiO_2 should progressively be reduced to below 60% while maintaining an arterial oxygen saturation greater than 92%. High inspired oxygen levels should be avoided in order to prevent the occurrence of absorption atelectasis [96] and toxicity to the alveolar epithelium.

14.8.2 Hypoxemia During VV ECMO

Recirculation should always be suspected when hypoxemia persists despite the establishment of VV ECMO therapy. Recirculation is inevitable during VV ECMO; however, the relative proportion of blood undergoing recirculation can range from less than 10% to more than 50% [97]. Clinically relevant recirculation is most often observed when the removal and return cannulas have been placed too close to each other. In such cases, the cannulae should be repositioned.

Intractable hypoxemia can also occur notwithstanding cannula placement during treatment with VV ECMO. In the CESAR trial, such hypoxemia lead to death in 9% of the cases [5]. Prone positioning has been shown to decrease mortality in severe ARDS when instituted in a timely and correct manner [98]. Prone positioning may also improve oxygenation in patients developing hypoxemia despite treatment with VV ECMO [99]. Several authors have reported that prone positioning may be feasible during pregnancy [100, 101]. However, this treatment option has not been properly evaluated for use in ARDS in pregnant women and should still be considered experimental at best.

Table 14.4 Causes of hypoxemia and recommendations for treating hypoxemia during venovenous extracorporeal membrane oxygenation

Causes	Recommendations
Insufficient preload (circuit line shaking)	Correct hypovolemia
Mismatched cardiac output and pump flow rate	Increase pump flow rate (≥60% of the theoretical cardiac output)
	Decrease cardiac output if possible by hypothermia and/or beta blocade
Recirculation	Decrease pump flow rate/Change cannula position
Optimise O_2 transport	Transfusion (Hb > 10/dL if SaO_2 < 88%)
Oygenator failure	Measure post-oxygenator blood gases
Inhibition of hypoxic pulmonary vasoconstriction and worsening of the pulmonary shunt	Measure pre, post-oxygenator and patient blood gases
Worsening of the pulmonary disease	

The possible causes of hypoxemia during VV ECMO and their respective treatment recommendations are summarized in Table 14.4.

14.8.3 Hypoxemia During VA ECMO

As myocardial function is gradually restored, the blood ejected from the left ventricle undergoes mixing in the aorta with the retrograde blood flow from the ECMO. If lung function is still impaired, mixed (and therefore poorly oxygenated) blood is then directed to the supra-aortic arteries. This leads to differential hypoxemia of the upper body and the coronary arteries. This situation, known as "North-South syndrome" or "Harlequin syndrome," is diagnosed when PaO_2 sampled from the right radial artery is significantly lower than that sampled from the left radial artery or leg arteries. During VV ECMO, the right radial artery should always be cannulated for the purpose of arterial blood gas monitoring. If North-South syndrome occurs, conversion to VV ECMO may be required [59,

78] provided that cardiac function has been sufficiently improved. If this is yet the case, VAV configuration may be a valuable option.

14.9 Weaning from ECMO

The decision to initiate the process of weaning from ECMO should be made as soon as the cause of lung and/or cardiac disease begins to resolve. Despite technical advances, ECMO remains associated with many severe complications.

For VV ECMO, a weaning trial should be considered after recovery of lung function as assessed by imaging, respiratory system compliance measurements, and blood gas analysis. During VV ECMO trial off, blood flow should be maintained, sweep gas stopped, and $F_{EC}O_2$ decreased to 21%. If gas exchanges are adequate with acceptable ventilator settings for several hours, the patient is ready for cannula removal.

For VA ECMO, a weaning trial could be undertaken when the patient is considered hemodynamically stable, i.e., with mean blood pressures >60 mmHg, a pulsatile arterial waveform, and no or low-dose inotropes or vasopressors [59]. Daily Doppler echocardiography parameter measurements on minimal ECMO support are an important adjunct to clinical assessment, as the measured values are good predictors of weaning success [102]. A trial of ECMO withdrawal during VA access requires clamping of the drainage and infusion bloodlines and circulating the circuit slowly through the AV bridge. Anticoagulation is continued, and the bloodlines are unclamped periodically to avoid stagnation. Cardiac function is assessed by echography. If acute cor pulmonale and/or major left ventricular dysfunction do not occur, decannulation can be performed.

14.10 Delivery and Bleeding Complications

14.10.1 Bleeding Complications

Bleeding is the most frequent complication associated with ECMO therapy during pregnancy and the postpartum period. Massive hemorrhage is frequently associated with disseminated intravascular coagulation (DIC); both may be attributed to the pregnancy and its complications (e.g., peripartum hemorrhage, amniotic fluid embolism), to the cause of cardiac or pulmonary failure that had initially led to ECMO therapy (e.g., severe sepsis, major trauma), or to the interaction with the ECMO circuit. In fact, DIC is more frequent during pregnancy and the postpartum period than in the general population, as reported in the ELSO registry [3, 32].

Major bleeding has been reported in several case reports describing ECMO therapy in pregnant women [16, 26, 32, 40, 49, 50, 52, 55]. The bleeding sites were intracranial or in multiple sites in cases with fatal hemorrhage. Other bleeding problems included hemothorax, upper gastrointestinal hemorrhage, nonfatal fetal intracranial hemorrhage, vaginal bleeding, and bleeding from the cannulation and tracheostomy sites.

In a retrospective study, Nair et al. [32] reported that 8 of their 12 pregnant/postpartum women (67%) suffered from bleeding complications (requiring transfusion) during ECMO support. This population required a median red blood packed volume transfusion volume of 3500 mL, and bleeding was reported as the leading cause of death. However, the authors found no difference in the incidence of severe bleeding between pregnant/postpartum women and other women of childbearing age who were treated with ECMO (67% vs. 50%, $p = 0.45$). Furthermore, in another cohort study, Agerstrand et al. [55] reported a much lower rate of severe hemorrhage (33%) in pregnant and postpartum women. The potential impact of hemorrhage on maternal and fetal survival therefore remains controversial and should not affect the decision to initiate ECMO therapy in pregnant and postpartum women.

14.10.2 Delivery

There is currently no evidence to support early induction of delivery to improve either maternal or neonatal outcomes during maternal ECMO therapy. Once the threshold of potential neonatal viability has been reached, fetal monitoring

should preferably be performed twice daily. Ideally, the pregnancy should be carried to term or until the mother has recovered cardiac/pulmonary function. We found 19 cases in the literature describing a wait-and-see approach [15–17, 19, 25–27, 31, 33, 35, 38, 40, 42, 52, 54, 55] with relatively good outcomes. Fifteen mothers (78.9%) and 12 fetuses (63.2%) survived.

Regardless, delivery should be anticipated, and the delivery plan should be outlined together with the intensive care, obstetric, and neonatal teams. Preplanning and shared goals are a prerequisite to ensure that adequate support is forthcoming should the criteria for fetal extraction be met, even in an emergency. Fetal extraction could theoretically improve maternal condition by improving diaphragmatic excursion, thereby increasing functional residual capacity. On the other hand, early induction of delivery or surgical cesarean delivery during ECMO therapy may be accompanied by severe bleeding. Agerstrand et al. [55] reported development of DIC in six cases and intra-abdominal hemorrhage and abdominal compartment syndrome several hours after delivery in four cases. It is therefore probably most prudent to allow both pregnancy and delivery to progress without intervention unless maternal condition continues to deteriorate irretrievably.

Should fetal distress occur during ECMO therapy, cesarean delivery may be performed at the bedside. Any decision regarding the location of surgery should take into consideration the capabilities of the treatment site alternatives and should prioritize the well-being of the mother. Maternal transport should not be undertaken if it would incur more risk to the mother than performing surgery on location. Conversely, surgery should not be undertaken in the ICU if the location is ill-equipped to treat significant hemorrhage. As the pregnant woman is probably receiving full anticoagulant therapy, the multidisciplinary team should anticipate peri- and postpartum hemorrhage (PPH). In the case of hemorrhage, hemostatic measures may rapidly be required (e.g., Bakri balloon tamponade) and should be sourced quickly. Ideally, maternal coagulation should be optimized, and anticoagulation may be interrupted as required. In addition, transfusion of platelets and fibrinogen may be needed (see Chap. 6 for further details on PPH management). There are several reports of women undergoing delivery during ECMO therapy. These reports note that these women have a high risk of bleeding complications if DIC is present prior to delivery. At the same time, they also describe good maternal and fetal outcomes [18, 20, 34, 52, 57].

In conclusion, ECMO can be used successfully during pregnancy and the postpartum period by a multidisciplinary and experienced team, which can be provided only by a referral center. We recommend early consultation with an ECMO referral center for pregnant patients with severe cardiorespiratory compromise to improve the chance of maternal and fetal survival.

References

1. Conrad SA, Rycus PT, Dalton H. Extracorporeal life support registry report 2004. ASAIO J. 2005;51(1):4–10.
2. Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators, Davies A, Jones D, Bailey M, Beca J, Bellomo R, et al. Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. JAMA. 2009;302(17):1888–95.
3. Patroniti N, Zangrillo A, Pappalardo F, Peris A, Cianchi G, Braschi A, et al. The Italian ECMO network experience during the 2009 influenza A (H1N1) pandemic: preparation for severe respiratory emergency outbreaks. Intensive Care Med. 2011;37(9):1447–57.
4. Abrams D, Combes A, Brodie D. Extracorporeal membrane oxygenation in cardiopulmonary disease in adults. J Am Coll Cardiol. 2014;63(25 Pt A):2769–78.
5. Paden ML, Conrad SA, Rycus PT, Thiagarajan RR, ELSO Registry. Extracorporeal life support organization registry report 2012. ASAIO J. 2013;59(3):202–10.
6. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet. 2009;374(9698):1351–63.
7. Neuzil KM, Reed GW, Mitchel EF, Simonsen L, Griffin MR. Impact of influenza on acute cardiopul-

monary hospitalizations in pregnant women. Am J Epidemiol. 1998;148(11):1094–102.
8. Rasmussen SA, Jamieson DJ, Bresee JS. Pandemic influenza and pregnant women. Emerg Infect Dis. 2008;14(1):95–100.
9. Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team, Dawood FS, Jain S, Finelli L, Shaw MW, Lindstrom S, et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med. 2009;360(25):2605–15.
10. Itoh Y, Shinya K, Kiso M, Watanabe T, Sakoda Y, Hatta M, et al. In vitro and in vivo characterization of new swine-origin H1N1 influenza viruses. Nature. 2009;460(7258):1021–5.
11. Jamieson DJ, Honein MA, Rasmussen SA, Williams JL, Swerdlow DL, Biggerstaff MS, et al. H1N1 2009 influenza virus infection during pregnancy in the USA. Lancet. 2009;374(9688):451–8.
12. ANZIC Influenza Investigators, Webb SAR, Pettilä V, Seppelt I, Bellomo R, Bailey M, et al. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. N Engl J Med. 2009;361(20):1925–34.
13. Louie JK, Acosta M, Jamieson DJ, Honein MA, California Pandemic (H1N1) Working Group. Severe 2009 H1N1 influenza in pregnant and postpartum women in California. N Engl J Med. 2010;362(1):27–35.
14. Clark GP, Dobson PM, Thickett A, Turner NM. Chickenpox pneumonia, its complications and management. A report of three cases, including the use of extracorporeal membrane oxygenation. Anaesthesia. 1991;46(5):376–80.
15. Greenberg LR, Moore TR. Staphylococcal septicemia and adult respiratory distress syndrome in pregnancy treated with extracorporeal carbon dioxide removal. Obstet Gynecol. 1995;86(4 Pt 2):657–60.
16. Lee WA, Kolla S, Schreiner RJ, Hirschl RB, Bartlett RH. Prolonged extracorporeal life support (ECLS) for varicella pneumonia. Crit Care Med. 1997;25(6):977–82.
17. King PT, Rosalion A, McMillan J, Buist M, Holmes PW. Extracorporeal membrane oxygenation in pregnancy. Lancet. 2000;356(9223):45–6.
18. Satoh H, Masuda Y, Izuta S, Yaku H, Obara H. Pregnant patient with primary pulmonary hypertension: general anesthesia and extracorporeal membrane oxygenation support for termination of pregnancy. Anesthesiology. 2002;97(6):1638–40.
19. Cunningham JA, Devine PC, Jelic S. Extracorporeal membrane oxygenation in pregnancy. Obstet Gynecol. 2006;108(3 Pt 2):792–5.
20. Parkins MD, Fonseca K, Peets AD, Laupland KB, Shamseddin K, Gill MJ. A potentially preventable case of serious influenza infection in a pregnant patient. CMAJ. 2007;177(8):851–3.
21. Scriven J, Mcewen R, Mistry S, Green C, Osman H, Bailey M, et al. Swine flu: a Birmingham experience. Clin Med (Lond). 2009;9(6):534–8.
22. Pagel PS, Lilly RE, Nicolosi AC. Use of ECMO to temporize circulatory instability during severe Brugada electrical storm. Ann Thorac Surg. 2009;88(3):982–3.
23. Ho CH, Chen KB, Liu SK, Liu YF, Cheng HC, Wu RS. Early application of extracorporeal membrane oxygenation in a patient with amniotic fluid embolism. Acta Anaesthesiol Taiwanica. 2009;47(2):99–102.
24. Shen HP, Chang WC, Yeh LS, Ho M. Amniotic fluid embolism treated with emergency extracorporeal membrane oxygenation: a case report. J Reprod Med. 2009;54(11–12):706–8.
25. Singh K, Vasoo S, Stevens J, Schreckenberger P, Trenholme G. Pitfalls in diagnosis of pandemic (novel) A/H1N1 2009 influenza. J Clin Microbiol. 2010;48(4):1501–3.
26. Oluyomi-Obi T, Avery L, Schneider C, Kumar A, Lapinsky S, Menticoglou S, et al. Perinatal and maternal outcomes in critically ill obstetrics patients with pandemic H1N1 Influenza A. J Obstet Gynaecol Can. 2010;32(5):443–7.
27. Robertson LC, Allen SH, Konamme SP, Chestnut J, Wilson P. The successful use of extra-corporeal membrane oxygenation in the management of a pregnant woman with severe H1N1 2009 influenza complicated by pneumonitis and adult respiratory distress syndrome. Int J Obstet Anesth. 2010;19(4):443–7.
28. Kunstyr J, Lips M, Belohlavek J, Prskavec T, Mlejnsky F, Koucky M, et al. Spontaneous delivery during veno-venous extracorporeal membrane oxygenation in swine influenza-related acute respiratory failure. Acta Anaesthesiol Scand. 2010;54(9):1154–5.
29. Dubar G, Azria E, Tesnière A, Dupont H, Le Ray C, Baugnon T, et al. French experience of 2009 A/H1N1v influenza in pregnant women. PLoS One. 2010;5(10):e13112.
30. Holzgraefe B, Broomé M, Kalzén H, Konrad D, Palmér K, Frenckner B. Extracorporeal membrane oxygenation for pandemic H1N1 2009 respiratory failure. Minerva Anestesiol. 2010;76(12):1043–51.
31. Wall CJ, Santamaria J. Extracorporeal membrane oxygenation: an unusual cause of acute limb compartment syndrome. Anaesth Intensive Care. 2010;38(3):560–2.
32. Nair P, Davies AR, Beca J, Bellomo R, Ellwood D, Forrest P, et al. Extracorporeal membrane oxygenation for severe ARDS in pregnant and postpartum women during the 2009 H1N1 pandemic. Intensive Care Med. 2011;37(4):648–54.
33. Courouble P, Geukens P, Laarbaui F, Beauloye C, Van Caenegem O, Jacquet LM. Adult respiratory distress syndrome caused by 2009 H1N1 influenza during pregnancy: success of ECMO for both the mother and the child. J Extra Corpor Technol. 2011;43(2):75–8.
34. Panarello G, D'Ancona G, Capitanio G, Occhipinti G, Attardo G, Bertani A, et al. Cesarean section during ECMO support. Minerva Anestesiol. 2011;77(6):654–7.

35. Bowkalow S, Brauer M, Gross W, Schleussner E. Severe H1N1-infection during pregnancy. Arch Gynecol Obstet. 2011;284(5):1133–5.
36. Jo YY, Park S, Choi YS. Extracorporeal membrane oxygenation in a patient with stress-induced cardiomyopathy after caesarean section. Anaesth Intensive Care. 2011;39(5):954–7.
37. Weinberg L, Kay C, Liskaser F, Jones D, Tay S, Jaffe S, et al. Successful treatment of peripartum massive pulmonary embolism with extracorporeal membrane oxygenation and catheter-directed pulmonary thrombolytic therapy. Anaesth Intensive Care. 2011;39(3):486–91.
38. Grasselli G, Bombino M, Patroniti N, Giuffrida A, Marcolin R, Vergani P, et al. Use of extracorporeal respiratory support during pregnancy: a case report and literature review. ASAIO J. 2012;58(3):281–4.
39. Takeda S, Kotani T, Nakagawa S, Ichiba S, Aokage T, Ochiai R, et al. Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) severe respiratory failure in Japan. J Anesth. 2012;26(5):650–7.
40. Grimme I, Winter R, Kluge S, Petzoldt M. Hypoxic cardiac arrest in pregnancy due to pulmonary haemorrhage. BMJ Case Rep. 2012;2012:bcr2012006741.
41. Ngatchou W, Ramadan ASE, Van Nooten G, Antoine M. Left tilt position for easy extracorporeal membrane oxygenation cannula insertion in late pregnancy patients. Interact Cardiovasc Thorac Surg. 2012;15(2):285–7.
42. Sim SS, Chou HC, Chen JW, Ma MH. Extracorporeal membrane oxygenation in maternal arrhythmic cardiogenic shock. Am J Emerg Med. 2012;30(6):1012.e3–5.
43. Hansen AJ, Sorrell VL, Cooper AD, Moulton MJ. Postpartum rupture of the posteromedial papillary muscle. J Card Surg. 2012;27(3):313–6.
44. Scherrer V, Lasgi C, Hariri S, Dureuil B, Savouré A, Tamion F, et al. Radiofrequency ablation under extracorporeal membrane oxygenation for atrial tachycardia in postpartum. J Card Surg. 2012;27(5):647–9.
45. Strecker T, Münch F, Weyand M. One hundred ten days of extracorporeal membrane oxygenation in a young woman with postpartum cerebral venous thrombosis and acute respiratory distress syndrome. Heart Surg Forum. 2012;15(4):E180–1.
46. Burrows K, Fox J, Biblo LA, Roth JA. Pregnancy and short-coupled torsades de pointes. Pacing Clin Electrophysiol. 2013;36(3):e77–9.
47. Koster AA, Pappalardo F, Silvetti S, Schirmer U, Lueth JU, Dummler R, et al. Cesarean section in a patient with non-compaction cardiomyopathy managed with ECMO. Heart Lung Vessel. 2013;5(3):183–6.
48. Leeper WR, Valdis M, Arntfield R, Ray GL. Extracorporeal membrane oxygenation in the acute treatment of cardiovascular collapse immediately post-partum. Interact Cardiovasc Thorac Surg. 2013;17(5):898–9.
49. Seczyńska B, Jankowski M, Nowak I, Szczeklik W, Szułdrzyński K, Królikowski W. Pregnancy-related H1N1 influenza and severe acute respiratory distress syndrome successfully treated with extracorporeal membrane oxygenation despite difficult vascular access. Pol Arch Med Wewn. 2014;124(3):136–7.
50. Itagaki T, Onodera M, Okuda N, Nakataki E, Imanaka H, Nishimura M. Successful use of extracorporeal membrane oxygenation in the reversal of cardiorespiratory failure induced by atonic uterine bleeding: a case report. J Med Case Rep. 2014;8:23.
51. Park SH, Chin JY, Choi MS, Choi JH, Choi YJ, Jung KT. Extracorporeal membrane oxygenation saved a mother and her son from fulminant peripartum cardiomyopathy. J Obstet Gynaecol Res. 2014;40(7):1940–3.
52. Sharma NS, Wille KM, Bellot SC, Diaz-Guzman E. Modern use of extracorporeal life support in pregnancy and postpartum. ASAIO J. 2015;61(1):110–4.
53. Bouabdallaoui N, Mastroianni C, Revelli L, Demondion P, Lebreton G. Predelivery extracorporeal membrane oxygenation in a life-threatening peripartum cardiomyopathy: save both mother and child. Am J Emerg Med. 2015;33(11):1713.e1–2.
54. Kaliyev R, Kapyshev T, Goncharov A, Lesbekov T, Pya Y. Maternal and fetal recovery after severe respiratory failure: a case report of air transportation of a pregnant woman on ECMO using the CentriMag transporter system. ASAIO J. 2015;61(5):e33–5.
55. Agerstrand C, Abrams D, Biscotti M, Moroz L, Rosenzweig EB, D'Alton M, et al. Extracorporeal membrane oxygenation for cardiopulmonary failure during pregnancy and postpartum. Ann Thorac Surg. 2016;102(3):774–9.
56. Imaeda T, Nakada T-A, Abe R, Tateishi Y, Oda S. Veno-arterial extracorporeal membrane oxygenation for Streptococcus pyogenes toxic shock syndrome in pregnancy. J Artif Organs. 2016;19(2):200–3.
57. McDonald C, Laurie J, Janssens S, Zazulak C, Kotze P, Shekar K. Successful provision of inter-hospital extracorporeal cardiopulmonary resuscitation for acute post-partum pulmonary embolism. Int J Obstet Anesth. 2017;30:65–8.
58. Biderman P, Carmi U, Setton E, Fainblut M, Bachar O, Einav S. Maternal salvage with extracorporeal life support: lessons learned in a single center. Anesth Analg. 2017;125(4):1275–80.
59. ELSO guidelines for cardiopulmonary extracorporeal life support. Extracorporeal Life Support Organization, Version 1.4 August 2017. Ann Arbor. https://www.elso.org/Portals/0/ELSO%20Guidelines%20General%20All%20ECLS%20Version%201_4.pdf. Accessed 6 Mar 2019.
60. Roch A, Hraiech S, Masson E, Grisoli D, Forel JM, Boucekine M, et al. Outcome of acute respiratory distress syndrome patients treated with extracorporeal membrane oxygenation and brought to a referral center. Intensive Care Med. 2014;40(1):74–83.

61. Schmidt M, Zogheib E, Rozé H, Repesse X, Lebreton G, Luyt C-E, et al. The PRESERVE mortality risk score and analysis of long-term outcomes after extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. Intensive Care Med. 2013;39(10):1704–13.
62. Makdisi G, Wang I-W. Extra corporeal membrane oxygenation (ECMO) review of a lifesaving technology. J Thorac Dis. 2015;7(7):E166–76.
63. Toomasian JM, Bartlett RH. Hemolysis and ECMO pumps in the 21st century. Perfusion. 2011;26(1):5–6.
64. Hilty WM, Hudson PA, Levitt MA, Hall JB. Real-time ultrasound-guided femoral vein catheterization during cardiopulmonary resuscitation. Ann Emerg Med. 1997;29(3):331–6; discussion 337.
65. Pranikoff T, Hirschl RB, Remenapp R, Swaniker F, Bartlett RH. Venovenous extracorporeal life support via percutaneous cannulation in 94 patients. Chest. 1999;115(3):818–22.
66. Sidebotham D, Allen SJ, McGeorge A, Ibbott N, Willcox T. Venovenous extracorporeal membrane oxygenation in adults: practical aspects of circuits, cannulae, and procedures. J Cardiothorac Vasc Anesth. 2012;26(5):893–909.
67. Ventetuolo CE, Muratore CS. Extracorporeal life support in critically ill adults. Am J Respir Crit Care Med. 2014;190(5):497–508.
68. Del Sorbo L, Cypel M, Fan E. Extracorporeal life support for adults with severe acute respiratory failure. Lancet Respir Med. 2014;2(2):154–64.
69. Guervilly C, Dizier S, Thomas G, Jaussaud N, Morera P, Hraiech S, et al. Comparison of femorofemoral and femorojugular configurations during venovenous extracorporeal membrane oxygenation for severe ARDS. Intensive Care Med. 2014;40(10):1598–9.
70. Sidebotham D, McGeorge A, McGuinness S, Edwards M, Willcox T, Beca J. Extracorporeal membrane oxygenation for treating severe cardiac and respiratory failure in adults: part 2-technical considerations. J Cardiothorac Vasc Anesth. 2010;24(1):164–72.
71. Lamb KM, DiMuzio PJ, Johnson A, Batista P, Moudgill N, McCullough M, et al. Arterial protocol including prophylactic distal perfusion catheter decreases limb ischemia complications in patients undergoing extracorporeal membrane oxygenation. J Vasc Surg. 2017;65(4):1074–9.
72. Martin DS, Grocott MPW. Oxygen therapy in critical illness: precise control of arterial oxygenation and permissive hypoxemia. Crit Care Med. 2013;41(2):423–32.
73. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. N Engl J Med. 2013;369(22):2126–36.
74. Rich PB, Awad SS, Crotti S, Hirschl RB, Bartlett RH, Schreiner RJ. A prospective comparison of atriofemoral and femoro-atrial flow in adult venovenous extracorporeal life support. J Thorac Cardiovasc Surg. 1998;116(4):628–32.
75. Broman M, Frenckner B, Bjällmark A, Broomé M. Recirculation during veno-venous extracorporeal membrane oxygenation—a simulation study. Int J Artif Organs. 2015;38(1):23–30.
76. Lhéritier G, Legras A, Caille A, Lherm T, Mathonnet A, Frat J-P, et al. Prevalence and prognostic value of acute cor pulmonale and patent foramen ovale in ventilated patients with early acute respiratory distress syndrome: a multicenter study. Intensive Care Med. 2013;39(10):1734–42.
77. Vieillard-Baron A, Charron C, Caille V, Belliard G, Page B, Jardin F. Prone positioning unloads the right ventricle in severe ARDS. Chest. 2007;132(5):1440–6.
78. Richard C, Argaud L, Blet A, Boulain T, Contentin L, Dechartres A, et al. Extracorporeal life support for patients with acute respiratory distress syndrome: report of a consensus conference. Ann Intensive Care. 2014;4:15.
79. Conseil français de réanimation cardiopulmonaire; Société française d'anesthésie et de réanimation; Société française de cardiologie; Société française de chirurgie thoracique et cardiovasculaire; Société française de médecine d'urgence; Société française de pédiatrie, et al. Guidelines for indications for the use of extracorporeal life support in refractory cardiac arrest. French Ministry of Health. [Article in English, French]. Ann Fr Anesth Reanim. 2009;28(2):182–90.
80. Barbaro RP, Odetola FO, Kidwell KM, Paden ML, Bartlett RH, Davis MM, et al. Association of hospital-level volume of extracorporeal membrane oxygenation cases and mortality. Analysis of the extracorporeal life support organization registry. Am J Respir Crit Care Med. 2015;191(8):894–901.
81. Noah MA, Peek GJ, Finney SJ, Griffiths MJ, Harrison DA, Grieve R, et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). JAMA. 2011;306(15):1659–68.
82. D'Ancona G, Capitanio G, Chiaramonte G, Serretta R, Turrisi M, Pilato M, et al. Extracorporeal membrane oxygenator rescue and airborne transportation of patients with influenza A (H1N1) acute respiratory distress syndrome in a Mediterranean underserved area. Interact Cardiovasc Thorac Surg. 2011;12(6):935–7.
83. Mendes PV, de Albuquerque GC, Besen BAMP, Hirota AS, de Oliveira NR, Dos Santos EV, et al. Transportation of patients on extracorporeal membrane oxygenation: a tertiary medical center experience and systematic review of the literature. Ann Intensive Care. 2017;7(1):14.
84. Lamarche Y, Chow B, Bédard A, Johal N, Kaan A, Humphries KH, et al. Thromboembolic events in patients on extracorporeal membrane oxygenation without anticoagulation. Innovations (Phila). 2010;5(6):424–9.

85. Schmidt M, Tachon G, Devilliers C, Muller G, Hekimian G, Bréchot N, et al. Blood oxygenation and decarboxylation determinants during veno-venous ECMO for respiratory failure in adults. Intensive Care Med. 2013;39(5):838–46.
86. Aoyama K, Seaward PG, Lapinsky SE. Fetal outcome in the critically ill pregnant woman. Crit Care. 2014;18(3):307.
87. Lapinsky SE. Acute respiratory failure in pregnancy. Obstet Med. 2015;8(3):126–32.
88. Bein T, Zimmermann M, Hergeth K, Ramming M, Rupprecht L, Schlitt HJ, et al. Pumpless extracorporeal removal of carbon dioxide combined with ventilation using low tidal volume and high positive end-expiratory pressure in a patient with severe acute respiratory distress syndrome. Anaesthesia. 2009;64(2):195–8.
89. Mauri T, Foti G, Zanella A, Bombino M, Confalonieri A, Patroniti N, et al. Long-term extracorporeal membrane oxygenation with minimal ventilatory support: a new paradigm for severe ARDS? Minerva Anestesiol. 2012;78(3):385–9.
90. Nielsen ND, Kjaergaard B, Koefoed-Nielsen J, Steensen CO, Larsson A. Apneic oxygenation combined with extracorporeal arteriovenous carbon dioxide removal provides sufficient gas exchange in experimental lung injury. ASAIO J. 2008;54(4):401–5.
91. Bein T, Weber-Carstens S, Goldmann A, Müller T, Staudinger T, Brederlau J, et al. Lower tidal volume strategy (≈3 ml/kg) combined with extracorporeal CO2 removal versus "conventional" protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent-study. Intensive Care Med. 2013;39(5):847–56.
92. Pham T, Combes A, Rozé H, Chevret S, Mercat A, Roch A, et al. Extracorporeal membrane oxygenation for pandemic influenza A(H1N1)-induced acute respiratory distress syndrome: a cohort study and propensity-matched analysis. Am J Respir Crit Care Med. 2013;187(3):276–85.
93. Amato MBP, Meade MO, Slutsky AS, Brochard L, Costa ELV, Schoenfeld DA, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med. 2015;372(8):747–55.
94. Gattinoni L, Pesenti A, Mascheroni D, Marcolin R, Fumagalli R, Rossi F, et al. Low-frequency positive-pressure ventilation with extracorporeal CO2 removal in severe acute respiratory failure. JAMA. 1986;256(7):881–6.
95. Gattinoni L, Agostoni A, Pesenti A, Pelizzola A, Rossi GP, Langer M, et al. Treatment of acute respiratory failure with low-frequency positive-pressure ventilation and extracorporeal removal of CO2. Lancet. 1980;2(8189):292–4.
96. Aboab J, Jonson B, Kouatchet A, Taille S, Niklason L, Brochard L. Effect of inspired oxygen fraction on alveolar derecruitment in acute respiratory distress syndrome. Intensive Care Med. 2006;32(12):1979–86.
97. Xie A, Yan TD, Forrest P. Recirculation in venovenous extracorporeal membrane oxygenation. J Crit Care. 2016;36:107–10.
98. Guérin C, Reignier J, Richard J-C, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013;368(23):2159–68.
99. Guervilly C, Hraiech S, Gariboldi V, Xeridat F, Dizier S, Toesca R, et al. Prone positioning during veno-venous extracorporeal membrane oxygenation for severe acute respiratory distress syndrome in adults. Minerva Anestesiol. 2014;80(3):307–13.
100. Samanta S, Samanta S, Wig J, Baronia AK. How safe is the prone position in acute respiratory distress syndrome at late pregnancy? Am J Emerg Med. 2014;32(6):687.e1–3.
101. Kenn S, Weber-Carstens S, Weizsaecker K, Bercker S. Prone positioning for ARDS following blunt chest trauma in late pregnancy. Int J Obstet Anesth. 2009;18(3):268–71.
102. Aissaoui N, Luyt C-E, Leprince P, Trouillet J-L, Léger P, Pavie A, et al. Predictors of successful extracorporeal membrane oxygenation (ECMO) weaning after assistance for refractory cardiogenic shock. Intensive Care Med. 2011;37(11):1738–45.

Part IV

The Immune System

15 Physiological Changes of the Immune System During Pregnancy

Bhaskar Narayan and Cathy Nelson-Piercy

Bullet Points

- Pregnancy is a unique immunological state, during which there are pro-inflammatory changes as well as increased immune tolerance. A shift occurs from a Th1- towards a Th2-predominant immunological profile.
- Certain infections cause more severe disease in pregnancy, resulting in higher mortality and morbidity.
- The immunological changes also influence the activity of acute and chronic autoimmune diseases, which are a relatively common cause of morbidity before, during and after pregnancy. A significant proportion of pregnant women presenting to hospital with these conditions require critical care admission. It is essential that intensive care physicians are able to recognise and manage these patients appropriately.
- Identifying autoimmune flares may be more challenging during pregnancy, as some of the symptoms and signs may overlap with normal pregnancy and/or pre-eclampsia.
- Many immunosuppressive and immunomodulatory treatments can be used during pregnancy and should not be withheld if clinically indicated.

15.1 Physiological Changes in the Immune System in Pregnancy

Pregnancy is a unique immunological state. The common perception that normal pregnancy is a state of immune compromise (in order to avoid "rejecting" the fetus) is an oversimplification. In reality, the changes are more subtle, but several important changes occur in the maternal immune response during pregnancy.

In early pregnancy, changes occur in the local immune response within the uterus. Macrophages, dendritic cells, neutrophils and natural killer (NK) cells participate in a coordinated, controlled inflammatory response, which is essential for implantation and progression of the pregnancy [1]. Therefore, *early pregnancy is actually a pro-inflammatory phase*, mediated by an active (rather than a suppressed) innate immune system.

B. Narayan
NHS Health Education England, London, UK

C. Nelson-Piercy (✉)
Guy's and St Thomas' NHS Foundation Trust, London, UK
e-mail: catherine.nelson-piercy@gstt.nhs.uk

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_15

The innate immune response also provides a defence against infection. The inflammatory state may (in combination with hormonal and other factors) contribute to systemic illness such as nausea and vomiting of pregnancy [1].

The adaptive immune system undergoes more complex changes, including diminished cytotoxic responses and enhanced regulatory responses. As part of the normal adaptive immune response, the Th1 subgroup of CD4 T-cells express cytokines such as IFN-γ and TNF-α and play a key role in cytotoxic immune responses. Overactivity of the Th1 system may play a role in the development of certain autoimmune diseases [2]. The Th2 subgroup express cytokines such as IL-4, IL-5 and IL-13 and are involved with humoral (antibody) responses and protection against some parasites. Overactivity of the Th2 system is thought to be implicated in the pathogenesis of allergies and atopy [3].

During normal pregnancy, there is a physiological shift in the maternal T-cell response towards a Th2 state. This finding was initially reported in several studies using mouse models of pregnancy and later confirmed in human studies [4].

In addition, a subset of CD4 T-cells, known as T-reg cells, are important regulators of the maternal immune response and tolerance to the fetus [5]. These cells produce IL10 and TGFβ, thereby suppressing local immunity [6]. During pregnancy, the population of T-reg cells increases [7]. However, when exposed to inflammatory stimuli (such as influenza or listeria), T-reg cells can rapidly differentiate into an additional class known as Th17 cells, which are highly inflammatory and associated with preterm labour and infection-related miscarriage [5]. In mouse models of pregnancy, T-reg depletion results in rejection of the fetus [8]. Women with recurrent miscarriage [7] or pre-eclampsia [9, 10] have lower numbers of decidual and circulating T-reg cells, compared to healthy human pregnant controls.

The changes in the innate and adaptive immune systems are driven by a number of cytokine and endocrine factors. Prostaglandin E (PGE_2) and TGFβ enhance the proliferation and function of T-reg cells [11]. High levels of progesterone and oestrogen during pregnancy modulate the immune response by suppressing Th1 and Th17 responses and promoting Th2 and T-reg responses [12, 13].

As previously described, the first stage of pregnancy is pro-inflammatory, allowing implantation and placentation, as well as protection against infection during this crucial period. The subsequent shift towards an immunologically tolerant, anti-inflammatory Th2-predominant state allows rapid growth and development of the fetus in the second trimester of pregnancy [14].

Finally, in the third trimester, there is a return to a more pro-inflammatory state. An influx of immune cells into the myometrium and increased production of pro-inflammatory cytokines culminate in contraction of the uterus and delivery of the baby [14, 15]. This may be one of the reasons maternal infection is associated with preterm labour; amniotic fluid TNFα and IL-1 levels are significantly increased in women with preterm labour and infection [15].

15.2 Clinical Implications of the Altered Immune Response in Pregnancy

In addition to enabling implantation, tolerance, growth and delivery of the fetus, the physiological changes occurring in the immune system during pregnancy have significant clinical implications related to infection and autoimmune disease.

15.2.1 Response to Infection

Pregnant women do not appear to have increased susceptibility to most infections (although there are a few notable exceptions including listeria and falciparum malaria—discussed below) [16]. However, with certain infections, there is an increased risk of severe disease resulting in a higher rate of mortality and morbidity than the general population [16]. In some (but not all) cases, this is related to the altered systemic immune status of the mother.

Influenza is an important cause of maternal morbidity and mortality. The 2009 H1N1 pandemic strain was particularly virulent, and pregnant women were at much higher risk of developing severe, complicated infections and respiratory failure. In the USA, there were 280 intensive care unit admissions and 56 deaths

among the 788 reported cases of influenza in pregnant women in the first 8 months of the pandemic. Initial data do not suggest that pregnant women are more susceptible to infection with SARS-CoV-2 (the coronavirus responsible for the COVID-19 pandemic), although severe disease leading to hospital admission is more common in the third trimester. Women over the age of 35 and those with obesity, hypertension and diabetes are at increased risk. In a nationwide study in the UK, 9% of pregnant women admitted required respiratory support, which is similar to the non-pregnant population [17, 18].

The reasons for this increased severity in pregnancy are not completely understood. The Th2-predominant T-cell profile may reduce viral clearance [19]. Animal models suggest that when the host is infected with influenza virus, the altered immunological state of pregnancy is associated with higher levels of pro-inflammatory mediators (IL-6, IL-1α, G-CSF and COX-2) in the lung tissue [20].

Hepatitis E usually causes a mild self-limiting illness in the nonpregnant population. However, it can cause severe disease in pregnancy, with a significant proportion progressing to fulminant hepatitis with a mortality rate varying from 30 to 100% [21]. The mechanisms are still unclear but may involve the human transcription factor NF-κB, which plays a key role in regulating the immune response to infection [22]. NF-κB is downregulated during normal pregnancy [23]. Animal experiments in mice studying the p65 component of NF-κB have shown its important role in liver development and regeneration and that mice lacking p65 develop liver degeneration due to widespread apoptosis [21]. This led to human studies, which have found that the activity of the p65 component of NF-κB was greatly diminished in peripheral blood mononuclear cells and post-mortem liver biopsy specimens in pregnant women (compared to the nonpregnant population) with fulminant hepatic failure (FHF) [24]. This suggests that the absence or reduced activity of NF-κB p65 is associated with severe liver damage in pregnant women that develop FHF.

Falciparum malaria may cause particularly severe disease in pregnancy because the parasites sequester in the placenta, causing inflammation and necrosis. Pregnant women are also more susceptible to hypoglycaemia [25, 26]. Acute infection appears to be more frequent in pregnant women [27]. Various explanations have been put forward, such as increased attractiveness to mosquitos [28] and impaired ability to limit parasite replication [27].

Acquired immunity against malaria is also diminished in women during their first pregnancy; they are susceptible to severe *P. falciparum* disease due to placental malaria causing a lack of immunity to placenta-specific cytoadherence proteins [29]. In subsequent pregnancies, immunity against placental-adherent strains may develop, reducing the risk of adverse effects of malaria on the mother and fetus.

Certain other infections are notable for the higher rate of mortality and morbidity in pregnancy but probably for reasons unrelated to the altered systemic immune status of the mother. *Listeria monocytogenes* has a particular predilection for the placenta and fetus; therefore, invasive listeriosis is much more common in pregnant women, but this is likely to be because the nonpregnant population lack the placental entry point for infection [16].

Rubella, CMV and parvovirus B19 are significant in pregnancy due to the deleterious effects on the fetus rather than because of increased susceptibility or the maternal immune response in pregnancy. Maternal infection is usually subclinical or mildly symptomatic [25, 30].

Maternal HIV infection has major implications around mother-to-child transmission [31], but pregnancy does not affect disease progression [25, 32].

15.2.2 Autoimmune Disease

Around 10–25% of the general population of patients with autoimmune diseases presenting to emergency departments require hospital admission [33], and up to 30% of these patients require intensive care admission [34]. Mortality ranges from 17 to 55% in case series from the general population of patients with autoimmune diseases admitted to the intensive care unit [35].

More than two-thirds of maternal deaths in industrialised countries occur in women known to have medical comorbidities [36], and autoimmune diseases contribute directly and indirectly to these deaths [37]. It is therefore unsurprising that autoimmune diseases are frequent causes of morbidity during pregnancy. Pregnant women with autoimmune diseases have higher rates of obstetric and non-obstetric complications (e.g. pre-eclampsia, thromboembolism, infection), poor pregnancy outcomes (i.e. fetal growth restriction, preterm delivery,) as well as pregnancy loss (Fig. 15.1). Good disease control improves not only maternal but also pregnancy outcomes [38].

The altered immune state of pregnancy has an effect on the activity of several autoimmune diseases, which is summarised in Fig. 15.2. The shift from a Th1- to a Th2-predominant state is relevant here. Hormonal changes contribute significantly to this; high levels of circulating oestrogen (as seen in pregnancy) have been shown to modulate the cytokine profile and suppress disease activity in experimental models of rheumatoid arthritis [39] and multiple sclerosis [40].

In humans, diseases that are driven by a Th1 response, including rheumatoid arthritis [41, 42], multiple sclerosis [43], psoriasis [44] and Graves' disease [45], tend to improve during pregnancy [13]. However, they may flare postpartum, possibly due to a rapid fall in oestrogen levels in this period, resulting in a diminished Th2 response and consequently tipping the balance back in favour of a Th1 response [13].

In contrast, diseases that are driven by a Th2 response, including atopic eczema, SLE and systemic sclerosis, have a higher rate of flaring during pregnancy compared to the nonpregnant population [13, 44]. Active flares of autoimmune

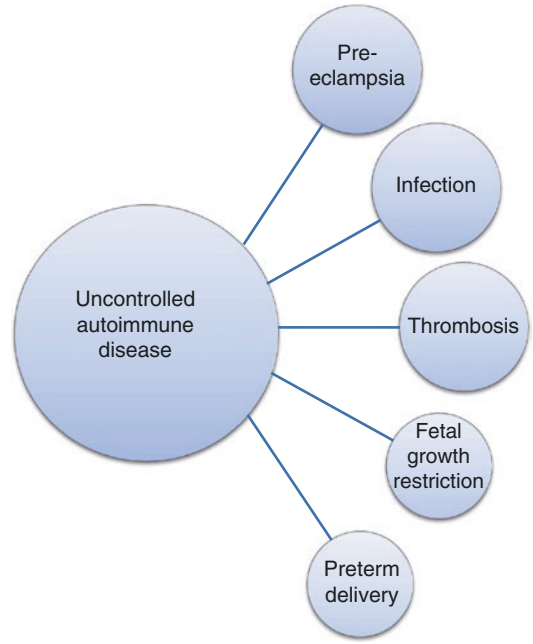


Fig. 15.1 Uncontrolled autoimmune/inflammatory disease during pregnancy increases the risk of complications for the mother and fetus. Control of the disease can ameliorate the risk of complications

Fig. 15.2 Influence of pregnancy on autoimmune diseases

Th1-type autoimmune disease	**Influence of pregnancy on disease**
Rheumatoid Arthritis	Tends to improve
Psoriasis	
Multiple Sclerosis	
Graves Disease	
Th2-type autoimmune disease	Higher rate of disease flare
Systemic Lupus Erythematosus	
Systemic Sclerosis	
Atopic Dermatitis (Eczema)	

disease should be treated aggressively to minimise adverse consequences for both mother and fetus.

Corticosteroids are usually the first-line treatment and can be used at any stage of pregnancy if clinically indicated. Dosing varies according to patient condition and should generally adhere to that administered to nonpregnant patients (see some details under subheadings). As with nonpregnant patients, steroids should be given at the lowest possible dose to control disease activity, but high doses should not be withheld if clinically indicated. Prednisolone and methylprednisolone are extensively metabolised by the placenta, and the fetal exposure is less than 10% of the maternal dose. Several large studies have not found any significant adverse effect on the fetus (major malformations, prematurity, low birthweight) attributable to these drugs [46]. However, treatment with these drugs has been associated with an increased maternal risk of gestational hypertension and diabetes.

There are also good safety data [47] in pregnancy for disease-modifying drugs, such as hydroxychloroquine, sulfasalazine, mesalazine and azathioprine, and the calcineurin inhibitors ciclosporin and tacrolimus. Non-steroidal anti-inflammatory drugs (NSAIDS) may also be used in the first and second trimesters [47, 48].

The newest class of immunomodulatory treatment is the "biologic" agents. These are monoclonal antibodies against specific targets involved in the disease process. There is now good evidence that infliximab, adalimumab, etanercept and certolizumab do not have any significant associations with a particular pattern of congenital malformations or adverse pregnancy outcomes. The use of these drugs in pregnancy is discussed further below in the section about antibodies and the placental barrier.

Intravenous immunoglobulin (IVIg) and therapeutic plasma exchange (TPE) can both be used in pregnancy [49–51] and should not be withheld if clinically indicated. It is important to note that IVIg and TPE are associated with risks of thromboembolism and fluid shifts in all patients, in particular those already at increased risk, such as critically ill and/or pregnant patients. The indications for these treatments would be the same as for nonpregnant patients. The aims of IVIg and TPE would vary slightly depending on the disease indication for treatment. For example, in GBS [52], there may be amelioration of disease and improved/faster recovery (see below). These treatments will be selected in addition to other supportive therapies such medications, physiotherapy, time and patience. A similar treatment principle would apply to conditions like immune thrombocytopenia purpura (Chap. 5) and myasthenia gravis (Chap. 26).

Methotrexate, mycophenolate mofetil, leflunomide and cyclophosphamide are teratogenic and should be avoided during pregnancy if possible. It is therefore important to address the use of these drugs in pre-pregnancy counselling and to aim for optimal disease control with an alternative drug prior to conception. However, the successful use of cyclophosphamide (500 mg IV pulsed dose every 2 weeks for 6 doses) in the second and third trimesters has been reported in the treatment of refractory life-threatening SLE and rapidly progressive interstitial lung disease [53]. This is a challenging scenario, and such decisions should only be reached after a detailed and frank discussion between the intensivist, treating physician, obstetrician and patient and/or her family (if she is unable to provide input). In the context of critical illness with a risk of death (or serious/permanent disability or organ damage), with no other effective treatment options, the conclusions of such discussions might be to use cyclophosphamide to prioritise maternal health while accepting the significant risk of fetal harm or loss. Of note, there are also data describing safe use of cyclophosphamide as part of chemotherapy regimens to treat breast cancer [54] and lymphomas [55] in pregnancy after 12 weeks gestation (Fig. 15.3).

15.2.2.1 SLE and Pregnancy

Systemic lupus erythematosus (SLE) is an idiopathic autoimmune condition which has multi-organ involvement. The disease process is incompletely understood, involving immune complex deposition resulting in widespread inflammation. There is polyclonal B-cell activa-

Drug / Treatment	Safety in pregnancy	Comments
Non-steroidal anti-inflammatory drugs (NSAIDs)	Acceptable for shorterm use up to 28 weeks gestation.	Avoid use in third trimester.
Corticosteroids (prednisolone/methylprednisolone)	Can be used throughout pregnancy if clinically indicated. Not associated with any increased risk of congenital malformations, although there is an increased risk of diabetes and hypertension in the mother.	Fluorinated corticosteroids (e.g. dexamethasone and beclomethasone) are less metabolised by the placenta and should be avoided unless treating a fetal problem.
Hydroxychloroquine	Can be used throughout pregnancy if clinically indicated. Not associated with any increased risk of congenital malformations.	
Sulfalazine, mesalazine	Can be used throughout pregnancy if clinically indicated. Not associated with any increased risk of congenital malformations.	Women taking sulfasalazine during pregnancy should also receive folate supplementation of at least 2mg/day.
Azathioprine	Can be used throughout pregnancy if clinically indicated. Not associated with any increased risk of congenital malformations.	
Ciclosporin, tacrolimus	Can be used throughout pregnancy if clinically indicated. Not associated with any increased risk of congenital malformations.	May require higher doses during pregnancy to maintain levels within therapeutic range.
Infliximab	No evidence of a teratogenic effect–can be used in first trimester if clinically indicated. If possible, stop at 20 weeks gestation.	Continued use throughout pregnancy can be justified if clinically indicated.
Adalimumab	No evidence of a teratogenic effect–can be used in first trimester if clinically indicated. If possible, stop at 28 weeks gestation.	
Etanercept	No evidence of a teratogenic effect–can be used in first trimester if clinically indicated. If possible, stop at 28 weeks gestation.	
Certolizumab pegol	Limited evidence, but early data suggest compatibility with all three trimesters of pregnancy and do not show any evidence of a teratogenic effect.	
Rituximab, golimumab, abatacept, tocilizumab, belimumab,anakinra.	Limited data, although registry and observational data suggest that unintentional exposure to these drugs in the first trimester is unlikely to be harmful.	Data too limited to make any recommendation for use in pregnancy.
Intravenous Immunoglobulin (IVIg)	Can be used throughout pregnancy if clinically indicated.	
Therapeutic Plasma Exchange (TPE)	Can be used throughout pregnancy if clinically indicated.	
Methotrexate	Teratogenic. Avoid during pregnancy.	These drugs should be withdrawn before a planned pregnancy.
Mycophenolate mofetil (MMF)		
Leflunomide		
Cyclophosphamide		

Fig. 15.3 Safety of immunomodulatory and immunosuppressive therapies in pregnancy

tion and antinuclear antibody production. There are also complement deficiencies and impaired T-cell regulation, which leads to a diminished ability to clear these immune complexes [56].

SLE is particularly prone to flaring during pregnancy. As many as 60% of women with pre-existing SLE experience a flare during or soon after pregnancy, compared with 40% of nonpregnant women over the same period [57]. The risk of flaring during pregnancy is highest for women with active disease at the time of conception, particularly if they have lupus nephritis [58]. SLE disease activity varies by organ system. Musculoskeletal flares are less common, while renal and hematologic flares are more common [59]. Severe morbidity requiring critical care may result from flares of lupus nephritis, interstitial lung disease, cardiovascular disease, neuropsychiatric lupus, thrombosis, thrombocytopenia or opportunistic infections.

Treatment of acute severe flares involves high-dose corticosteroids (e.g. pulsed IV methylprednisolone 500–1000 mg/day for 3 days followed by prednisolone 0.25–0.5 mg/kg/day) [60, 61].

Identifying SLE flares may be more challenging during pregnancy, as some of the symptoms and signs may overlap with normal pregnancy (e.g. lethargy, facial flushing, oedema, mild anaemia and thrombocytopenia) [62]. Good clinical judgement and specific laboratory tests such as declining serum complement levels and/or rising anti-dsDNA antibody titres may aid diagnosis of a lupus flare during pregnancy.

One of the biggest challenges is the differentiation between pre-eclampsia and a lupus nephritis flare. Both conditions may present with hypertension, proteinuria and deteriorating renal function. Here again, falling complement levels and rising anti-dsDNA antibody titres make lupus nephritis more likely, as does the detection of an active urinary sediment. A history of lupus nephritis also increases the likelihood of a renal flare in pregnancy, although lupus nephritis may present for the first time during pregnancy [56].

Despite these distinguishing features, the only investigation that can definitively distinguish pre-eclampsia from lupus nephritis is renal biopsy. This is not usually performed during pregnancy due to the risk of bleeding complications. It may occasionally be indicated in the first or second trimester if it is felt that the result is likely to alter management, for example, if appropriate treatment with immunosuppressive agents may allow prolongation of the pregnancy (see Chap. 31) [56]. If pre-eclampsia and lupus flare cannot be differentiated beyond 24–28 weeks gestation (when the fetus is viable) and maternal health is significantly compromised, then multidisciplinary discussion should be undertaken regarding early delivery. Delivery will both cure the pre-eclampsia and enable renal biopsy to guide immunosuppressive therapy if lupus nephritis is confirmed.

Box 15.1 IVIg and Plasma Exchange in Pregnancy: A Case-Based Example

A 33-year-old female attends the antenatal unit at 21 weeks gestation, with a 5-day history of progressive weakness. She is struggling to walk and reports that she is more breathless than usual. She was previously fit and well, although she did report a diarrhoeal illness a few weeks prior to this presentation. She has been assessed by the neurology team, who have concluded that she has Guillain-Barre syndrome. A critical care opinion has been requested, as she is slightly dyspnoeic, although she is able to communicate in full sentences. The patient is very concerned about the safety and availability of treatment options for her condition, given that she is pregnant.

In this case, the patient was observed on the critical care unit but fortunately did not deteriorate to the point of needing invasive ventilation. She responded well to IVIg, was discharged from the ICU after 5 days and made a full recovery over the following 8 weeks. She delivered a healthy baby by spontaneous vaginal delivery at 39 weeks.

Guillain-Barre syndrome (GBS) is an acute immune-mediated polyneuropathy (Box 15.1). It presents as an acute, monophasic paralysing illness, usually provoked by a preceding infection. Although the condition has been reported in pregnancy [63], it is a rare condition, and there are insufficient data to make recommendations other than to manage the condition in the same way as in the nonpregnant patient. Respiratory failure is common (17–30%) [64] and is the usual reason for admission to the intensive care unit. Forced vital capacity (FVC) of less than 20 mL/kg is the widely accepted threshold to consider invasive ventilation. FVC does not change significantly in pregnancy [65], so a low FVC measurement should be attributed to genuine neuromuscular weakness rather than to the pregnancy. Indeed, the increased oxygen and ventilatory demands and the decreased lung compliance in pregnancy may result in more rapid exhaustion, decompensation and respiratory embarrassment. These patients must be closely observed for any early signs of respiratory muscle weakness, with a low threshold to admit to the high dependency or intensive care unit.

Treatment of pregnant women with GBS is the same as that in nonpregnant patients. There is clear evidence that IVIg and plasma exchange (one or the other, not both in combination) is of benefit in GBS [52, 66]. Corticosteroids are ineffective and may even delay recovery [67].

Both plasma exchange and IVIg can be used in pregnancy. Trials have demonstrated that plasma exchange is associated with reduced duration of mechanical ventilation, reduced time to motor recovery and reduced time to walking without assistance [52]. If plasma exchange is used, care must be taken to avoid hypovolaemia or fluid overload. There may be a transient prolongation of prothrombin and activated partial thromboplastin times due to removal of clotting factors. Although significant bleeding is uncommon, this effect can be avoided by using plasma rather than albumin as the replacement fluid [68].

IVIg is equally as efficacious as plasma exchange and is often used as first-line therapy due to its relative ease of use. A suggested dosing regimen for IVIg is 0.4 g/kg/day for 5 days [69]. IVIg therapy is associated with an increased risk of thromboembolic events, particularly in patients with additional thrombotic risk factors [70]. Pregnancy is a pro-thrombotic state, and immobile patients in the critical care unit are at particularly high risk of venous thromboembolism. Adequate thromboprophylaxis (usually with low molecular weight heparin) is therefore essential.

15.3 Antibodies and the Placental Barrier

An important function of the placenta is to form a selective barrier between the maternal and fetal circulation. Most low molecular weight compounds (<500 Da) can move across the placenta by passive diffusion. Certain ions and amino acids are also actively transported. In contrast, high molecular weight compounds do not usually traverse the placenta, but an important exception is immunoglobulin G (IgG), which has a molecular mass of approximately 160 kDa. Of the five antibody classes, IgG is the only class that crosses the placenta in significant quantities, although it is only transferred in significant quantities after 16 weeks gestation [71]. This is clinically relevant for three main reasons:

- Neonatal "passive" immunity to infection
- Effects of autoantibodies on the fetus/neonate
- Implications for use of "biologic" drugs

15.3.1 Neonatal "Passive" Immunity to Infection

The neonatal immune system is immature and unable to mount an adequate adaptive immune response when exposed to pathogens during or soon after birth. Placental transfer of maternal IgG antibodies therefore plays an important role in protecting the neonate against infection during the initial weeks and months of life. For example, if the mother has circulating antibodies to pathogens such as varicella zoster virus, herpes simplex virus, or measles (due to prior vaccination or exposure to the pathogen), then these antibodies are detectable in the neonate too. This "passive" immunisation confers a degree of protection against these infections. This physiological process can be and often is exploited by vaccinating the mother during pregnancy for specific diseases (e.g. pertussis) [72, 73]. Similarly, IVIg has been used extensively in pregnancy without adverse effect on the fetus. It does cross the placenta (as it is IgG) but there is no association with harm. Indeed, IVIg is actually used to treat neonatal sepsis.

15.3.2 Direct Effects of Autoantibodies on the Fetus/Neonate

Certain autoimmune conditions are associated with autoantibodies that may have a direct adverse effect on the fetus. Patients with these conditions, for a variety of reasons, often require critical care admission; it is therefore vital that intensive care physicians are aware of the potential immunological complications specific to pregnancy.

Anti-Ro/SSA antibodies may be present in mothers with Sjogren's syndrome, SLE or rheumatoid arthritis [74]. Women with these autoimmune conditions should be screened for the presence of these antibodies in order to inform the treating neonatologist following delivery. These antibodies cross the placenta and are associated with fetal cardiac abnormalities and transient neonatal cutaneous lupus [75]. The risk of congenital heart block is 1–5%, and there is also a risk of myocardial inflammation, endocardial fibroelastosis or atrioventricular (AV) valve apparatus dysfunction [76]. The risk is particularly high if a previous fetus has been affected.

Several other autoimmune disease-associated IgG antibodies can cross the placenta to cause harm to the fetus. These are summarised in Fig. 15.4. However, it is important to note that the presence/titres of these antibodies don't necessarily correlate with the degree of pathology.

15.3.3 Implications for Use of "Biologic" Drugs

Most "biologic" drugs are monoclonal derivatives of IgG and therefore cross the placenta.

Infliximab and adalimumab are monoclonal antibodies against TNFα. Etanercept is a fusion molecule comprising of a soluble TNFα receptor and the Fc-fragment of IgG1. These drugs can be initiated or continued during pregnancy if clinically indicated. In the intensive care setting, they are likely to be used in combination with corticosteroids to treat acute flares or de novo inflammatory disease. In mothers treated with these drugs, fetal exposure is minimal in the first trimester, and there is no evidence of a teratogenic effect [48, 77]. However, from 16 weeks gestation onwards, the antibody molecules are actively transported across the placenta and, by the third trimester, can result in higher drug levels in the fetus/neonate than in the mother.

To minimise neonatal levels at birth, these drugs are often discontinued in the second trimester (by 20 weeks for infliximab and 28 weeks for adalimumab or etanercept). However, if the drug is required to control active maternal inflammatory disease, it is acceptable to continue treatment throughout pregnancy. Moreover, while there have been theoretical concerns about neonatal immune suppression, data from the PIANO registry [77] are reassuring: third trimester anti-TNFα use had no effect on infant growth, development or immune development in the first year of life, and a systematic review [78] found no increased risk of infections up to 1 year of age. The British Society of Rheumatologists and European League Against Rheumatism have recently issued detailed guidance [47, 48] on this topic. All of these drugs may be detectable in breast milk at very low levels, but they are very poorly absorbed via the oral route, so breastfeeding is considered safe [48].

There are a number of newer anti-TNFα drugs, some of which have been modified to alter the pharmacokinetic profile. Certolizumab pegol is a monoclonal antigen-binding fragment (Fab) of an anti-TNFα antibody (lacking the Fc region) that has been conjugated with polyethylene glycol. It has low rates of placental transfer, and early data suggest that it is compatible with all three trimesters of pregnancy. Safety data are limited for rituximab, golimumab, abatacept, tocilizumab, belimumab and anakinra, although registry and observational data suggest that unintentional fetal exposure to these drugs in the first trimester is unlikely to be harmful [48].

15.4 Conclusion

The immunological changes in pregnancy are complex. There are pro-inflammatory changes as well as increased immune tolerance, with a shift from a Th1- towards a Th2-predominant immunological profile. Certain infections, such as influenza, hepatitis E and falciparum malaria, tend to cause more severe disease in pregnancy, with higher morbidity and mortality. Pregnancy also influences the activity of autoimmune diseases, which are relatively common in women of childbearing age. Severe flares of autoimmune disease often require critical care admission for observation and treatment. Identifying autoimmune flares may be more challenging during pregnancy, as

Autoimmune disease	Autoantibodies	Potential effect of antibodies on fetus/neonate	Management	Comments
Sjogrens Syndrome, SLE, Rheumatoid arthritis, other connective tissue diseases	Anti-Ro/SSA	Complete heart block and other cardiac pathologies (see main text). Transient neonatal cutaneous lupus	**Mother:** Hydroxychloroquine **Fetus:** surveillance	A history of connective tissue disease disease should prompt antibody screening, even if the mother is asymptomatic.
Graves Disease	TSH Recepter stimulating antibodies	Thyrotoxicosis, goitre	**Mother and/or neonate**: Anti-thyroid drugs (Propylthiouracil or carbimazole).	A history of Graves disease should prompt antibody screening, even if the mother is euthyroid.
Pemphigoid gestationis (severe but rare pregnancy-specific dermatosis)	Antibodies to Bullous Pemhigoid Antigen 2	Bullous skin eruption (in 10%; usually mild and transient).	**Mother:** Corticosteroids, immunosuppression.	
Pemphigus Vulgaris	Antibodies to Desmoglein 3 or 1	Neonatal pemphigus	**Mother:** Corticosteroids, immunosuppression, therapeutic plasma exchange.	
Myasthenia Gravis	Anti-AChR (90%) Anti-MuSK (10%)	Transient neonatal myasthenia gravis: floppy baby, difficulty breathing, respiratory compromise. Becomes apparent in first 2 days after birth and usually resolves within 2 months.	**Mother and/or neonate:** Acetylcholinesterase inhibitor drugs **Mother:** Corticosteroids, immunosuppression, IVIg, therapeutic plasma exchange.	
	High titres of antibodies to fetal γ-subunit of AChR	Arthrogryposis: contractures and impaired swallowing; often fatal. Milder cases may survive with persistent myopathy.		
Immune thrombocytopenic purpura (ITP)	Anti-platelet antibodies (testing not readily available, and not required to make diagnosis)	Neonatal thrombocytopenia. There is a small risk of fetal/neonatal intracranial haemorrhage.	**Mother and/or neonate:** IVIg **Mother:** Corticosteroids, immunosuppression.	Neonatal platelet count reaches lowest point 2-5 days after birth in affected infants and most haemorrhages occur 24-48h after delivery. There is no evidence that caesarean section reduces the risk of intracranial haemorrhage.

Fig. 15.4 Autoimmune disease-associated antibodies and the potential direct effects on the fetus during and after pregnancy

some features may overlap with normal pregnancy and/or pre-eclampsia. Some autoimmune diseases are associated with antibodies that cross the placenta, with potential to affect the fetus. Many immunosuppressive treatments can be used during pregnancy and should not be withheld, as uncontrolled maternal disease results in poorer outcomes for both mother and fetus. There is now good evidence that "biologic" anti-TNFα therapies can be used during pregnancy.

References

1. Mor G, Cardenas I. The immune system in pregnancy: a unique complexity. Am J Reprod Immunol. 2010;63(6):425–33.
2. Raphael I, Nalawade S, Eagar TN, Forsthuber TG. T cell subsets and their signature cytokines in autoimmune and inflammatory diseases. Cytokine. 2015;74(1):5–17.
3. Berker M, Frank LJ, Geßner AL, et al. Allergies—a T cells perspective in the era beyond the TH1/TH2 paradigm. Clin Immunol. 2017;174:73–83.
4. Marzi M, Vigano A, Trabattoni D, et al. Characterization of type 1 and type 2 cytokine production profile in physiologic and pathologic human pregnancy. Clin Exp Immunol. 1996;106(1):127–33.
5. Bonney EA. Immune regulation in pregnancy: a matter of perspective? Obstet Gynecol Clin North Am. 2016;43(4):679–98.
6. Aluvihare VR, Kallikourdis M, Betz AG. Regulatory T cells mediate maternal tolerance to the fetus. Nat Immunol. 2004;5(3):266–71.
7. Figueiredo AS, Schumacher A. The T helper type 17/regulatory T cell paradigm in pregnancy. Immunology. 2016;148(1):13–21.
8. Robertson SA, Moldenhauer LM. Immunological determinants of implantation success. Int J Dev Biol. 2014;58(2–4):205–17.
9. Sasaki Y, Darmochwal-Kolarz D, Suzuki D, et al. Proportion of peripheral blood and decidual CD4(+) CD25(bright) regulatory T cells in pre-eclampsia. Clin Exp Immunol. 2007;149(1):139–45.
10. Williams Z. Inducing tolerance to pregnancy. N Engl J Med. 2012;367(12):1159–61.
11. Baratelli F, Lin Y, Zhu L, et al. Prostaglandin E2 induces FOXP3 gene expression and T regulatory cell function in human CD4+ T cells. J Immunol. 2005;175(3):1483–90.
12. Khan D, Ansar AS. The immune system is a natural target for estrogen action: opposing effects of estrogen in two prototypical autoimmune diseases. Front Immunol. 2016;6:635.
13. Piccinni MP, Lombardelli L, Logiodice F, et al. How pregnancy can affect autoimmune diseases progression? Clin Mol Allergy. 2016;14:11.
14. Mor G. Inflammation and pregnancy: the role of toll-like receptors in trophoblast-immune interaction. Ann N Y Acad Sci. 2008;1127:121–8.
15. Romero R, Espinoza J, Kusanovic J, et al. The preterm parturition syndrome. BJOG. 2006;113(Suppl 3):17–42.
16. Kourtis AP, Read JS, Jamieson DJ. Pregnancy and infection. N Engl J Med. 2014;370(23):2211–8.
17. Knight, M et al, The UK Obstetric Surveillance System SARS-CoV-2 Infection in Pregnancy Collaborative Group, May 2020.
18. Siston AM, Rasmussen SA, Honein MA, et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. JAMA. 2010;303(15):1517–25.
19. Raj RS, Bonney EA, Phillippe M. Influenza, immune system, and pregnancy. Reprod Sci. 2014;21(12):1434–51.
20. Littauer EQ, Esser ES, Antao OQ, Vassilieva EV, Compans RW, Skountzou I. H1N1 influenza virus infection results in adverse pregnancy outcomes by disrupting tissue-specific hormonal regulation. PLoS Pathog. 2017;13(11):e1006757.
21. Navaneethan U, Mohajer MA, Shata MT. Hepatitis E and pregnancy—understanding the pathogenesis. Liver Int. 2008;28(9):1190–9.
22. Lawrence T. The nuclear factor NF-κB pathway in inflammation. Cold Spring Harb Perspect Biol. 2009;1(6):a001651.
23. McCracken SA, Drury CL, Lee HS, Morris JM. Pregnancy is associated with suppression of the nuclear factor kappaB/IkappaB activation pathway in peripheral blood mononuclear cells. J Reprod Immunol. 2003;58:27–47.
24. Prusty BK, Hedau S, Singh A, Kar P, Das BC. Selective suppression of NF-kBp65 in hepatitis virus-infected pregnant women manifesting severe liver damage and high mortality. Mol Med. 2007;13:518–26.
25. Nelson-Piercy C. Handbook of obstetric medicine. 5th ed. Boca Raton: CRC Press; 2015.
26. The diagnosis and treatment of malaria in pregnancy. Royal College of Obstetricians and Gynaecologists Green–top Guideline No. 54b. 2010. https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_54b.pdf. Accessed 13 Aug 2018.
27. Rogerson SJ, Mwapasa V, Meshnick SR. Malaria in pregnancy: linking immunity and pathogenesis to prevention. In: Breman JG, Alilio MS, White NJ, editors. Defining and defeating the intolerable burden of malaria III: progress and perspectives: supplement to volume 77(6) of American Journal of Tropical Medicine and Hygiene. Northbrook: American Society of Tropical Medicine and Hygiene; 2007.
28. Lindsay S, Ansell J, Selman C, Cox V, Hamilton K, Walraven G. Effect of pregnancy on exposure to malaria mosquitoes. Lancet. 2000;355(9219):1972.

29. Maestre A, Carmona-Fonseca J. Immune responses during gestational malaria: a review of the current knowledge and future trend of research. J Infect Dev Ctries. 2014;8(4):391–402.
30. To M, Kidd M, Maxwell D. Prenatal diagnosis and management of fetal infections. Obstetrician Gynaecologist. 2009;11:108–16.
31. de Ruiter A, Taylor GP, Clayden P, Dhar J, Gandhi K, Gilleece Y, Harding K, Hay P, Kennedy J, Low-Beer N, Lyall H, Palfreeman A, O'Shea S, Tookey P, Tosswill J, Welch S, Wilkins E, British HIV Association. British HIV Association guidelines for the management of HIV infection in pregnant women 2012 (2014 interim review). HIV Med. 2014;15(Suppl 4):1–77.
32. Sappenfield E, Jamieson DJ, Kourtis AP. Pregnancy and susceptibility to infectious diseases. Infect Dis Obstet Gynecol. 2013;2013:752852.
33. Ranzani OT, Battaini LC, Moraes CE, et al. Outcomes and organ dysfunctions of critically ill patients with systemic lupus erythematosus and other systemic rheumatic diseases. Braz J Med Biol Res. 2011;44(11):1184–93.
34. Janssen NM, Karnad DR, Guntupalli KK. Rheumatologic diseases in the intensive care unit: epidemiology, clinical approach, management, and outcome. Crit Care Clin. 2002;18(4):729–48.
35. Quintero OL, Rojas-Villarraga A, Mantilla RD, et al. Autoimmune diseases in the intensive care unit. An update. Autoimmun Rev. 2013;12:380–95.
36. Knight M, Nair M, Kenyon S, et al. (Eds.) on behalf of MBRRACE-UK. Saving lives, improving mothers' care—surveillance of maternal deaths in the UK 2012–14 and lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009–14. Oxford: National Perinatal Epidemiology Unit, University of Oxford. 2016. https://www.npeu.ox.ac.uk/downloads/files/mbrrace-uk/reports/MBRRACE-UK%20Maternal%20Report%202015.pdf. Accessed 13 Aug 2018.
37. Cooper GS, Stroehla BC. The epidemiology of autoimmune diseases. Autoimmun Rev. 2003;2:119–25.
38. Brouwer J, Hazes JM, Laven JS, Dolhain RJ. Fertility in women with rheumatoid arthritis: influence of disease activity and medication. Ann Rheum Dis. 2015;74(10):1836–41.
39. Engdahl C, Jochems C, Windahl SH, et al. Amelioration of collagen-induced arthritis and immune-associated bone loss through signaling via estrogen receptor α, and not estrogen receptor β or G protein–coupled receptor 30. Arthritis Rheum. 2010;62(2):524–33.
40. Lélu K, Laffont S, Delpy L, et al. Estrogen receptor α signaling in T lymphocytes is required for estradiol-mediated inhibition of Th1 and Th17 cell differentiation and protection against experimental autoimmune encephalomyelitis. J Immunol. 2011;187(5):2386–93.
41. de Jong PH, Dolhain RJ. Fertility, pregnancy, and lactation in rheumatoid arthritis. Rheum Dis Clin North Am. 2017;43(2):227–37.
42. de Man YA, Dolhain RJ, van de Geijn FE, et al. Disease activity of rheumatoid arthritis during pregnancy: results from a nationwide prospective study. Arthritis Rheum. 2008;59(9):1241–8.
43. Confavreux C, Hutchinson M, Hours MM, et al. Rate of pregnancy-related relapse in multiple sclerosis. Pregnancy in Multiple Sclerosis Group. N Engl J Med. 1998;339(5):285–91.
44. Vaughan Jones S, Ambros-Rudolph C, Nelson-Piercy C. Skin disease in pregnancy. BMJ. 2014;348:g3489.
45. Weetman AP. Immunity, thyroid function and pregnancy: molecular mechanisms. Nat Rev Endocrinol. 2010;6(6):311–8.
46. Hviid A, Mølgaard-Nielsen D. Corticosteroid use during pregnancy and risk of orofacial clefts. CMAJ. 2011;183(7):796–804.
47. Götestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis. 2016;75(5):795–810.
48. Flint J, Panchal S, Hurrell A, van de Venne M, Gayed M, Schreiber K, Arthanari S, Cunningham J, Flanders L, Moore L, Crossley A, Purushotham N, Desai A, Piper M, Nisar M, Khamashta M, Williams D, Gordon C, Giles I, BSR and BHPR Standards, Guidelines and Audit Working Group. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-part I: standard and biologic disease modifying antirheumatic drugs and corticosteroids. Rheumatology (Oxford). 2016;55(9):1693–7.
49. Andreoli L, Bertsias GK, Agmon-Levin N, et al. EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. Ann Rheum Dis. 2017;76(3):476–85.
50. Cox JL, Koepsell SA, Shunkwiler SM. Therapeutic plasma exchange and pregnancy: a case report and guidelines for performing plasma exchange in a pregnant patient. J Clin Apher. 2017;32(3):191–5.
51. Ahmed AR, Gürcan HM. Use of intravenous immunoglobulin therapy during pregnancy in patients with pemphigus vulgaris. J Eur Acad Dermatol Venereol. 2011;25(9):1073–9.
52. Chevret S, Hughes RAC, Annane D. Plasma exchange for Guillain-Barré syndrome. Cochrane Database Syst Rev. 2017;2:CD001798.
53. Nelson-Piercy C, Agarwal S, Lams B. Lesson of the month: selective use of cyclophosphamide in pregnancy for severe autoimmune respiratory disease. Thorax. 2016;71(7):667–8.
54. Amant F, Loibl S, Neven P, Van Calsteren K. Breast cancer in pregnancy. Lancet. 2012;379(9815):570–9.

55. Lee EJ, Ahn KH, Hong SC, Lee EH, Park Y, Kim BS. Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy for diffuse large B-cell lymphoma in pregnancy may be associated with preterm birth. Obstet Gynecol Sci. 2014;57(6):526–9.
56. Cauldwell M, Nelson-Piercy C. Maternal and fetal complications of systemic lupus erythematosus. Obstetrician Gynaecologist. 2012;14:167–74.
57. Khamashta MA. Systemic lupus erythematosus and pregnancy. Best Pract Res Clin Rheumatol. 2006;20(4):685–94.
58. Soh M, Nelson-Piercy C. High-risk pregnancy and the rheumatologist. Rheumatology (Oxford). 2015;54(4):572–87.
59. Petri M. The Hopkins Lupus Pregnancy Center: ten key issues in management. Rheum Dis Clin North Am. 2007;33(2):227–35.
60. Lateef A, Petri M. Systemic lupus erythematosus and pregnancy. Rheum Dis Clin North Am. 2017;43(2):215–26.
61. Bertsias GK, Tektonidou M, Amoura Z, et al. Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis. 2012;71(11):1771–82.
62. Lateef A, Petri M. Managing lupus patients during pregnancy. Best Pract Res Clin Rheumatol. 2013;27(3):435–47.
63. Brooks H, Christian AS, May AE. Pregnancy, anaesthesia and Guillain-Barré syndrome. Anaesthesia. 2000;55(9):894–8.
64. Hughes RAC, Wijdicks EFM, Benson E, et al. Supportive care for patients with Guillain-Barré syndrome. Arch Neurol. 2005;62(8):1194–8.
65. Bedson R, Riccoboni A. Physiology of pregnancy: clinical anaesthetic implications. Cont Educ Anaesth Crit Care Pain. 2014;14:69–72.
66. Hughes RAC, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-Barré syndrome. Cochrane Database Syst Rev. 2014;(9):CD002063.
67. Hughes RAC, Brassington R, Gunn A, van Doorn PA. Corticosteroids for Guillain-Barré syndrome. Cochrane Database Syst Rev. 2016;10:CD001446.
68. Kaplan AA, Fridey JL. Therapeutic apheresis (plasma exchange or cytapheresis): complications. In: Post TW, editor. UpToDate. Waltham: UpToDate; 2014. https://www.uptodate.com/contents/therapeutic-apheresis-plasma-exchange-or-cytapheresis-complications. Accessed 27 Apr 2018.
69. Donofrio PD, Berger A, Brannagan TH 3rd, Bromberg MB, Howard JF, Latov N, Quick A, Tandan R. Consensus statement: the use of intravenous immunoglobulin in the treatment of neuromuscular conditions report of the AANEM Ad Hoc Committee. Muscle Nerve. 2009;40(5):890–900.
70. Caress JB, Hobson-Webb L, Passmore LV, Finkbiner AP, Cartwright MS. Case-control study of thromboembolic events associated with IV immunoglobulin. J Neurol. 2009;256(3):339–42.
71. Palmeira P, Quinello C, Silveira-Lessa AL, et al. IgG placental transfer in healthy and pathological pregnancies. Clin Dev Immunol. 2012;2012:985646.
72. McMillan M, Clarke M, Parrella A, et al. Safety of tetanus, diphtheria, and pertussis vaccination during pregnancy: a systematic review. Obstet Gynecol. 2017;129(3):560–73.
73. Donegan K, King B, Bryan P. Safety of pertussis vaccination in pregnant women in UK: observational study. BMJ. 2014;349:g4219.
74. Martínez-Sánchez N, Pérez-Pinto S, Robles-Marhuenda Á, Arnalich-Fernández F, Martín Cameán M, Hueso Zalvide E, Bartha JL. Obstetric and perinatal outcome in anti-Ro/SSA-positive pregnant women: a prospective cohort study. Immunol Res. 2017;65(2):487–94.
75. Donofrio MT, Moon-Grady AJ, Hornberger LK, et al. Diagnosis and treatment of fetal cardiac disease: a scientific statement from the American Heart Association. Circulation. 2014;129:2183–242.
76. Cuneo BF, Fruitman D, Benson DW, et al. Spontaneous rupture of atrioventricular valve tensor apparatus as late manifestation of anti-Ro/SSA antibody mediated cardiac disease. Am J Cardiol. 2011;107:761–6.
77. Mahadevan U, Martin C, Sandler R, et al. PIANO: a 1000 patient prospective registry of pregnancy outcomes in women with IBD exposed to immunomodulators and biologic therapy (abstr 865). Gastroenterology. 2012;142(suppl 1):S-149.
78. Nielsen OH, Loftus EV Jr, Jess T. Safety of TNF-alpha inhibitors during IBD pregnancy: a systematic review. BMC Med. 2013;11:174.

Hypertension, Preeclampsia, and Eclampsia

16

Erin J. Ciampa and Philip E. Hess

Bullet Points

- Complications of the hypertensive disorders of pregnancy are among the most common indications for intensive care unit admission of pregnant and peripartum women.
- Preeclampsia is a multisystem disease defined as onset of elevated blood pressure after 20 weeks of gestation or later, accompanied by one or more manifestation of organ dysfunction/failure.
- Early-onset preeclampsia (diagnosis prior to 34 weeks gestational age) is an accelerated variant of the disease that carries increased risk of maternal and fetal complications.
- Major complications that can occur as a result of preeclampsia include cardiomyopathy, pulmonary edema, seizure, intracranial hemorrhage, thrombocytopenia, renal failure, hepatic injury and liver hemorrhage, fetal growth restriction, and placental abruption.
- The cornerstones of management of a patient with critical illness due to preeclampsia include blood pressure control, parenteral magnesium sulfate infusion for prevention of eclamptic seizures, and delivery of the infant irrespective of gestational age in the presence of maternal clinical instability.
- Fluid administration should be conservative and based on volume status and not urine output, as pulmonary edema is strongly associated with excessive fluid administration and with poor outcome.
- Monitoring and additional therapeutic interventions should be tailored to the specific organ systems involved.

16.1 Introduction

Hypertensive disorders are a leading cause of maternal mortality and severe maternal morbidity during pregnancy [1, 2]. The potentially life-threatening complications of the hypertensive disorders of pregnancy include stroke, hemorrhage, kidney failure, liver failure, and respiratory distress, among others and occur at a rate approximately 50 times higher than that of maternal death. No cure exists for the disease at the current time; treatment is focused on prevention of organ injury and timely delivery of the fetus. Reviews of maternal mortality due to preeclampsia consistently demonstrate that half of all deaths are associated with inadequate care.

E. J. Ciampa · P. E. Hess (✉)
Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
e-mail: phess@bidmc.harvard.edu

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_16

16.2 Epidemiology

The incidence of hypertensive disorders of pregnancy varies by country and approaches 10% of all pregnancies worldwide [1, 3, 4]. Hypertensive disorders of all classifications affect between 2% and 17% of all pregnancies in developing nations [5], and rates of preeclampsia are estimated to be seven times higher than in developed nations [6]. The incidence of eclampsia also varies widely by country, with rates as high as 1 per 100 births in Africa to 1 in 1700 births in other developing countries, versus 6 per 1000 in the developed world. However, even in developed countries, the hypertensive disorders of pregnancy are on the rise. An analysis of delivery hospitalizations in the United States shows a steady increase in hypertensive disorders between 1998 and 2006 (Fig. 16.1); this trend parallels rises in the frequency of both chronic hypertension and gestational hypertension [1]. During the studied period, chronic hypertension increased to the greatest degree (from 11.0 to 16.9 per 1000 deliveries), and a moderate increase was also noted for eclampsia/severe preeclampsia from 9.4 to 12.4 per 1000 deliveries.

16.3 Maternal Mortality

Hypertensive disorders in pregnancy represent one of the major causes of maternal mortality; in a review of the years 2003 to 2009, these accounted for approximately 14% of maternal deaths worldwide [7]. The most recent review in the United States, covering the years 2006 to 2010, found that the relative contribution of hypertensive disorders to maternal mortality had decreased slightly and now accounted for 11% of maternal deaths, behind only four other causes of maternal death. The case fatality rate at delivery (defined as a death occurring during the delivery admission) was 3.4 per 10,000 for women with preeclampsia, but almost 20 times higher among women with eclampsia [8]. The most common causes of death among women with preeclampsia were cerebrovascular events (specifically intracranial hemorrhage), which occurred in one-third of fatalities. This was followed by organ failure (renal or hepatic) and HELLP syndrome. Disseminated intravascular coagulation complicated 15% of all deaths [8]. Data from mortality reviews consistently suggest that there is significant room for improvement, with up to 50% to 60% of cases of maternal death being potentially preventable with timely, appropriate care [9, 10].

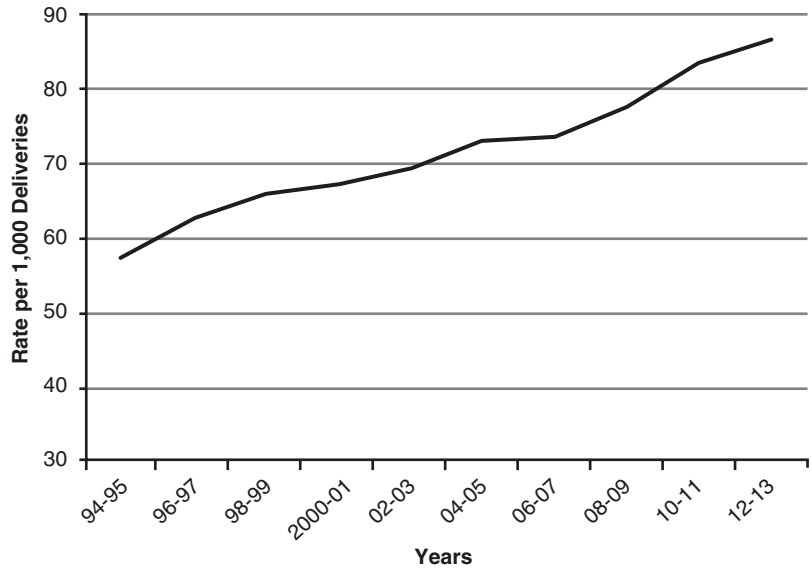


Fig. 16.1 The rate of hypertensive disorders in pregnancy in the United States over the previous 20 years. Adapted from the Centers for Disease Control using data from the Nationwide Inpatient Sample www.cdc.gov/reproductivehealth/maternalinfanthealth/pregnancy-complications-data.htm accessed 6/18/2017

16.4 Maternal Morbidity

In addition to the higher risk of death, hypertensive disorders of pregnancy are a risk factor for severe maternal morbidity (SMM), a term defined as unexpected outcomes of labor and delivery that result in significant short- or long-term consequences to a woman's health [11]. Up to 10% of pregnant women who suffer one or more SMM have hypertensive disorders of pregnancy as a direct cause. The incidence of SMM among women with preeclampsia is higher in early-onset disease than in late-onset disease (12.2 and 5.5 per 100 deliveries, respectively, conferring adjusted odds ratios of 3.7 [95%CI 3.2–4.3] and 1.7 [95%CI 1.6–1.9], respectively, versus women without preeclampsia) [12]. Furthermore, the complications associated with hypertensive disorders of pregnancy are among the most common indications for maternal peripartum admission to an ICU [13, 14]. For example, hypertensive disease of pregnancy generated 30% of 2927 obstetric ICU admissions according to a Maryland State Inpatient Database 1999–2008 [15], and 22% of 11,824 obstetric ICU admissions in France between 2006 and 2009 [14].

Hypertensive disorders of pregnancy are also associated with long-term adverse outcomes. Women with preeclampsia are more likely to have diabetes, ischemic heart disease, stroke, renal disease, and Alzheimer's disease [16–18]. Additionally, women with recurrent or severe preeclampsia are at increased risk compared with those women with preeclampsia without severe features. Finally, even women with gestational hypertension are at risk for cerebrovascular disease later in life [19].

16.5 Definitions of Hypertensive Disorders in Pregnancy

The American College of Obstetricians and Gynecologists (ACOG) Task Force on Hypertension in Pregnancy proposed the most recent classification and management guideline in 2013 [20]. Four categories of hypertensive disorders of pregnancy were defined: (1) preeclampsia-eclampsia, (2) chronic hypertension, (3) chronic hypertension with superimposed preeclampsia, and (4) gestational hypertension (Table 16.1). Similar to the general population, hypertension is defined as systolic blood pressures exceeding 140 mm Hg and/or diastolic pressures exceeding 90 mm Hg, while systolic and diastolic pressures above 160 mm Hg and 110 mm Hg, respectively, qualify as "severe-range" hypertension. Some important clarifications are found in the ACOG

Table 16.1 Classification of hypertensive disorders of pregnancy and major subtypes

Disorder	Characteristic
Gestational hypertension	Hypertension after 20 weeks No end-organ involvement
Chronic hypertension	Hypertension <20 weeks or > 12 weeks after delivery No end-organ involvement
Chronic hypertension with superimposed preeclampsia	Above diagnosis with end-organ involvement
Preeclampsia without severe features	Hypertension after 20 weeks with proteinuria[a]
Preeclampsia with severe features (see Table 16.2)	Hypertension after 20 weeks with ≥1severe feature Proteinuria (renal injury) not necessary for diagnosis
Subtypes	
Eclampsia	New-onset seizure without identifiable cause in the setting of preeclampsia
HELLP syndrome	Hemolysis Elevation of markers of hepatic injury Low platelets
Early-onset preeclampsia	Onset of disease prior to 34 weeks
Fetal syndrome	Disease with predominant fetal implications (growth restriction). May not have maternal features [75]
Postpartum hypertensive disorder	Onset 3–30 days after delivery. May not have had hypertension in pregnancy Often limited to hypertension and central nervous system symptoms/eclampsia [76]

[a]Proteinuria, signifying renal injury, can be identified by the presence of ≥300 mg of urine protein in a 24-h collection, *or* a urine protein/creatinine ratio (each measured in mg/dL) of ≥0.3 measured from a spot urine sample, *or* (when the above quantitative measures are not possible) a dipstick urine test reveals 1+ urine protein

Table 16.2 Characteristics that define preeclampsia with severe features

Injured organ	Sign or symptom
Vasculature	Severe hypertension (systolic BP > 160 mm Hg or diastolic BP > 110 mm Hg)
Myocardium	Pulmonary edema
Liver	> twofold increase in AST or ALT Persistent right upper quadrant or epigastric pain
Spleen	Thrombocytopenia (<100,000/mm^3)
Kidney	Serum creatinine >1.1 mg/dl, or doubling of baseline serum creatinine
Central nervous system	Persistent headache Visual disturbances

guidelines. First, although elevated blood pressures should technically be documented on two occasions at least 4 h apart, if severe-range pressures are noted, hypertension may be quickly confirmed with a second reading (even within minutes) in order to hasten initiation of antihypertensive medications. Second, the requirement for evidence of renal involvement was eliminated from diagnostic criteria for "preeclampsia with severe features," and renal involvement was better defined. Finally, "severe features of preeclampsia" was clarified as the onset of any of *one* of the features found in Table 16.2.

16.6 Risk Factors

Several risk factors for the development of hypertensive disorders of pregnancy have been recognized (Table 16.3). These are useful for identifying vulnerable populations who may benefit from prophylactic therapies, such as low-dose aspirin; this should be offered to women with >1 prior pregnancy affected by preeclampsia or in the presence of multiple other risk factors [20, 21].

16.7 Pathogenesis

Although a single cause of preeclampsia has not yet been identified, significant progress into the molecular pathogenesis has been made in the last decade. Specifically, placental ischemia appears to be a key event which initiates downstream signaling pathways associated with preeclampsia [22]. Ultimately, these pathways converge upon a state of angiogenic imbalance, which results in endothelial dysfunction with associated inflammatory response [23] and increased oxidative stress [24]. The cause of placental ischemia may vary among women (Table 16.4); incomplete implantation of the placenta has been identified

Table 16.3 Risk factors implicated in the development of preeclampsia

Maternal factors
- Age—Increase of 30% risk for each year of maternal age past 34 [77]. Twice the relative risk after age 40 years [78, 79]
- Obesity—Risk correlates with higher body mass index (BMI) [80, 81]. A Finnish longitudinal cohort study reported that first trimester BMI >30 kg/m^2 conferred an odds ratio of 2.1 (95%CI 1.1–3.6) and 5.2 (95%CI 2.1–10.5) to develop preeclampsia and severe preeclampsia, respectively [80]
- Race—Women of African descent have higher rates of chronic hypertension, preeclampsia [3, 82], and an increased risk of death [83–85]

Genetics[a]
- Maternal genetics—Account for one-third to one-half of the susceptibility to hypertensive disorders of pregnancy [79, 86–88]
- Paternal genetics—Both paternal and fetal genetics account for 10–20% of the risk of preeclampsia [89, 90]

Maternal comorbidities
- Chronic hypertension—Approximately 10fold increased risk [91, 92]
- Insulin resistance—Strong association with gestational diabetes [93], metabolic syndrome [94], and prepregnancy diabetes [95]

Pregnancy-related factors
- Nulliparity—Approximately threefold increased risk over multiparous women [79, 96–98]
- Previous pregnancy with preeclampsia—Particularly with multiple affected pregnancies and previous early-onset preeclampsia [79, 99, 100, 101]
- Multiple gestations—Nearly threefold for each additional fetus [102–104]
- Molar pregnancies—Risk of severe, early-onset forms of the disease [105]

[a]Hypertensive disorders of pregnancy result from a confluence of multiple interacting genetic and environmental factors. More than 200 genes have been linked to preeclampsia via genome-wide association studies [106–108], candidate gene approaches [109, 110], linkage studies [111, 112], and transcriptome analyses [113–115]

as one cause, especially in women with early-onset disease [25, 26].

The vascular supply of the placenta is constructed via a combination of the maternal endothelium and fetal cytotrophoblasts under the influence of angiogenic hormones vascular endothelial growth factor (VEGF), placental growth factor (PlGF), and transforming growth factor (TGF), a vasculogenesis hormone. VEGF is a potent angiogenic hormone that is responsible for endothelial health and multiplication. VEGF-A is also responsible for maintaining the fenestrated endothelial beds of the kidney, brain, and reticular endothelial system of the liver and spleen [27]. Recent studies have demonstrated that under hypoxic conditions, the placental cytotrophoblasts produce splice variants of the VEGF and TGF receptors which are solubilized and absorbed into the maternal circulation [28, 29]. These antiangiogenic receptors include soluble FMS-like tyrosine-1 (sFlt-1), sFlt-14, and endoglin, the receptor component responsible for hereditary hemorrhagic telangiectasia. Under the influence of these factors, the maternal circulation is dominated by an antiangiogenic state, which in combination with primary endothelial cell dysfunction can account for the clinical findings of preeclampsia.

Multiple theories compete with this description of the pathogenesis of preeclampsia (Table 16.5). Discussion of each of these processes is beyond the scope of this chapter.

Table 16.4 Potential causes of placental ischemia

Disease of the placenta
• Incomplete placental insertion
• Chronic maternal hypoxemia
– Asthma
– Diabetes
– Sickle cell disease
• Multiple gestation (increased demand)
• Placental infarction or abruption
• Vasculitis
• Chronic hypertension
• Placental aging

16.8 Clinical Features

Preeclampsia affects both maternal and fetal well-being due to the primary involvement of the endothelium in the pathogenesis of the disease. Preeclampsia can affect every organ in the body, but the clinical presentation varies among individuals. To better understand the clinical features, it is helpful to discuss the impact on each organ system (Table 16.6).

Table 16.5 Additional hypotheses for pathogenesis of preeclampsia

• Hyperdynamic cardiovascular state
• Inflammatory response
• Oxidative stress
• Maternal immunologic intolerance of pregnancy
• Genetic predisposition
• Nutritional deficiency
• Environmental factors

Table 16.6 Clinical complications of the hypertensive diseases of pregnancy

Feature	Symptom	Sign	Severe outcome
CNS	Headache	Hyperdynamic reflexes	Subarachnoid hemorrhage Cerebral edema
	Visual disturbance	Papilledema	PRES syndrome
	Irritability		Eclampsia
Cardiac		Hypertension	Abruption
		Diastolic dysfunction	Pulmonary edema
		Subclinical systolic dysfunction	Cardiomyopathy
Vascular		Hypertension	Nondependent edema
		Hemoconcentration	
Renal		Proteinuria	Acute tubular necrosis
		Nephrotic syndrome	Acute renal failure
Liver/spleen	Abdominal pain (RUQ)	Hepatic necrosis	Subcapsular hematoma
		Hemolysis	HELLP syndrome
Fetal		Growth restriction	Fetal distress
		Abruption	Fetal demise

Cardiac: Women with hypertensive disorders of pregnancy, and especially preeclampsia with severe features, experience significantly more myocardial stress. The systemic vascular resistance is increased due to loss of capillary volume and excessive responsiveness to vasoconstrictive hormones [30]. The capillary volume in the myocardium is similarly affected, resulting in reduced blood supply to the cardiac myocytes. This results in additional hypertrophy and strain as the heart attempts to respond to the stress. On echocardiography, the myocardium has evidence of diastolic dysfunction [31]. Despite the appearance of a hyperdynamic left ventricle with elevated cardiac output, evidence of subclinical systolic dysfunction can be found using speckle strain measurements [31].

Women with preeclampsia can have varied presentations of cardiac function on admission, depending on the severity of their disease and when they are admitted. The more common presentation consists of decreased preload, increased contractility, and cardiac output, with an elevated systemic vascular resistance [32]. This pattern changes significantly with volume administration to either a decrease in systemic vascular resistance and increased cardiac output or cardiogenic failure with elevated filling pressures [33].

The clinical consequences of these changes can be catastrophic. Women with preeclampsia have a high incidence of cardiogenic pulmonary edema. One of the most significant effects of preeclampsia is a possible association with peripartum cardiomyopathy. This association has been demonstrated in population studies. However, other studies do not support a link, as the myocardial features of preeclampsia and peripartum cardiomyopathy are disparate [34]. One study identified the association between antiangiogenic hormones and a genetic defect that leads to lethal cardiomyopathy in mice, and the presence of this genetic defect in humans could link preeclampsia and peripartum cardiomyopathy [35].

Vascular: The hallmark of the hypertensive disorders of pregnancy is an elevation of blood pressure due, at least in part, to elevation of systemic vascular resistance (SVR) [33]. SVR has two components: a responsive component determined by the arteriolar tone that represents the majority of SVR, and a fixed component due to capillary volume that represents approximately 40% of SVR in the nonpregnant, healthy person. The loss of capillary bed volume to the antiangiogenic environment results in an increase in the fixed component of SVR. This leads to progressive hypertension that can be resistant to medical therapy and often requires upward titration of medications at short intervals. Administration of crystalloid volume expansion to a woman with severe preeclampsia will result in a significant decrease in SVR, consistent with a reduction in systemic stress [33]; however, this is no longer recommended without evidence of hypovolemia, because aggressive administration of fluid may lead to pulmonary edema as a result of the accompanying endothelial dysfunction. Predicting the response to a fluid challenge requires echocardiographic imaging of patient volume status, as approximately half may not respond as clinically expected [36].

Central nervous system: Central nervous system (CNS) involvement is one of the hallmarks of the hypertensive disorders of pregnancy and is a unique feature not seen in essential hypertension. Precisely why women with preeclampsia have a predilection for CNS complications remains unclear, but may relate to the importance of VEGF-A in maintaining the fenestrated endothelium of the cerebral choroid plexus and vascular permeability. The most common CNS manifestation seen in preeclamptic women is peripheral hyperreflexia. Severe CNS complications include cerebral hemorrhage, cerebral edema, posterior reversible encephalopathy syndrome (PRES), retinal blindness, and eclampsia. Women with eclampsia are at the highest risk for morbidity and mortality. Although delivery should occur promptly, it is possible to safely have a vaginal delivery once the woman has been treated and stabilized [37]. Eclampsia should be considered any time a woman of childbearing age presents with seizures.

Airway and respiration: The nondependent edema that is characteristic of preeclampsia can have a significant effect on the swelling found in the upper torso and airway. This is especially true

for women who have gone through labor, particularly the second stage of labor [38–40]. Women with hypertensive disorders of pregnancy have a higher incidence of snoring and sleep apnea [38].

Consistent with the increase in cardiac output, women with hypertensive disorders of pregnancy have an elevated minute ventilation, despite a decreased forced vital capacity; however, exercise tolerance is decreased [41]. Similarly, ventilation perfusion mismatch is increased in women with severe preeclampsia [42], resulting in a higher incidence of saturation abnormalities, especially when the woman lies supine. Approximately 3% of women with preeclampsia experience pulmonary edema. Most cases occur after birth and are associated with the severity of preeclampsia, especially HELLP syndrome, and the amount of fluid given during labor and delivery [43, 44]. Possible explanations for the propensity for pulmonary edema in this population include increased capillary permeability due to endothelial injury, a reduction in colloid oncotic pressure, elevated hydrostatic pressure, and high incidence of diastolic dysfunction [45].

Hepatic: Liver injury is commonly seen in women with hypertensive disorders of pregnancy. Autopsies on women with eclampsia frequently demonstrate focal areas of ischemic injury in the liver [46]. Similar findings have been demonstrated by computer tomography in women with severe preeclampsia with HELLP syndrome and are typically associated with symptoms of right upper quadrant pain and elevated hepatic enzymes [47, 48].

One potentially disastrous consequence of preeclampsia is focal peripheral hepatic ischemia with subsequent hemorrhage within the liver capsule. A subcapsular liver hematoma is an emergency, as rupture is reportedly accompanied by maternal death rates of more than 30% [49]. Persistent right upper quadrant pain in a pregnant woman with preeclampsia (often despite epidural analgesia and control of hypertension) should immediately trigger referral to imaging. Diagnosis can be often made with ultrasound; however, computed tomography (CT) or magnetic resonance imaging (MRI) may also be required to confirm the diagnosis. Hesitation to use imaging due to concerns regarding fetal exposure to ionizing irradiation has no place in this circumstance as it may lead to maternal death. Once confirmed, the woman should be treated with minimal manipulation. A surgeon with expertise in trauma or liver surgery should be consulted, and the operating room, angiography, intensive care, and neonatology teams should be informed. Hepatic artery embolization can be used with expectant management in cases with a small focal area of hemorrhage [50, 51]. Capsular rupture frequently occurs with laparotomy, as the decrease in intraabdominal pressure relieves tamponade [49].

Hematologic: Preeclampsia can result in significant, sometimes dangerous, changes in the hematologic system. The most common finding is an elevation of the hemoglobin concentration, consistent with the third spacing of fluid due to endothelial injury and increased hydrostatic pressure. This may be the first identifiable sign of an impending hypertensive disorder. On the other hand, women with HELLP syndrome experience hemolytic anemia with circulating schistocytes; this occurs primarily due to the injury to the reticular endothelial system in the spleen. The presence of HELLP syndrome calls for prompt delivery.

Thrombocytopenia, defined as a platelet count less than 150,000/mm^3, is uncommon in gestational and chronic hypertension but is present in 50% of preeclampsia with severe features. Evidence of platelet dysfunction may also be seen in the preeclamptic patient with thrombocytopenia. The maximum amplitude value of the clot formed during thromboelastography, a measure that is believed to correlate with the effect of platelet function on clotting, begins to fall when the platelet count decreases below 100,000/mm^3 [52]. This is different than pregnant women without a hypertensive disorder, in whom the maximum amplitude begins to fall at a platelet count of 75,000/mm^3 [53]. Platelet dysfunction may be due to splenic injury or to autoantibodies; approximately one-third of women with preeclampsia have identifiable anti-platelet autoantibodies [54, 55]. The clinical importance of this finding is

unknown and should not prohibit platelet transfusion when indicated.

In severe cases, women may develop fulminant disseminated intravascular coagulation, with depletion of clotting factors. This can be found in cases of placental abruption, fetal demise, intracranial hemorrhage, and multisystem organ failure. This results in a hypocoagulable state that may require aggressive repletion of fibrinogen and plasma clotting proteins (see also Chap. 5).

Renal: The pathologic renal injury, glomerular endotheliosis, is pathognomonic for preeclampsia. While nephritic and even nephrotic syndrome occur with regularity in preeclampsia, oliguria (<400 mL/day) should be investigated because mismanagement can lead to iatrogenic injury. Management of oliguria should be undertaken with care due to the propensity these women have for developing pulmonary edema. An initial judicious bolus of fluids (250–500 ml) may be administered if hypovolemia is suspected. However, further fluid challenges must be based on measurable evidence of hypovolemia (i.e., echocardiographic assessment or indirect measures of volume responsiveness such as pulse pressure variation (see also Chap. 13)) given the lack of accuracy of calculated glomerular filtration rate, fractional excretion of sodium, and protein/creatinine ratio in this population [56].

Of significant concern is the use of nonsteroidal anti-inflammatory medications after cesarean delivery, and these should be avoided in women with known renal dysfunction. With advanced disease, acute tubular necrosis can lead to fulminant renal failure, requiring dialysis. The need for dialysis during pregnancy or after delivery is uncommon, with an incidence of 1 per 10,000 pregnancies reported in Canada between 1997 and 2011 [57]; however, preeclampsia is the most common pregnancy-related cause [58] (see also Chap. 31).

Fetal impact: The hypertensive disorders of pregnancy also take their toll on the fetus. The presence of chronic placental ischemia has a direct impact on fetal oxygen exchange, resulting in high rates of intrauterine growth restriction [59]. The impact of this is more commonly experienced among pregnancies affected by early-onset disease [60] and is likely associated with dysfunctional implantation and morphology of the placenta [26, 61]. Furthermore, preeclampsia is the leading cause of iatrogenic preterm birth, which is associated with significant morbidity. Even accounting for prematurity, preeclampsia is associated with greater neonatal morbidity, including increased odds of perinatal mortality, NICU admission, respiratory distress syndrome, peri- or intraventricular hemorrhage, apnea, and asphyxia [59, 62, 63]. In addition to reduced placental perfusion, women with preeclampsia have a high risk of placental abruption [64], which can be a fetal emergency.

16.9 Clinical Management

The goals of treatment for preeclampsia are (1) prevention of eclampsia, (2) control of blood pressure, (3) guided fluid management, and (4) prompt delivery of the fetus. The use of standard protocols developed from published guidelines and visual aids to ensure that appropriate care is provided should help in achieving optimal care [10]. Continual staff education and simulation training would be important [65].

16.10 Monitoring

Upon diagnosis of a hypertensive disorder of pregnancy, both mother and fetus should receive increased monitoring until delivery, and the mother should continue to receive close monitoring after delivery (Table 16.7). The setting should be determined based on the local capabilities; in some places, high-acuity centers have capabilities that approach those of intensive care units. A nurse-to-patient ratio of no less than 1–2 is indicated, and the patient should be evaluated every hour at minimum. The care setting must have capabilities for invasive monitoring and administration of intravenous cardiovascular medications. Any woman with hypertensive disease of pregnancy who requires mechanical ventilatory support should be in an intensive care unit.

Table 16.7 Clinical monitoring of the patients with hypertensive disorders of pregnancy

Monitor	Indication	Frequency
Blood pressure	Identification of severe hypertension	Weekly (gestational/chronic hypertension) Every 30–60 min (preeclampsia with severe features)
Pulse oximetry	Pulmonary edema	On admission Every shift change Continuous after delivery or upon worsening clinical status
Fluid input/output	Volume overload Volume restricted Renal insufficiency	Every shift change
Deep tendon reflexes (if on magnesium)	Magnesium monitoring	Every 4–8 h Measure serum magnesium if depressed
Fetal monitoring (pre-delivery)	Fetal compromise	Weekly with outpatient Daily ultrasound assessment for severe features Continuous monitoring in labor
Blood sampling	Complete blood count (platelet count, hemoglobin) Creatinine/BUN AST/ALT Magnesium	As needed depending on disease severity

16.11 Eclampsia Prophylaxis

Magnesium sulfate has become the standard therapy for prophylaxis in women with preeclampsia, especially those with severe features, reducing the incidence of seizures by approximately half [66]. Magnesium has also been shown to be effective for the treatment of an eclamptic seizure, both in halting the convulsion and in preventing further seizures (Table 16.8) [67]. Women should be closely monitored with serial peripheral reflex checks, and serum magnesium levels should be checked if reflexes are absent or if the woman becomes sedated. The therapeutic target is a serum concentration of 4–7 mEq/L.

Table 16.8 Medical therapy for the treatment or prophylaxis of eclampsia

Loading dose	4 g intravenous over 20 min	Hypotension Respiratory depression
Maintenance	1 g per hour over 24 h	Accumulation due to renal insufficiency
If seizures persist	Repeat loading dose	
	Consider benzodiazepine or anticonvulsant therapy	Lorazepam 0.5–2 mg IV Phenytoin 10–15 mg/kg at a rate not exceeding 50 mg/min

16.12 Blood Pressure Management

Pre-delivery monitoring after admission should include blood pressure measurements at least every hour. There should be a low threshold for arterial cannulation in severe cases. Indications for invasive blood pressure monitoring include persistent hypertension, need for intravenous infusion of potent vasodilators, or the inability to accurately measure blood pressure with an automated cuff. Automated blood pressure cuffs that use an oscillometry are often unreliable in patients with severe preeclampsia [68], and the accuracy of the measurements should verified with manual auscultation.

The primary goal of antihypertensive treatment is to prevent maternal complications associated with hypertensive emergencies; however, care must be taken if possible to avoid decreasing uteroplacental perfusion. Treatment approaches depend on the severity of blood pressure derangement and the expected time to delivery. Treatment of severe-range blood pressure (160 mmHg systolic and 110 mmHg diastolic) should be initiated with intravenous medications with a target blood pressure of 130–150/80–100 mmHg prior to

Table 16.9 Medications for the treatment of hypertension in preeclampsia

	Medication	Dose	Side effect
Oral			
Beta-blockade	Labetalol	100–300 mg thrice daily	
Calcium channel blockade	Nifedipine	10–40 mg daily	Headache Tachycardia
Alpha-1 blockade	Urapidil	30–180 mg daily	
	Ketanserin	40 mg twice daily	
Intravenous			
Direct vasodilation	Hydralazine	5 mg every 20 min (20 mg maximum)	Hypotension Tachycardia/palpitations Headache Oliguria
Beta-blockade	Labetalol	10–200 mg	
	Esmolol	10–100 mg	Fetal bradycardia
Nitrates	Nitroprusside	0.3–10 mcg/kg/min	Tachycardia Hypotension Cyanide toxicity especially with renal impairment
	Nitroglycerin	0.4–10 mcg/kg/min	Tachycardia Hypotension Headache

delivery (Table 16.9). Fetal monitoring can be used to ensure that adequate perfusion is maintained upon reduction in blood pressure. However, it is imperative to avoid under-treating the mother due to concerns regarding the fetus.

Beta-blockade has become a popular choice for the initial treatment of hypertension in pregnancy. Labetalol is generally considered first-line therapy for both oral and intravenous treatment due to a low frequency of side effects; however, a second agent is sometimes required to treat persistent hypertension [69]. Esmolol is usually avoided due to an association with fetal bradycardia [70, 71]. One specific use of esmolol might be for blunting of the hemodynamic response to endotracheal intubation.

Direct-acting vasodilator medications are considered second-line agents for the treatment of persistent hypertension, although they are associated with greater risk of hypoperfusion of the fetus. Hydralazine is associated with a higher frequency of hypotension during initial therapy, as well as with a trend toward a higher incidence of fetal heart rate abnormalities and urgent cesarean delivery in randomized trials [69]. Both nitroprusside and nitroglycerin may be used in the pregnant woman; however, the high incidence of hypotension and headache associated with the cerebral vasodilation limit their use to resistant cases. Titration may be guided by invasive direct arterial monitoring.

Calcium channel blockers are also highly effective medications for the treatment of hypertension in pregnancy. Compared with beta-blockade, alpha-1 blockade, and hydralazine, women treated with calcium channel blockers are less likely to experience persistent hypertension, to need a second-line agent, or to have fetal heart rate abnormalities [69]. The primary deterrent to the front line use of calcium channel blockers is the high incidence of maternal headache, which can confuse the diagnosis of preeclampsia with severe features.

16.13 Oxygenation

Pulmonary edema, which complicates up to 3% of pregnancies affected by hypertensive disorders, is associated with a significantly worse prognosis [45]. We recommend use of continuous pulse oximetry upon escalation of medication regimens or worsening clinical status. Desaturations should be investigated with a chest

X-ray and arterial blood gas. Lung ultrasound, specifically the presence of B-lines, has been shown to be of value in early identification of pulmonary edema in this population [72]. Treatment includes supplemental oxygen, diuresis with furosemide (5–40 mg), fluid restriction, and respiratory support (e.g., mechanical ventilation) in severe cases. The differential diagnosis includes magnesium toxicity, which can cause hypoventilation and respiratory depression and pneumonia, pulmonary thromboembolism, and noncardiogenic pulmonary edema, including that secondary to amniotic fluid embolism.

16.14 Fluid Administration

Accurate volume assessment can be challenging in the patient with severe preeclampsia. Pulse pressure variation may not accurately predict volume responsiveness in these patients [36]. Similarly, urine output may be inaccurate due to the high incidence of renal injury in these patients. Urine output of less than 1 cc/kg/h. should be investigated for potential renal impairment. Fluid administration should be used only after demonstrating that the patient has prerenal failure, as the volume of fluid administered during labor and delivery correlates with postpartum complications including pulmonary edema. Until volume status and cardiac function are assessed, women with hypertensive disorders of pregnancy should be treated with mild fluid restriction prior to delivery. Intravenous fluid should be minimized to <1 mL/kg/h, except for the treatment of medically induced hypotension (e.g., antihypertensive medication or regional anesthesia) or blood loss. A retrospective review of cases in which fluid restriction was practiced found a low complication rate, including less than 1% incidence of renal insufficiency [73].

Central venous catheterization may be appropriate in order to administer potent vasodilatory medications, such as nitroprusside or nitroglycerine, or for repeated venous blood sampling when peripheral venous access is difficult in the absence of arterial access, but it is rarely justified nowadays for assessing central venous or pulmonary pressures. Studies have demonstrated that measurements of central venous pressures do not correlate with cardiac volumes and function [30].

Regarding the use of a pulmonary artery (PA) catheter, there is no randomized study in the obstetric population which demonstrates benefit from its use. Even those studies claiming that the use of a PA catheter was subjectively beneficial in 93% of 100 cases noted a 4% incidence of complications due to catheter placement and a high rate of severe renal failure (11%) and even death (3%) [74]. Furthermore, studies in other populations failed to demonstrate that management directed following PA catheter data improved outcome. Thus, routine placement of PA catheters in women with hypertensive disorders of pregnancy is not recommended.

Instead, transthoracic echocardiography (TTE) is gaining popularity for use in these cases [34]. At this time, in part due to the lack of universal training in this modality, and also the lack of comparative outcome studies, this remains speculative but promising. This modality is discussed in more detail in the chapter on Echocardiography (see Chap. 13).

16.15 Delivery of the Fetus

Because removal of the fetus and placenta are the definitive treatment for preeclampsia, the timing of delivery must be considered. In the stable patient, expectant management can be used safely, providing time to administer corticosteroids to the fetus between 24 and 34 weeks of gestation. Worsening maternal condition, or evidence of other complications, such as placental abruption and DIC, should lead to immediate delivery.

16.16 Conclusion

Preeclampsia is one of the leading causes of maternal mortality and major morbidity, and one of the more frequent causes of ICU admission in pregnancy. Reviews of the quality of care have suggested that close to half of women who die have received inadequate care that contributed to

their demise. While the only "cure" for preeclampsia is delivery, additional care should focus on preventing further organ injury. This includes prevention of eclampsia, control of hypertension, and supportive care. Monitoring should be focused on identification and prevention of progressive organ injury.

References

1. Kuklina EV, Ayala C, Callaghan WM. Hypertensive disorders and severe obstetric morbidity in the United States. Obstet Gynecol. 2009;113(6):1299–306. https://doi.org/10.1097/AOG.0b013e3181a45b25.
2. Callaghan WM, Mackay AP, Berg CJ. Identification of severe maternal morbidity during delivery hospitalizations, United States, 1991–2003. Am J Obstet Gynecol. 2008;199(2):133. e131-138. https://doi.org/10.1016/j.ajog.2007.12.020.
3. Caughey AB, Stotland NE, Washington AE, Escobar GJ. Maternal ethnicity, paternal ethnicity, and parental ethnic discordance: predictors of preeclampsia. Obstet Gynecol. 2005;106(1):156–61. https://doi.org/10.1097/01.AOG.0000164478.91731.06.
4. Wallis AB, Saftlas AF, Hsia J, Atrash HK. Secular trends in the rates of preeclampsia, eclampsia, and gestational hypertension, United States, 1987–2004. Am J Hypertens. 2008;21(5):521–6. https://doi.org/10.1038/ajh.2008.20.
5. Osungbade KO, Ige OK. Public health perspectives of preeclampsia in developing countries: implication for health system strengthening. J Pregnancy. 2011;2011:481095. https://doi.org/10.1155/2011/481095.
6. WHO. Make every mother and child count, in The world health report 2005. 2005. Last accessed 13-Sep-2018 at http://www.who.int/whr/2005/whr2005_en.pdf
7. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller A-B, Daniels J, Gülmezoglu AM, Temmerman M, Alkema L. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014;2(6):e323–33. https://doi.org/10.1016/S2214-109X(14)70227-X.
8. MacKay AP, Berg CJ, Atrash HK. Pregnancy-related mortality from preeclampsia and eclampsia. Obstet Gynecol. 2001;97(4):533–8.
9. Main EK, McCain CL, Morton CH, Holtby S, Lawton ES. Pregnancy-related mortality in California: causes, characteristics, and improvement opportunities. Obstet Gynecol. 2015;125(4):938–47. https://doi.org/10.1097/AOG.0000000000000746.
10. Saucedo M, Deneux-Tharaux C, Bouvier-Colle MH, French National Experts Committee on Maternal M. Ten years of confidential inquiries into maternal deaths in France, 1998–2007. Obstet Gynecol. 2013;122(4):752–60. https://doi.org/10.1097/AOG.0b013e31829fc38c.
11. Gynecologists ACoOa, The Society for Maternal-Fetal M, Kilpatrick SK, Ecker JL. Severe maternal morbidity: screening and review. Am J Obstet Gynecol. 2016;215(3):B17–22. https://doi.org/10.1016/j.ajog.2016.07.050.
12. Lisonkova S, Sabr Y, Mayer C, Young C, Skoll A, Joseph KS. Maternal morbidity associated with early-onset and late-onset preeclampsia. Obstet Gynecol. 2014;124(4):771–81. https://doi.org/10.1097/AOG.0000000000000472.
13. Umo-Etuk J, Lumley J, Holdcroft A. Critically ill parturient women and admission to intensive care: a 5-year review. Int J Obstet Anesth. 1996;5(2):79–84.
14. Chantry AA, Deneux-Tharaux C, Bonnet MP, Bouvier-Colle MH. Pregnancy-related ICU admissions in France: trends in rate and severity, 2006–2009. Crit Care Med. 2015;43(1):78–86. https://doi.org/10.1097/CCM.0000000000000601.
15. Wanderer JP, Leffert LR, Mhyre JM, Kuklina EV, Callaghan WM, Bateman BT. Epidemiology of obstetric-related ICU admissions in Maryland: 1999-2008*. Crit Care Med. 2013;41(8):1844–52. https://doi.org/10.1097/CCM.0b013e31828a3e24.
16. Theilen LH, Fraser A, Hollingshaus MS, Schliep KC, Varner MW, Smith KR, Esplin MS. All-cause and cause-specific mortality after hypertensive disease of pregnancy. Obstet Gynecol. 2016;128(2):238–44. https://doi.org/10.1097/AOG.0000000000001534.
17. Kessous R, Shoham-Vardi I, Pariente G, Sergienko R, Sheiner E. Long-term maternal atherosclerotic morbidity in women with pre-eclampsia. Heart. 2015;101(6):442–6. https://doi.org/10.1136/heartjnl-2014-306571.
18. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ. 2007;335(7627):974. https://doi.org/10.1136/bmj.39335.385301.BE.
19. Poorthuis MH, Algra AM, Algra A, Kappelle LJ, Klijn CJ. Female- and male-specific risk factors for stroke: a systematic review and meta-analysis. JAMA Neurol. 2017;74(1):75–81. https://doi.org/10.1001/jamaneurol.2016.3482.
20. American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' task force on hypertension in pregnancy. Obstet Gynecol. 2013;122(5):1122–31. https://doi.org/10.1097/01.AOG.0000437382.03963.88.
21. Duley L, Henderson-Smart DJ, Meher S, King JF. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database Syst Rev. 2007;2:CD004659. https://doi.org/10.1002/14651858.CD004659.pub2.
22. Soleymanlou N, Jurisica I, Nevo O, Ietta F, Zhang X, Zamudio S, Post M, Caniggia I. Molecular evidence of placental hypoxia in preeclampsia. J Clin

Endocrinol Metab. 2005;90(7):4299–308. https://doi.org/10.1210/jc.2005-0078.
23. Sharma A, Satyam A, Sharma JB. Leptin, IL-10 and inflammatory markers (TNF-alpha, IL-6 and IL-8) in pre-eclamptic, normotensive pregnant and healthy non-pregnant women. Am J Reprod Immunol. 2007;58(1):21–30. https://doi.org/10.1111/j.1600-0897.2007.00486.x.
24. Many A, Hubel CA, Fisher SJ, Roberts JM, Zhou Y. Invasive cytotrophoblasts manifest evidence of oxidative stress in preeclampsia. Am J Pathol. 2000;156(1):321–31. https://doi.org/10.1016/S0002-9440(10)64733-5.
25. Brosens IA, Robertson WB, Dixon HG. The role of the spiral arteries in the pathogenesis of preeclampsia. Obstet Gynecol Annu. 1972;1:177–91.
26. Meekins JW, Pijnenborg R, Hanssens M, McFadyen IR, van Asshe A. A study of placental bed spiral arteries and trophoblast invasion in normal and severe pre-eclamptic pregnancies. Br J Obstet Gynaecol. 1994;101(8):669–74.
27. Esser S, Wolburg K, Wolburg H, Breier G, Kurzchalia T, Risau W. Vascular endothelial growth factor induces endothelial fenestrations in vitro. J Cell Biol. 1998;140(4):947–59.
28. Nagamatsu T, Fujii T, Kusumi M, Zou L, Yamashita T, Osuga Y, Momoeda M, Kozuma S, Taketani Y. Cytotrophoblasts up-regulate soluble fms-like tyrosine kinase-1 expression under reduced oxygen: an implication for the placental vascular development and the pathophysiology of preeclampsia. Endocrinology. 2004;145(11):4838–45. https://doi.org/10.1210/en.2004-0533.
29. Gu Y, Lewis DF, Wang Y. Placental productions and expressions of soluble endoglin, soluble fms-like tyrosine kinase receptor-1, and placental growth factor in normal and preeclamptic pregnancies. J Clin Endocrinol Metab. 2008;93(1):260–6. https://doi.org/10.1210/jc.2007-1550.
30. Cotton DB, Gonik B, Dorman K, Harrist R. Cardiovascular alterations in severe pregnancy-induced hypertension: relationship of central venous pressure to pulmonary capillary wedge pressure. Am J Obstet Gynecol. 1985;151(6):762–4.
31. Shahul S, Rhee J, Hacker MR, Gulati G, Mitchell JD, Hess P, Mahmood F, Arany Z, Rana S, Talmor D. Subclinical left ventricular dysfunction in preeclamptic women with preserved left ventricular ejection fraction: a 2D speckle-tracking imaging study. Circ Cardiovasc Imaging. 2012;5(6):734–9. https://doi.org/10.1161/CIRCIMAGING.112.973818.
32. Lees MM. Central circulatory responses in normotensive and hypertensive pregnancy. Postgrad Med J. 1979;55(643):311–4.
33. Visser W, Wallenburg HC. Central hemodynamic observations in untreated preeclamptic patients. Hypertension. 1991;17(6 Pt 2):1072–7.
34. Dennis AT. Transthoracic echocardiography in women with preeclampsia. Curr Opin Anaesthesiol. 2015;28(3):254–60. https://doi.org/10.1097/ACO.0000000000000182.
35. Patten IS, Rana S, Shahul S, Rowe GC, Jang C, Liu L, Hacker MR, Rhee JS, Mitchell J, Mahmood F, Hess P, Farrell C, Koulisis N, Khankin EV, Burke SD, Tudorache I, Bauersachs J, del Monte F, Hilfiker-Kleiner D, Karumanchi SA, Arany Z. Cardiac angiogenic imbalance leads to peripartum cardiomyopathy. Nature. 2012;485(7398):333–8. https://doi.org/10.1038/nature11040.
36. Brun C, Zieleskiewicz L, Textoris J, Muller L, Bellefleur JP, Antonini F, Tourret M, Ortega D, Vellin A, Lefrant JY, Boubli L, Bretelle F, Martin C, Leone M. Prediction of fluid responsiveness in severe preeclamptic patients with oliguria. Intensive Care Med. 2013;39(4):593–600. https://doi.org/10.1007/s00134-012-2770-2.
37. Seal SL, Ghosh D, Kamilya G, Mukherji J, Hazra A, Garain P. Does route of delivery affect maternal and perinatal outcome in women with eclampsia? A randomized controlled pilot study. Am J Obstet Gynecol. 2012;206(6):484.e1-7. https://doi.org/10.1016/j.ajog.2012.04.009.
38. Izci B, Riha RL, Martin SE, Vennelle M, Liston WA, Dundas KC, Calder AA, Douglas NJ. The upper airway in pregnancy and pre-eclampsia. Am J Respir Crit Care Med. 2003;167(2):137–40. https://doi.org/10.1164/rccm.200206-590OC.
39. Ahuja P, Jain D, Bhardwaj N, Jain K, Gainder S, Kang M. Airway changes following labor and delivery in preeclamptic parturients: a prospective case control study. Int J Obstet Anesth. 2018;33:17–22. https://doi.org/10.1016/j.ijoa.2017.10.005.
40. Boutonnet M, Faitot V, Katz A, Salomon L, Keita H. Mallampati class changes during pregnancy, labour, and after delivery: can these be predicted? Br J Anaesth. 2010;104(1):67–70. https://doi.org/10.1093/bja/aep356.
41. da Silva EG, de Godoy I, de Oliveira Antunes LC, da Silva EG, Peracoli JC. Respiratory parameters and exercise functional capacity in preeclampsia. Hypertens Pregnancy. 2010;29(3):301–9. https://doi.org/10.3109/10641950902779271.
42. Templeton AA, Kelman GR. Arterial blood gases in pre-eclampsia. Br J Obstet Gynaecol. 1977;84(4):290–3.
43. Gandhi S, Sun D, Park AL, Hladunewich M, Silversides CK, Ray JG. The pulmonary edema preeclampsia evaluation (PEPE) study. J Obstet Gynaecol Can. 2014;36(12):1065–70. https://doi.org/10.1016/S1701-2163(15)30383-2.
44. Easterling TR, Benedetti TJ. Preeclampsia: a hyperdynamic disease model. Am J Obstet Gynecol. 1989;160(6):1447–53.
45. Dennis AT, Solnordal CB. Acute pulmonary oedema in pregnant women. Anaesthesia. 2012;67(6):646–59. https://doi.org/10.1111/j.1365-2044.2012.07055.x.
46. Hecht JL, Ordi J, Carrilho C, Ismail MR, Zsengeller ZK, Karumanchi SA, Rosen S. The pathology of eclampsia: an autopsy series. Hypertens Pregnancy.

2017;36(3):259–68. https://doi.org/10.1080/10641955.2017.1329430.
47. Manas KJ, Welsh JD, Rankin RA, Miller DD. Hepatic hemorrhage without rupture in preeclampsia. N Engl J Med. 1985;312(7):424–6. https://doi.org/10.1056/NEJM198502143120707.
48. Barton JR, Sibai BM. Hepatic imaging in HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count). Am J Obstet Gynecol. 1996;174(6):1820–5. discussion 1825-1827
49. Wicke C, Pereira PL, Neeser E, Flesch I, Rodegerdts EA, Becker HD. Subcapsular liver hematoma in HELLP syndrome: evaluation of diagnostic and therapeutic options—a unicenter study. Am J Obstet Gynecol. 2004;190(1):106–12. https://doi.org/10.1016/j.ajog.2003.08.029.
50. Terasaki KK, Quinn MF, Lundell CJ, Finck EJ, Pentecost MJ. Spontaneous hepatic hemorrhage in preeclampsia: treatment with hepatic arterial embolization. Radiology. 1990;174(3 Pt 2):1039–41. https://doi.org/10.1148/radiology.174.3.174-3-1039.
51. Yang SB, Goo DE, Chang YW, Kim YJ, Hwang IC, Han HS, Yoon JH, Lee TI. Spontaneous hepatic rupture associated with preeclampsia: treatment with hepatic artery embolization. J Korean Soc Radiol. 2010;63(1):29–32. https://doi.org/10.3348/jksr.2010.63.1.29.
52. Sharma SK, Philip J, Whitten CW, Padakandla UB, Landers DF. Assessment of changes in coagulation in parturients with preeclampsia using thromboelastography. Anesthesiology. 1999;90(2):385–90.
53. Wong CA, Liu S, Glassenberg R. Comparison of thrombelastography with common coagulation tests in preeclamptic and healthy parturients. Reg Anesth. 1995;20(6):521–7.
54. Samuels P, Main EK, Tomaski A, Mennuti MT, Gabbe SG, Cines DB. Abnormalities in platelet antiglobulin tests in preeclamptic mothers and their neonates. Am J Obstet Gynecol. 1987;157(1):109–13.
55. Zhang S, Dong J, Liu B. Evaluation and its clinical significance of anti-platelet granule membrane protein-140 autoantibodies and anticalmodulin antibody in patients with severe pregnancy-induced hypertension. Zhonghua Fu Chan Ke Za Zhi. 1995;30(11):665–7.
56. Nguyen MT, Maynard SE, Kimmel PL. Misapplications of commonly used kidney equations: renal physiology in practice. Clin J Am Soc Nephrol. 2009;4(3):528–34. https://doi.org/10.2215/CJN.05731108.
57. Hildebrand AM, Liu K, Shariff SZ, Ray JG, Sontrop JM, Clark WF, Hladunewich MA, Garg AX. Characteristics and outcomes of AKI treated with dialysis during pregnancy and the postpartum period. J Am Soc Nephrol. 2015;26(12):3085–91. https://doi.org/10.1681/ASN.2014100954.
58. Prakash J, Kumar H, Sinha DK, Kedalaya PG, Pandey LK, Srivastava PK, Raja R, Usha. Acute renal failure in pregnancy in a developing country: twenty years of experience. Ren Fail. 2006;28(4):309–13.
59. Basso O, Rasmussen S, Weinberg CR, Wilcox AJ, Irgens LM, Skjaerven R. Trends in fetal and infant survival following preeclampsia. JAMA. 2006;296(11):1357–62. https://doi.org/10.1001/jama.296.11.1357.
60. Klungsoyr K, Morken NH, Irgens L, Vollset SE, Skjaerven R. Secular trends in the epidemiology of pre-eclampsia throughout 40 years in Norway: prevalence, risk factors and perinatal survival. Paediatr Perinat Epidemiol. 2012;26(3):190–8. https://doi.org/10.1111/j.1365-3016.2012.01260.x.
61. Egbor M, Ansari T, Morris N, Green CJ, Sibbons PD. Morphometric placental villous and vascular abnormalities in early- and late-onset pre-eclampsia with and without fetal growth restriction. BJOG. 2006;113(5):580–9. https://doi.org/10.1111/j.1471-0528.2006.00882.x.
62. Mendola P, Mumford SL, Mannisto TI, Holston A, Reddy UM, Laughon SK. Controlled direct effects of preeclampsia on neonatal health after accounting for mediation by preterm birth. Epidemiology. 2015;26(1):17–26. https://doi.org/10.1097/EDE.0000000000000213.
63. Ananth CV, Basso O. Impact of pregnancy-induced hypertension on stillbirth and neonatal mortality. Epidemiology. 2010;21(1):118–23. https://doi.org/10.1097/EDE.0b013e3181c297af.
64. Ananth CV, Lavery JA, Vintzileos AM, Skupski DW, Varner M, Saade G, Biggio J, Williams MA, Wapner RJ, Wright JD. Severe placental abruption: clinical definition and associations with maternal complications. Am J Obstet Gynecol. 2016;214(2):272.e1–9. https://doi.org/10.1016/j.ajog.2015.09.069.
65. Druzin ML, Shields LE, Peterson NL, Cape V. Preeclampsia toolkit: improving health care response to preeclampsia. California Maternal Quality Care Collaborative. 2013. Last accessed 16-Sep-2018 at https://pqcnc-documents.s3.amazonaws.com/cmop/cmopresources/CMQCC_Preeclampsia_Toolkit_1.17.14.pdf
66. Altman D, Carroli G, Duley L, Farrell B, Moodley J, Neilson J, Smith D, Magpie Trial Collaboration G. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. Lancet. 2002;359(9321):1877–90.
67. Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. Lancet. 1995;345(8963):1455–63.
68. Natarajan P, Shennan AH, Penny J, Halligan AW, de Swiet M, Anthony J. Comparison of auscultatory and oscillometric automated blood pressure monitors in the setting of preeclampsia. Am J Obstet Gynecol. 1999;181(5 Pt 1):1203–10.
69. von Dadelszen P, Magee LA. Antihypertensive medications in management of gestational hypertension-preeclampsia. Clin Obstet Gynecol. 2005;48(2):441–59.

70. Larson CP Jr, Shuer LM, Cohen SE. Maternally administered esmolol decreases fetal as well as maternal heart rate. J Clin Anesth. 1990;2(6):427–9.
71. Ducey JP, Knape KG. Maternal esmolol administration resulting in fetal distress and cesarean section in a term pregnancy. Anesthesiology. 1992;77(4):829–32.
72. Zieleskiewicz L, Contargyris C, Brun C, Touret M, Vellin A, Antonini F, Muller L, Bretelle F, Martin C, Leone M. Lung ultrasound predicts interstitial syndrome and hemodynamic profile in parturients with severe preeclampsia. Anesthesiology. 2014;120(4):906–14. https://doi.org/10.1097/ALN.0000000000000102.
73. Tuffnell DJ, Jankowicz D, Lindow SW, Lyons G, Mason GC, Russell IF, Walker JJ, Yorkshire Obstetric Critical Care G. Outcomes of severe pre-eclampsia/eclampsia in Yorkshire 1999/2003. BJOG. 2005;112(7):875–80. https://doi.org/10.1111/j.1471-0528.2005.00565.x.
74. Gilbert WM, Towner DR, Field NT, Anthony J. The safety and utility of pulmonary artery catheterization in severe preeclampsia and eclampsia. Am J Obstet Gynecol. 2000;182(6):1397–403. https://doi.org/10.1067/mob.2000.106179.
75. Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. Obstet Gynecol. 2003;102(1):181–92.
76. Chames MC, Livingston JC, Ivester TS, Barton JR, Sibai BM. Late postpartum eclampsia: a preventable disease? Am J Obstet Gynecol. 2002;186(6):1174–7.
77. Saftlas AF, Olson DR, Franks AL, Atrash HK, Pokras R. Epidemiology of preeclampsia and eclampsia in the United States, 1979–1986. Am J Obstet Gynecol. 1990;163(2):460–5.
78. Bianco A, Stone J, Lynch L, Lapinski R, Berkowitz G, Berkowitz RL. Pregnancy outcome at age 40 and older. Obstet Gynecol. 1996;87(6):917–22.
79. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. BMJ. 2005;330(7491):565. https://doi.org/10.1136/bmj.38380.674340.E0.
80. Villa PM, Marttinen P, Gillberg J, Lokki AI, Majander K, Orden MR, Taipale P, Pesonen A, Raikkonen K, Hamalainen E, Kajantie E, Laivuori H. Cluster analysis to estimate the risk of pre-eclampsia in the high-risk prediction and prevention of preeclampsia and intrauterine growth restriction (PREDO) study. PLoS One. 2017;12(3):e0174399. https://doi.org/10.1371/journal.pone.0174399.
81. O'Brien TE, Ray JG, Chan WS. Maternal body mass index and the risk of preeclampsia: a systematic overview. Epidemiology. 2003;14(3):368–74.
82. Bateman BT, Shaw KM, Kuklina EV, Callaghan WM, Seely EW, Hernandez-Diaz S. Hypertension in women of reproductive age in the United States: NHANES 1999–2008. PLoS One. 2012;7(4):e36171. https://doi.org/10.1371/journal.pone.0036171.
83. Goodwin AA, Mercer BM. Does maternal race or ethnicity affect the expression of severe preeclampsia? Am J Obstet Gynecol. 2005;193(3 Pt 2):973–8. https://doi.org/10.1016/j.ajog.2005.05.047.
84. Tucker MJ, Berg CJ, Callaghan WM, Hsia J. The Black-White disparity in pregnancy-related mortality from 5 conditions: differences in prevalence and case-fatality rates. Am J Public Health. 2007;97(2):247–51. https://doi.org/10.2105/AJPH.2005.072975.
85. Wolf M, Shah A, Jimenez-Kimble R, Sauk J, Ecker JL, Thadhani R. Differential risk of hypertensive disorders of pregnancy among Hispanic women. J Am Soc Nephrol. 2004;15(5):1330–8.
86. Esplin MS, Fausett MB, Fraser A, Kerber R, Mineau G, Carrillo J, Varner MW. Paternal and maternal components of the predisposition to preeclampsia. N Engl J Med. 2001;344(12):867–72. https://doi.org/10.1056/NEJM200103223441201.
87. Nilsson E, Salonen Ros H, Cnattingius S, Lichtenstein P. The importance of genetic and environmental effects for pre-eclampsia and gestational hypertension: a family study. BJOG. 2004;111(3):200–6.
88. Salonen Ros H, Lichtenstein P, Lipworth L, Cnattingius S. Genetic effects on the liability of developing pre-eclampsia and gestational hypertension. Am J Med Genet. 2000;91(4):256–60.
89. Lie RT, Rasmussen S, Brunborg H, Gjessing HK, Lie-Nielsen E, Irgens LM. Fetal and maternal contributions to risk of pre-eclampsia: population based study. BMJ. 1998;316(7141):1343–7.
90. Cnattingius S, Reilly M, Pawitan Y, Lichtenstein P. Maternal and fetal genetic factors account for most of familial aggregation of preeclampsia: a population-based Swedish cohort study. Am J Med Genet A. 2004;130A(4):365–71. https://doi.org/10.1002/ajmg.a.30257.
91. Bateman BT, Bansil P, Hernandez-Diaz S, Mhyre JM, Callaghan WM, Kuklina EV. Prevalence, trends, and outcomes of chronic hypertension: a nationwide sample of delivery admissions. Am J Obstet Gynecol. 2012;206(2):134. e131-138. https://doi.org/10.1016/j.ajog.2011.10.878.
92. Sibai BM. Chronic hypertension in pregnancy. Obstet Gynecol. 2002;100(2):369–77.
93. Garner PR, D'Alton ME, Dudley DK, Huard P, Hardie M. Preeclampsia in diabetic pregnancies. Am J Obstet Gynecol. 1990;163(2):505–8.
94. Mazar RM, Srinivas SK, Sammel MD, Andrela CM, Elovitz MA. Metabolic score as a novel approach to assessing preeclampsia risk. Am J Obstet Gynecol. 2007;197(4):411.e1-5. https://doi.org/10.1016/j.ajog.2007.07.014.
95. Bartsch E, Medcalf KE, Park AL, Ray JG, High Risk of Pre-eclampsia Identification G. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. BMJ. 2016;353:i1753. https://doi.org/10.1136/bmj.i1753.
96. Coonrod DV, Hickok DE, Zhu K, Easterling TR, Daling JR. Risk factors for preeclampsia in twin

pregnancies: a population-based cohort study. Obstet Gynecol. 1995;85(5 Pt 1):645–50.
97. Lee CJ, Hsieh TT, Chiu TH, Chen KC, Lo LM, Hung TH. Risk factors for pre-eclampsia in an Asian population. Int J Gynaecol Obstet. 2000;70(3):327–33.
98. Eskenazi B, Fenster L, Sidney S. A multivariate analysis of risk factors for preeclampsia. JAMA. 1991;266(2):237–41.
99. Hernandez-Diaz S, Toh S, Cnattingius S. Risk of pre-eclampsia in first and subsequent pregnancies: prospective cohort study. BMJ. 2009;338:b2255. https://doi.org/10.1136/bmj.b2255.
100. Wikstrom AK, Stephansson O, Cnattingius S. Previous preeclampsia and risks of adverse outcomes in subsequent nonpreeclamptic pregnancies. Am J Obstet Gynecol. 2011;204(2):148.e1-6. https://doi.org/10.1016/j.ajog.2010.09.003.
101. Mostello D, Kallogjeri D, Tungsiripat R, Leet T. Recurrence of preeclampsia: effects of gestational age at delivery of the first pregnancy, body mass index, paternity, and interval between births. Am J Obstet Gynecol. 2008;199(1):55.e1-7. https://doi.org/10.1016/j.ajog.2007.11.058.
102. Odegard RA, Vatten LJ, Nilsen ST, Salvesen KA, Austgulen R. Risk factors and clinical manifestations of pre-eclampsia. BJOG. 2000;107(11):1410–6.
103. Santema JG, Koppelaar I, Wallenburg HC. Hypertensive disorders in twin pregnancy. Eur J Obstet Gynecol Reprod Biol. 1995;58(1):9–13.
104. Skupski DW, Nelson S, Kowalik A, Polaneczky M, Smith-Levitin M, Hutson JM, Rosenwaks Z. Multiple gestations from in vitro fertilization: successful implantation alone is not associated with subsequent preeclampsia. Am J Obstet Gynecol. 1996;175(4 Pt 1):1029–32.
105. Koga K, Osuga Y, Tajima T, Hirota Y, Igarashi T, Fujii T, Yano T, Taketani Y. Elevated serum soluble fms-like tyrosine kinase 1 (sFlt1) level in women with hydatidiform mole. Fertil Steril. 2010;94(1):305–8. https://doi.org/10.1016/j.fertnstert.2009.02.015.
106. Zhao L, Bracken MB, DeWan AT. Genome-wide association study of pre-eclampsia detects novel maternal single nucleotide polymorphisms and copy-number variants in subsets of the hyperglycemia and adverse pregnancy outcome (HAPO) study cohort. Ann Hum Genet. 2013;77(4):277–87. https://doi.org/10.1111/ahg.12021.
107. Johnson MP, Brennecke SP, East CE, Goring HH, Kent JW Jr, Dyer TD, Said JM, Roten LT, Iversen AC, Abraham LJ, Heinonen S, Kajantie E, Kere J, Kivinen K, Pouta A, Laivuori H, Group FS, Austgulen R, Blangero J, Moses EK. Genome-wide association scan identifies a risk locus for preeclampsia on 2q14, near the inhibin, beta B gene. PLoS One. 2012;7(3):e33666. https://doi.org/10.1371/journal.pone.0033666.
108. Zhao L, Triche EW, Walsh KM, Bracken MB, Saftlas AF, Hoh J, Dewan AT. Genome-wide association study identifies a maternal copy-number deletion in PSG11 enriched among preeclampsia patients. BMC Pregnancy Childbirth. 2012;12:61. https://doi.org/10.1186/1471-2393-12-61.
109. Chappell S, Morgan L. Searching for genetic clues to the causes of pre-eclampsia. Clin Sci (Lond). 2006;110(4):443–58. https://doi.org/10.1042/CS20050323.
110. Jebbink J, Wolters A, Fernando F, Afink G, van der Post J, Ris-Stalpers C. Molecular genetics of preeclampsia and HELLP syndrome—a review. Biochim Biophys Acta. 2012;1822(12):1960–9. https://doi.org/10.1016/j.bbadis.2012.08.004.
111. Moses EK, Fitzpatrick E, Freed KA, Dyer TD, Forrest S, Elliott K, Johnson MP, Blangero J, Brennecke SP. Objective prioritization of positional candidate genes at a quantitative trait locus for pre-eclampsia on 2q22. Mol Hum Reprod. 2006;12(8):505–12. https://doi.org/10.1093/molehr/gal056.
112. van Dijk M, Mulders J, Poutsma A, Konst AA, Lachmeijer AM, Dekker GA, Blankenstein MA, Oudejans CB. Maternal segregation of the Dutch preeclampsia locus at 10q22 with a new member of the winged helix gene family. Nat Genet. 2005;37(5):514–9. https://doi.org/10.1038/ng1541.
113. Yong HE, Melton PE, Johnson MP, Freed KA, Kalionis B, Murthi P, Brennecke SP, Keogh RJ, Moses EK. Genome-wide transcriptome directed pathway analysis of maternal pre-eclampsia susceptibility genes. PLoS One. 2015;10(5):e0128230. https://doi.org/10.1371/journal.pone.0128230.
114. Loset M, Mundal SB, Johnson MP, Fenstad MH, Freed KA, Lian IA, Eide IP, Bjorge L, Blangero J, Moses EK, Austgulen R. A transcriptional profile of the decidua in preeclampsia. Am J Obstet Gynecol. 2011;204(1):84. e81-27. https://doi.org/10.1016/j.ajog.2010.08.043.
115. Kleinrouweler CE, van Uitert M, Moerland PD, Ris-Stalpers C, van der Post JA, Afink GB. Differentially expressed genes in the pre-eclamptic placenta: a systematic review and meta-analysis. PLoS One. 2013;8(7):e68991. https://doi.org/10.1371/journal.pone.0068991.

Viral Infections in Obstetric Critical Care

17

Ryan C. Maves

Bullet Points

- Viral infections are common causes of critical illness in pregnancy and may be more severe than in the nonpregnant woman.
- Influenza viruses are the most common infectious cause of acute respiratory failure in pregnancy.
- PCR-based diagnostics are preferred when testing for influenza, and early treatment with neuraminidase inhibitors reduces mortality.
- Bacterial superinfection is common in severe viral respiratory infection. In cases of respiratory failure, empiric antibacterial therapy directed against pneumococci and staphylococci is advisable pending culture results.
- Viral encephalitis may be due to many different pathogens, but empiric intravenous acyclovir should be administered early to all pregnant women with suspected viral encephalitis until HSV and VZV infections have been excluded.
- There are limited effective therapies for viral encephalitis due to non-herpesviruses. IVIG, methylprednisolone, or plasmapheresis may be considered for acute disseminated encephalitis (ADEM).
- Fulminant hepatic failure (FHF) in pregnancy should receive treatment with N-acetylcysteine, in addition to any specific antiviral therapies if available.
- Specific therapies exist for acute viral hepatitis due to hepatitis B and herpesviruses (HSV, VZV, CMV, and possibly EBV).
- Dengue, Zika, and chikungunya virus infections have overlapping regions of endemicity and similar clinical syndromes.
- Severe dengue is managed supportively with fluids, organ support, and rarely blood products. Glucocorticoids are not effective in the treatment of dengue.

R. C. Maves (✉)
Infectious Diseases Division, Naval Medical Center, San Diego, CA, USA

Critical Care Medicine Service, Naval Medical Center, San Diego, CA, USA

Uniformed Services University, Bethesda, MD, USA
e-mail: Ryan.c.maves.mil@mail.mil

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_17

17.1 Introduction

Viral infections are common in pregnancy, with consequences for the health of both the fetus and the expectant mother. The exposures of a pregnant woman to viruses may be comparable to that of the larger community and are essentially unchanged from that of her prepregnancy self. However, changes in host immunology increase the pregnant woman's risk of disease as well as the severity of that disease following exposure to a circulating virus.

The immunologic changes of pregnancy are described in greater detail in Chap. 15. To briefly summarize, cell-mediated immunity typically downregulates in the third trimester and early postpartum period, increasing the woman's risk of infection by certain pathogens, including bacteria (e.g., listeriosis), fungi (e.g., coccidioidomycosis) and, most commonly, viruses. Physiologic changes inherent to pregnancy, such as decreased functional residual capacity in the respiratory system, may additionally increase the risk of severe disease requiring critical care following such an infection.

Although numerous viruses may infect pregnant women, infections of the respiratory tract, the central nervous system, and the liver are most likely to lead to critical illness. In addition, arboviral infections may produce severe syndromes that are becoming more common in our increasingly globalized world. It is unusual for the attending obstetrician, intensivist, or even infectious diseases specialist to know the specific etiology of a viral infection at the time of presentation. Therefore, the presenting syndrome should guide initial workup and empiric therapy while awaiting a specific diagnosis. In general, viral infections leading to critical illness do not specifically require expedited delivery of the fetus or consideration of pregnancy termination, unlike some other causes of obstetric critical illness (e.g., the HELLP syndrome, massive uterine hemorrhage). In addition, certain viral infections are associated with a high risk of transmission to healthcare staff, and precautions must be implemented to reduce risk to caregivers and other patients.

Viral infections associated with significant fetal abnormalities, such as rubella or cytomegalovirus, rarely produce life-threatening maternal disease and will not be discussed in detail here, except as they relate to maternal illness.

17.2 Influenza and Other Respiratory Viruses

Severe acute respiratory infection (ARI) is among the most common illnesses leading to intensive care unit admission among pregnant women, leading to 25% [1] of cases of respiratory failure and 12% of deaths [2] of pregnant women. A wide diversity of RNA and DNA viruses cause ARI in pregnant women. Influenza viruses, in particular, have a unique virulence: pregnant women represented 5% of cases of acute respiratory distress syndrome and 6–13% of deaths [3, 4] in the 2009–2010 H1N1 influenza epidemic. Overall mortality for pregnant women with severe influenza requiring critical care admission is estimated to be as high as 24% [1, 5], particularly in women requiring mechanical ventilation, despite a less than 10% overall mortality rate of pregnant women with acute respiratory failure in developed countries [1] (see Chap. 23). Extracorporeal membrane oxygenation (ECMO) has been used successfully in pregnant women with influenza, with a meta-analysis suggesting a maternal survival rate of 75% and a 70% rate of live birth, although this is limited by a small number of included studies [6] (see Chap. 14).

The burden of viral ARI has become easier to estimate in recent years, with the advent of widely available and rapid molecular diagnostic testing in resource-rich settings. Polymerase chain reaction (PCR)-based testing is the diagnostic test of choice for suspected viral ARI in a critically ill patient, regardless of pregnancy. These specimens may be obtained at the bedside via nasopharyngeal, oropharyngeal, or endotracheal aspiration and should be obtained routinely for hospitalized women with compatible clinical syndromes (i.e., fever, cough, airspace opacities, or hypoxemia). Existing commercial tests such as the GeneXpert Xpert Flu assay (Cepheid, Sunnyvale, California, USA) have a sensitivity and specificity for the detection of influenza in excess of 95% [7]; multiplex assays such as the FilmArray RP panel (BioFire Diagnostics, Salt Lake City, Utah, USA) detect a wider variety of respiratory viruses but at a potentially lower sensitivity of approximately 85% [8]. Rapid antigen testing for influenza is an alternative, but the lower sensitivity of these assays (60–65%) reduces their utility, especially with negative test results [9].

Evaluation for suspected viral ARI in the critically ill pregnant women includes PCR testing for relevant viruses where available, in addition to chest radiography and bacterial cultures of sputum. If multiplex PCR is not readily available, either influenza-specific PCR or rapid antigen testing is an alternative. If no such viral diagnostics are available, then empiric antiviral therapy for women with a compatible syndrome should be strongly considered.

Antiviral therapy with the neuraminidase inhibitor oseltamivir is associated with improved outcomes in severe influenza, based on retrospective studies that have included pregnant women; therapy within the first 48 h of symptom onset is preferred [10, 11]. There are no prospective studies of oseltamivir use in critically ill pregnant women. A retrospective series conducted by US Centers for Disease Control and Prevention (CDC) studied pregnant women requiring hospitalization during the 2009 H1N1 pandemic; in this study, women who received early neuraminidase inhibitor treatment (<2 days after the onset of symptoms) had decreased rates of ICU admission (9.4% versus 56.9%) and of death (0.5% versus 27%) compared with women treated more than 4 days after symptom onset, with the greatest risk noted in women in the third trimester [12]. Follow-up data on children born to pregnant women treated with oseltamivir have not shown evidence of drug-specific fetal complications [13, 14]. The standard dose of 75 mg twice daily for 5 days is given either orally or via an enteric tube [15]. Higher doses (150 mg twice daily) or more prolonged courses (up to 10 days) have not been associated with improved survival in either critically ill patients or pregnant women [16, 17].

In patients for whom enteral medications are not possible, peramivir is an intravenous neuraminidase inhibitor that is an acceptable alternative to oseltamivir. Peramivir is normally administered as a single 600 mg dose but may be considered for 5 days of therapy in severely ill patients, based on limited data. Specifically in pregnancy, there is some evidence of increased peramivir clearance which may support the more extended course of treatment [18–21]. Oseltamivir- and peramivir-resistant strains of influenza are well-described but unusual [22–24]. For such cases, intravenous zanamivir may be considered as an investigational agent (available via GlaxoSmithKline at gskclinicalsupportHD@gsk.com) [25, 26]. A small number of pregnant women have received intravenous zanamivir, but outcomes in those women have not been reported [26]. Inhaled zanamivir is not recommended in intubated patients [15].

As of 2020, there is an ongoing pandemic due to the Severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2), leading to a clinical syndrome known as coronavirus disease 2019 (Covid-19). At the time of this writing, clinical evidence regarding the severity of Covid-19 in pregnant women is limited to case series and retrospective observational data. An early case series from Wuhan, Hubei Province, China, at the onset of the pandemic described the course of 116 pregnant women with Covid-19; 8/116 (6.9%) of affected women had severe pneumonia requiring ICU admission, of whom 2/116 (1.7%) required endotracheal intubation and 1/116 (0.9%) required ECMO [27]. A systematic review of 33 studies more recently reported a total of 385 pregnant women with Covid-19 infection, of whom 17/385 (4.4%) required ICU admission and 6/385 (1.6%) required mechanical ventilation, with one death identified (1/385, 0.26%) [28]. Overall, the mortality risk of Covid-19 in pregnancy seems comparable to that of the general population, unlike the specific increased risk of influenza, although limitations in data quality at this phase of the pandemic require clinicians to be cautious in interpreting this information. Vertical transmission seems rare (and difficult to exclude from the possibility of iatrogenic, rather than maternal origin) [29].

Therapy for Covid-19 in pregnancy is presently limited to supportive care. Empiric therapy for community-acquired pneumonia is recommended for mechanically ventilated patients; it is reasonable to include pregnant women in this practice. Hydrocortisone for vasopressor-resistant shock, low tidal volume ventilation, and consideration of intravenous methylprednisolone for the acute respiratory distress syndrome (ARDS) are also recommended, in accordance with routine critical care practice [30]. A large number of investigational agents are under study for Covid-19, including novel antiviral agents such as remdesivir, inhibitors of the inflammatory cascade such as tociluzimab, and repurposed agents such as hydroxychloroquine. Remdesivir,

a nucleotide inhibitor of viral RNA-dependent RNA polymerase, has been administered to pregnant women with Covid-19 through compassionate use programs, but data on their outcomes are not currently available. Remdesivir has been administered safely to pregnant women with Ebola virus disease in a randomized trial, however, without evidence of increased risk [31].

There are limited specific antiviral therapies available for other respiratory viruses. Data in pregnancy is invariably limited, with much of the available evidence derived from the management of patients with hematologic malignancy. Ribavirin (administered intravenously, orally, or inhaled) has in vitro activity against several non-influenza respiratory viruses including adenoviruses, human metapneumovirus, respiratory syncytial virus (RSV), and parainfluenza; however, clinical evidence for its utility in patients without malignancy is limited [32–34]. Ribavirin has historically been considered to be contraindicated in pregnancy due to concern for teratogenicity as well as hemolysis. More recent data of ribavirin when used for chronic hepatitis C infection shows little direct evidence of teratogenicity, although the doses used are smaller than those used for critically ill patients [35]. As such, the use of ribavirin may be appropriate as a lifesaving intervention for the mother [35].

Cidofovir, a long-acting intravenous nucleotide analogue, may be considered for severe adenovirus infections, although embryotoxicity and fetal harm have been seen in animal studies at doses that are maternally toxic, and it is associated with nephrotoxicity [32, 36, 37]. Enterally administered brincidofovir is a prodrug of cidofovir that may have an improved safety profile in terms of nephrotoxicity [38]. Data regarding teratogenicity is currently lacking due to exclusion of pregnant women from studies using this drug for treatment of Ebola.

Intravenous immune globulin given in combination with aerosolized ribavirin may be preferred for severe RSV infection [39]. Palivizumab, an anti-RSV monoclonal antibody, is recommended only for prophylaxis and not for therapy; therefore it is not a relevant option once a pregnant woman is critically ill. Adjunctive glucocorticoids appear harmful in severe influenza and are not recommended [40].

Bacterial superinfection is common in severe viral ARI. Pneumococci and staphylococci (including methicillin-resistant *Staphylococcus aureus*) are frequent coinfections in severe influenza infections, occurring in 25–50% of critically ill patients [41]. The rate of post-influenza bacterial pneumonia in critically ill pregnant women does not appear to be higher than that in nonpregnant women (and may in fact be somewhat lower) [42]. Regardless, empiric therapy for community-acquired bacterial pneumonia is advisable in severe ARI until bacterial superinfection can be excluded, including coverage directed against MRSA in patients with influenza, metapneumovirus, or respiratory failure.

Staff protection: Respiratory viruses are contagious to hospital staff and to other patients. Appropriate precautions must be taken in the management of all patients infected with respiratory viruses to reduce the risk of transmission. In general, patients with suspected or confirmed respiratory viruses require the use of dedicated hospital room separated from other patients; if this is not feasible, cohorting of patients with a common infection (i.e., influenza A with other influenza A patients) may be acceptable. Seasonal influenza vaccination should be encouraged for all hospital staff, and clinical staff should wear masks when caring for these patients [43]. Standard surgical masks appear to be acceptable; studies comparing the risk of influenza acquisition showed comparable protective efficacy between surgical masks and N95 respirators, although N95 masks may be preferred in cases of airway procedures known to produce aerosols, i.e., endotracheal intubation and bronchoscopy [44, 45].

Certain highly pathogenic respiratory viruses require higher levels of respiratory protection, including the use of negative pressure isolation rooms, N95 respirators, or powered air-purifying respirators (PAPRs). Such viruses include SARS-CoV-2, related coronaviruses such as the Severe Acute Respiratory Syndrome-associated coronavirus (SARS-CoV), and the Middle East Respiratory Syndrome-associated coronavirus (MERS-CoV), as well as highly pathogenic avian influenza strains (H5N1, H7N9) [46]. The Infectious Diseases Society of America (IDSA) has recently published interim guidance on the appropriate use of personal protective equipment for staff safety in the care of patients with Covid-19; such recommendations are likely to be broadly applicable to other highly pathogenic respiratory viruses [47].

17.3 Neurotropic Viruses

Encephalitis is the typical presenting syndrome among pregnant women with neurologic viral infections requiring ICU admission and must be considered in women with unexplained delirium, fever, or focal neurologic signs including new-onset seizures. A specific pathogen may be elusive for many patients with suspected viral encephalitis. In all cases, infectious disease and neurology specialty consultation should be obtained.

Cerebrospinal fluid (CSF) analysis is required for the diagnosis of encephalitis. A lymphocyte-predominant pleocytosis with relatively normal protein and glucose levels is typical, although neutrophil predominance may be seen in early infections. Elevated CSF erythrocyte counts in the absence of traumatic lumbar puncture may be noted in cases of herpes simplex virus type 1 (HSV-1) encephalitis [48]. Bacterial infections, most notably *Listeria monocytogenes*, may present similarly with a comparable CSF lymphocytosis. Magnetic resonance imaging (MRI) with gadolinium enhancement may demonstrate pathogen-specific features that can aid in the diagnosis. HSV-1, for example, commonly localizes to the temporal lobes. None of these features are pathognomic, but they may support an existing suspicion or guide further evaluation. Although gadolinium is recommended for use in pregnancy only if the benefits of imaging outweigh potential risks, there is currently no evidence of adverse neonatal effects of gadolinium in human studies [49].

Nucleic acid amplification testing (NAAT), such as PCR, of CSF is the mainstay of diagnosis. Qualitative PCR for HSV, varicella-zoster virus (VZV), and enteroviruses is widely available and confirms the diagnosis [50, 51]. Less common neurotropic herpesviruses, such as human herpesvirus 6 (HHV-6), Epstein-Barr virus (EBV), and cytomegalovirus (CMV), may be detected in the CSF but are most often reactivations of latent infections in the setting of a different severe illness; in these cases, quantitative PCR may be necessary to determine causality [52, 53]. Commercially available NAAT platforms, such as the FilmArray Meningitis/Encephalitis panel (BioFire Diagnostics), can rapidly detect a wide array of bacterial and viral pathogens and can minimize the duration of unnecessary empiric antimicrobial therapy [54].

Empiric therapy for encephalitis in pregnancy should include intravenous acyclovir, 10 mg/kg every 8 h [55]. Early empiric therapy is critical, and treatment must not be delayed while awaiting the results of confirmatory assays. Although acyclovir is generally safe, it may crystallize in the renal tubules in settings of low urine output; volume expansion with isotonic crystalloid may be considered in order to maintain adequate urine output [56]. In situations where intracranial hypertension and cerebral edema are a concern, hypertonic saline may be an alternative to isotonic saline to maintain urine output, although there is no prospective data to guide this practice. Treatment with acyclovir should continue until HSV and VZV have been excluded; repeat testing at 3–7 days may be considered in patients with a compatible syndrome and imaging findings but an initially negative CSF PCR [57]. Empiric antibacterial therapy with vancomycin, ceftriaxone or cefotaxime, and ampicillin (for empiric listeriosis coverage) is recommended until bacterial infection can be excluded, either by negative cultures after 48 h of incubation, a negative CSF NAAT, or with the verification of an alternate diagnosis [55, 58].

For confirmed CMV encephalitis, intravenous ganciclovir (pregnancy Category C) 5 mg/kg IV every 12 h may be given in combination with foscarnet (Category C) 90 mg IV every 12 h, although foscarnet carries a significant risk of nephrotoxicity and the combination of these two agents is best validated in HIV-infected persons [55]. Primary CMV infection in pregnancy has been associated with a very high risk of vertical transmission (30–40%) and is the most common viral cause of neonatal neurosensory hearing loss and mental retardation [53–55]. As such, the risk-benefit ratio to both the mother and the unborn child usually justifies treatment despite the potential teratogenicity of both treatment drugs.

Numerous other viruses may occasionally present as encephalitis, including measles (rubeola), mumps, lymphocytic choriomeningitis virus, the equine encephalitides, and others beyond the scope of this chapter. There are limited specific therapies

for these other viral encephalitides. Intravenous immunoglobulin (IVIG) has been utilized with limited success in West Nile virus and Japanese encephalitis virus infections [59, 60]. Postinfectious acute disseminated encephalomyelitis (ADEM) may benefit from treatment with either IVIG or plasmapheresis, in combination with intravenous methylprednisolone [61]. Plasmapheresis can affect maternal hemodynamics and placental blood flow during pregnancy but may improve maternal outcome in ADEM [59].

17.4 Hepatitis and Herpes Viruses

Fulminant hepatic failure (FHF) is rare in pregnancy. Uniquely obstetric disorders, such as HELLP and acute fatty liver of pregnancy, are described elsewhere (see Chap. 33). Worldwide, viral hepatitis is the most common cause of FHF, although acetaminophen (paracetamol) overdose is more common in some industrialized countries such as the United States and the United Kingdom [62]. Supportive care for severe viral hepatitis is similar to that for other causes of FHF, including intracranial pressure management, control of bleeding and coagulopathy, endotracheal intubation and mechanical ventilation if necessary, and management of hemodynamics and secondary infections [62]. N-acetylcysteine (NAC) is the cornerstone of therapy for acetaminophen-induced FHF, but empiric use of NAC for all-cause FHF may be of benefit, especially when the initial diagnosis is in doubt [62, 63]. NAC has no proven risk in pregnancy and has even been associated with improved pregnancy outcomes in both animal models and humans [63–65]. For all cases of viral FHF, liver transplantation may be indicated, and FHF cases should be referred promptly for transplant evaluation [64, 65]. Successful deliveries of healthy infants have occurred even following maternal liver transplantation, and transplantation referral is not an absolute indication for pregnancy termination [66, 67].

Acute hepatitis A (HAV) has declined in incidence in the general and obstetric populations with the advent of widespread immunization [68], although cases remain common in developing settings as well as in localized outbreaks. Acute hepatitis B (HBV) is more strongly associated with fulminant hepatic failure than HAV [68–70], but it too has seen a decline in incidence due to vaccination [71]. Unlike HAV, specific therapies exist for HBV, including tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF, similar in efficacy to TDF but with less long-term nephrotoxicity), telbivudine, entecavir, and lamivudine. Among these agents, TDF, TAF, and entecavir are generally considered the preferred agents and may be initiated safely during pregnancy [71, 72]. Tenofovir is one of the cornerstones of HIV therapy and has been safely administered to HIV-infected pregnant women for many years. Given the high risk of HBV transmission following percutaneous exposure, all hospital staff should be immunized against HBV; HAV vaccination is also highly effective and is advisable for all patient care staff.

Hepatitis C therapy has been revolutionized in the past decade, with modern antiviral therapy producing durable cure rates of greater than 95%, although cost may be a limiting factor in some settings. Acute hepatitis C rarely causes symptomatic disease but may be diagnosed during the course of pregnancy [73]. Advanced HCV liver disease is physiologically incompatible with pregnancy. Treatment of chronic hepatitis C is rarely an emergency. Hence in the event of diagnosis of HCV, delay of treatment until delivery is safe. In this situation the goal is prevention of long-term complications rather than saving the mother's life. Deferment of hepatitis C therapy until after delivery is actually advised, given the lack of safety and efficacy data during pregnancy at present [74].

Hepatitis E (HEV) has a global distribution but is markedly more common in developing countries. HEV is responsible for over 25% of cases of acute non-A/non-B hepatitis in much of northern and eastern Africa as well as western, central, and south Asia, with a lower prevalence in industrialized countries [75]. Like HAV, HEV is transmitted via contaminated food and water and produces a usually self-limited disease in adults, but acute HEV in pregnancy is uniquely severe, with 15–20% progressing to FHF; of those women with HEV-associated FHF, mortality may exceed 60% [75–78]. Obstetric complications (e.g., hemorrhage, preterm delivery, intrauterine fetal death, stillbirth) are also significantly more common [76, 79, 80] during acute HEV infection. Diagnosis of

acute HEV infection is made by detection of anti-HEV IgM from patient serum. Therapy with ribavirin has been utilized in immunocompromised patients in whom HEV infection has become chronic, but there are limited data in the immunocompetent or pregnant patient [5]. Despite this lack of data, the use of ribavirin in the critically ill pregnant woman with acute HEV infection is advocated by some experts, especially in light of the limited fetal toxicity of ribavirin described previously [35, 81].

Herpesviruses, including HSV types 1 and 2, VZV, CMV, and EBV have all been implicated in rare but severe infections during pregnancy. Primary HSV infection rarely leads to severe illness, with the exceptions of encephalitis, as described above, and a rare but severe hepatitis that may be distinguished from other hepatitides by the presence of mucocutaneous lesions, although these lesions may absent or delayed in many cases [82]. Primary VZV infection in pregnant women is similarly associated with both encephalitis and a rare but severe hepatitis. Serologic testing is rarely useful in the diagnosis of HSV or VZV infections, given the high prevalence of antibodies to both in the general population.

HSV and VZV may be distinguished clinically from other viral hepatitides by the presence of a typical vesicular exanthem (typically cutaneous in VZV and mucocutaneous in HSV) although these lesions may absent or delayed in many cases [82]. As with other severe forms of HSV and VZV infection, treatment with IV acyclovir at 10 mg/kg IV every 8 h is recommended. In both cases, definitive diagnosis is based on liver biopsy, although the isolation of either virus by PCR from blood is strongly consistent with acute infection and is sufficient to start therapy [83–85]. The risk of liver biopsy in pregnancy appears to be low; pregnancy outcomes for women undergoing liver biopsy are similar to those of women with comparable degrees of liver disease who do not undergo biopsy, with the exception of an increased risk of earlier delivery (by 6 days) and smaller size for gestational age (RR = 5.2) [86].

Maternal mortality is high in both HSV and VZV hepatitis. In the general population, the mortality is approximately 75% for HSV [87], but published data suggests that mortality in pregnant woman, while still high, may be lower than 40% [88]. In addition, HSV and VZV may lead to significant neonatal morbidity. Maternal and newborn antiviral therapy is also indicated to reduce the risk of neonatal herpes simplex in HSV. The risk of caesarean section to maternal health during critical illness may make caesarean delivery inadvisable, depending on the health status and hemodynamic stability of the mother. VZV is associated with congenital varicella syndrome, with musculoskeletal deformity, liver calcifications, facial scarring, and microcephaly, and perinatal VZV infection with widespread visceral involvement; both syndromes carry a high mortality rate for the infant.

Staff protection: Herpes viruses with cutaneous or respiratory manifestations, including HSV and VZV, may pose risks of transmission to hospital staff. Patients with active mucocutaneous lesions due to HSV should be placed into contact precautions, with hospital staff wearing gowns and gloves during patient care until all lesions are dry and crusted. Patients with active cutaneous or respiratory VZV infections should be placed into contact precautions as above, in addition to the use of a negative pressure isolation room and surgical masks by all staff. Hospital staff without documented VZV immunity (either by prior infection or immunization) should not care for VZV-infected patients or enter the patient's room. For those nonimmune staff members accidentally exposed to a VZV-infected patient, postexposure prophylaxis with valacyclovir and/or varicella hyper-immune globulin (VariZIG, Cangene Corporation, Winnipeg, Manitoba, Canada) is recommended [89].

17.5 Arboviral Infections

With changes in global climate and increases in international travel, insect-borne viral infections are becoming more common in temperate climates [90, 91]. Dengue, Zika, and chikungunya virus infections are particularly endemic in tropical countries, share a common day-biting vector (*Aedes aegypti* and occasionally *Aedes albopictus* mosquitoes) that favors urban and semi-urban areas, and produce similar febrile syndromes that may lead to severe maternal and fetal outcomes.

Dengue infections are produced by four closely related single-stranded RNA viruses of the flavivirus family, designated DENV1-DENV4. Infection with a single dengue subtype most often leads to subclinical disease or to a symptomatic illness consisting of fever, rash, and myalgia. Leukopenia, thrombocytopenia, and elevations in liver transaminases are typical laboratory findings [92]. Dengue is most often diagnosed through serologic testing by enzyme-linked immunoassay, by viral detection through PCR of blood or urine, or (in some countries) by point-of-care testing of whole blood for the viral nonstructural protein 1 (NS1) [93]. Each of these assays is sensitive at different phases of the primary infection, and multiple methods may be advisable if suspicion is high.

Pregnancy complicated by dengue is common in endemic areas. Dengue-associated mortality rates are three times higher in pregnant women than in nonpregnant women of similar age and almost nine times higher in the third trimester. One study demonstrated that the proportion of severe cases among pregnant women with probable dengue almost approximated the fatality rate (1.7% and 1.6%, respectively) [94, 95]. Following primary infection, patients may develop long-term (although not necessarily lifelong) immunity to that given subtype but are at risk for severe disease if infected later with a different subtype. This more severe dengue infection, also known as dengue hemorrhagic fever (DHF), or as dengue shock syndrome in its most severe form, may also affect neonates due to an interaction with heterologous maternal antibodies [96]. Vertical transmission of dengue viruses occurs in fewer than 2% of cases of recent dengue infection [97], although case series of hospitalized women suggest rates closer to 12% in severe disease [98]. There is also a markedly increased risk of miscarriage (odds ratio 3.51), preterm delivery (OR 1.71), and low birth weight (OR 1.41) according to a recent meta-analysis [99].

Severe dengue is noteworthy for marked capillary leakage with pleural effusions and ascites, thrombocytopenia, consumptive coagulopathy, hemoconcentration, and (in its most severe form) hypotension and shock with a narrowed pulse pressure. Pulmonary complications of severe dengue include pneumonitis, hemoptysis, and pulmonary edema, all of which may lead to respiratory failure requiring mechanical ventilation [100]. The typical duration of illness requiring hospitalization is between 3 and 7 days [101]. There are no specific therapies for severe dengue. Blood product replacement is rarely indicated except in marked hemorrhage. Crystalloid and colloid resuscitation are essentially equivalent in efficacy [102] (for a more detailed discussion of fluid therapy, also see Chap. 7). There is no role for glucocorticoids in severe dengue [103]. In general, dengue is a self-limited disease, and survivors usually return to their baseline level of health barring specific complications (e.g., intracranial hemorrhage).

The Zika virus is a closely related flavivirus, presenting with a similar syndrome as dengue. Similar to dengue, Zika is diagnosed through PCR of blood or urine or via detection of anti-Zika IgM [104]. Severe Zika infection is less common than severe dengue [105], although cases have been described of a DHF-like syndrome due to Zika in patients with prior dengue infections, suggesting that Zika may interact with anti-dengue antibodies in a manner similar to that of varying dengue subtypes [79, 80]. Neurologic complications, including encephalitis and Guillain-Barre syndrome, may complicate Zika infection; supportive therapy is currently the only available intervention [106, 107]. The principal unique features of Zika to the obstetrician are its propensity for sexual transmission, which may occur months following exposure, and for its effects on fetal neurologic development and the risk for microcephaly. Surveys of neonatal outcomes in fetuses born to Zika-infected mothers have shown between 5% and 15% of such infants with evidence of birth defects [108, 109].

Chikungunya is an alphavirus, unrelated to the aforementioned flaviviruses but transmitted similarly with a comparable zone of endemicity. Like dengue and Zika, fever and rash are common presenting symptoms, but chikungunya is marked by a severe arthralgia and arthritis that may persist for years, in some cases requiring therapy with glucocorticoids or methotrexate in nonpregnant patients [110]. Severe disease does not appear to be more common in pregnancy, although sepsis-like syndromes have been described [111, 112], and pregnancy outcomes in infected women are generally comparable to those of non-infected women [113].

17.6 Conclusion

Viral infections are common and ubiquitous. With the physiologic and immunologic changes of pregnancy, affected pregnant women are at an increased risk of severe disease. The presenting syndromes of severe viral illnesses have been historically difficult to distinguish from those of bacterial, fungal, or parasitic diseases. Recent advances in molecular diagnostics have now given bedside clinicians the ability to diagnose viral disease with greater precision, with the potential for targeted therapy and, hopefully, improved maternal outcomes.

Disclaimer The author is a US military member. This work was prepared as part of his official duties. Title 17 U.S.C. §105 provides that "Copyright protection under this title is not available for any work of the US Government." Title 17 U.S.C. §101 defines a US Government work as a work prepared by a military service member or official employee of the US Government as part of that person's official duties. The views expressed in this article are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the US Government.

The author has no funding or conflicts of interest to disclose.

References

1. Rush B, Martinka P, Kilb B, McDermid RC, Boyd JH, Celi LA. Acute respiratory distress syndrome in pregnant women. Obstet Gynecol. 2017;129:530–5.
2. Callaghan WM, Creanga AA, Jamieson DJ. Pregnancy-related mortality resulting from influenza in the United States during the 2009–2010 pandemic. Obstet Gynecol. 2015;126:486–90.
3. Bonmarin I, Belchior E, Bergounioux J, et al. Intensive care unit surveillance of influenza infection in France: the 2009/10 pandemic and the three subsequent seasons. Euro Surveill. 2015;20 https://doi.org/10.2807/1560-7917.ES.2015.20.46.30066.
4. Mosby LG, Rasmussen SA. Jamieson DJ. 2009 pandemic influenza a (H1N1) in pregnancy: a systematic review of the literature. Am J Obstet Gynecol. 2011;205:10–8.
5. Adler SP, Nigro G, Pereira L. Recent advances in the prevention and treatment of congenital cytomegalovirus infections. Semin Perinatol. 2007;31:10–8.
6. Fowler KB, Stagno S, Pass RF, et al. The outcome of congenital cytomegalovirus infection in relation to maternal antibody status. N Engl J Med. 1992;326:663–7.
7. Dugas AF, Valsamakis A, Gaydos CA, et al. Evaluation of the Xpert Flu rapid PCR assay in high-risk emergency department patients. J Clin Microbiol. 2014;52:4353–5.
8. Popowitch EB, O'Neill SS, Miller MB. Comparison of the Biofire FilmArray RP, Genmark eSensor RVP, Luminex xTAG RVPv1, and Luminex xTAG RVP fast multiplex assays for detection of respiratory viruses. J Clin Microbiol. 2013;51:1528–33.
9. Chartrand C, Leeflang MM, Minion J, Brewer T, Pai M. Accuracy of rapid influenza diagnostic tests: a meta-analysis. Ann Intern Med. 2012;156:500–11.
10. Rodriguez A, Diaz E, Martin-Loeches I, et al. Impact of early oseltamivir treatment on outcome in critically ill patients with 2009 pandemic influenza A. J Antimicrob Chemother. 2011;66:1140–9.
11. Oboho IK, Reed C, Gargiullo P, et al. Benefit of early initiation of influenza antiviral treatment to pregnant women hospitalized with laboratory-confirmed influenza. J Infect Dis. 2016;214:507–15.
12. Siston AM, Rasmussen SA, Honein MA, et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. JAMA. 2010;303:1517–25.
13. Beau AB, Hurault-Delarue C, Vial T, Montastruc JL, Damase-Michel C, Lacroix I. Safety of oseltamivir during pregnancy: a comparative study using the EFEMERIS database. BJOG. 2014;121:895–900.
14. Wollenhaupt M, Chandrasekaran A, Tomianovic D. The safety of oseltamivir in pregnancy: an updated review of post-marketing data. Pharmacoepidemiol Drug Saf. 2014;23:1035–42.
15. Fiore AE, Fry A, Shay D, et al. Antiviral agents for the treatment and chemoprophylaxis of influenza—recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2011;60:1–24.
16. Lee N, Hui DS, Zuo Z, et al. A prospective intervention study on higher-dose oseltamivir treatment in adults hospitalized with influenza A and B infections. Clin Infect Dis. 2013;57:1511–9.
17. South East Asia Infectious Disease Clinical Research N. Effect of double dose oseltamivir on clinical and virological outcomes in children and adults admitted to hospital with severe influenza: double blind randomised controlled trial. BMJ. 2013;346:f3039.
18. Clay PG, Adiga RB, Taylor TA, Alsup R, Gerk PM, McRae M. Postpartum pharmacokinetics of peramivir in the treatment of 2009 H1N1 influenza. Obstet Gynecol. 2011;118:463–7.
19. de Jong MD, Ison MG, Monto AS, et al. Evaluation of intravenous peramivir for treatment of influenza in hospitalized patients. Clin Infect Dis. 2014;59:e172–85.
20. Ison MG, Fraiz J, Heller B, et al. Intravenous peramivir for treatment of influenza in hospitalized patients. Antivir Ther. 2014;19:349–61.
21. Ison MG, Hui DS, Clezy K, et al. A clinical trial of intravenous peramivir compared with oral oseltamivir for the treatment of seasonal influenza in hospitalized adults. Antivir Ther. 2013;18:651–61.
22. Hibino A, Kondo H, Masaki H, et al. Community- and hospital-acquired infections with oseltamivir- and peramivir-resistant influenza A(H1N1)pdm09 viruses during the 2015–2016 season in Japan. Virus Genes. 2017;53:89–94.

23. Spanakis N, Pitiriga V, Gennimata V, Tsakris A. A review of neuraminidase inhibitor susceptibility in influenza strains. Expert Rev Anti Infect Ther. 2014;12:1325–36.
24. Takashita E, Fujisaki S, Kishida N, et al. Characterization of neuraminidase inhibitor-resistant influenza A(H1N1)pdm09 viruses isolated in four seasons during pandemic and post-pandemic periods in Japan. Influenza Other Respi Viruses. 2013;7:1390–9.
25. Marty FM, Vidal-Puigserver J, Clark C, et al. Intravenous zanamivir or oral oseltamivir for hospitalised patients with influenza: an international, randomised, double-blind, double-dummy, phase 3 trial. Lancet Respir Med. 2017;5:135–46.
26. Chan-Tack KM, Kim C, Moruf A, Birnkrant DB. Clinical experience with intravenous zanamivir under an emergency IND program in the United States (2011–2014). Antivir Ther. 2015;20:561–4.
27. Yan J, Guo J, Fan C, et al. Coronavirus disease 2019 (COVID-19) in pregnant women: a report based on 116 cases. Am J Obstet Gynecol. 2020.
28. Elshafeey F, Magdi R, Hindi N, et al. A systematic scoping review of COVID-19 during pregnancy and childbirth. Int J Gynaecol Obstet. 2020.
29. Lamouroux A, Attie-Bitach T, Martinovic J, Leruez-Ville M, Ville Y. Evidence for and against vertical transmission for SARS-CoV-2 (COVID-19). Am J Obstet Gynecol. 2020.
30. Alhazzani W, Moller MH, Arabi YM, et al. Surviving sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Crit Care Med. 2020.
31. Mulangu S, Dodd LE, Davey RT Jr, et al. A randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med. 2019;381:2293–303.
32. von Lilienfeld-Toal M, Berger A, Christopeit M, et al. Community acquired respiratory virus infections in cancer patients-guideline on diagnosis and management by the infectious diseases working party of the German Society for Haematology and Medical Oncology. Eur J Cancer. 2016;67:200–12.
33. Gross AE, Bryson ML. Oral ribavirin for the treatment of noninfluenza respiratory viral infections: a systematic review. Ann Pharmacother. 2015;49:1125–35.
34. Yoon BW, Song YG, Lee SH. Severe community-acquired adenovirus pneumonia treated with oral ribavirin: a case report. BMC Res Notes. 2017;10:47.
35. Sinclair SM, Jones JK, Miller RK, Greene MF, Kwo PY, Maddrey WC. The ribavirin pregnancy registry: an interim analysis of potential teratogenicity at the mid-point of enrollment. Drug Saf. 2017;40:1205–18.
36. Lee M, Kim S, Kwon OJ, et al. Treatment of adenoviral acute respiratory distress syndrome using cidofovir with extracorporeal membrane oxygenation. J Intensive Care Med. 2017;32:231–8.
37. Lenaerts L, De Clercq E, Naesens L. Clinical features and treatment of adenovirus infections. Rev Med Virol. 2008;18:357–74.
38. Matthes-Martin S, Boztug H, Lion T. Diagnosis and treatment of adenovirus infection in immunocompromised patients. Expert Rev Anti Infect Ther. 2013;11:1017–28.
39. Hynicka LM, Ensor CR. Prophylaxis and treatment of respiratory syncytial virus in adult immunocompromised patients. Ann Pharmacother. 2012;46:558–66.
40. Brun-Buisson C, Richard JC, Mercat A, Thiebaut AC, Brochard L, Group R-SAHNvR. Early corticosteroids in severe influenza A/H1N1 pneumonia and acute respiratory distress syndrome. Am J Respir Crit Care Med. 2011;183:1200–6.
41. Rynda-Apple A, Robinson KM, Alcorn JF. Influenza and bacterial superinfection: illuminating the immunologic mechanisms of disease. Infect Immun. 2015;83:3764–70.
42. Maravi-Poma E, Martin-Loeches I, Regidor E, et al. Severe 2009 A/H1N1v influenza in pregnant women in Spain. Crit Care Med. 2011;39:945–51.
43. Centers for Disease Control and Prevention. Prevention Strategies for Seasonal Influenza in Healthcare Settings. Accessed on 20 February 2018 at https://www.cdc.gov/flu/professionals/infectioncontrol/healthcaresettings.htm.)
44. Gralton J, McLaws ML. Protecting healthcare workers from pandemic influenza: N95 or surgical masks? Crit Care Med. 2010;38:657–67.
45. Offeddu V, Yung CF, Low MSF, Tam CC. Effectiveness of masks and respirators against respiratory infections in healthcare workers: a systematic review and meta-analysis. Clin Infect Dis. 2017;65:1934–42.
46. Weber DJ, Rutala WA, Fischer WA, Kanamori H, Sickbert-Bennett EE. Emerging infectious diseases: focus on infection control issues for novel coronaviruses (severe acute respiratory syndrome-CoV and Middle East Respiratory Syndrome-CoV), hemorrhagic fever viruses (Lassa and Ebola), and highly pathogenic avian influenza viruses, A(H5N1) and A(H7N9). Am J Infect Control. 2016;44:e91–e100.
47. Lynch JB, Davitkov P, Anderson DJ, et al. Infectious Diseases Society of America Guidelines on infection prevention in patients with suspected or known COVID-19. Accessed on 11 May 2020 at https://www.idsociety.org/practice-guideline/covid-19-guideline-infection-prevention/.
48. Nahmias AJ, Whitley RJ, Visintine AN, Takei Y, Alford CA Jr. Herpes simplex virus encephalitis: laboratory evaluations and their diagnostic significance. J Infect Dis. 1982;145:829–36.
49. Amin R, Darrah T, Wang H, Amin S. Editor's highlight: in utero exposure to gadolinium and adverse neonatal outcomes in premature infants. Toxicol Sci. 2017;156:520–6.
50. Domingues RB, Lakeman FD, Mayo MS, Whitley RJ. Application of competitive PCR to cerebrospinal fluid samples from patients with herpes simplex encephalitis. J Clin Microbiol. 1998;36:2229–34.
51. Lakeman FD, Whitley RJ. Diagnosis of herpes simplex encephalitis: application of polymerase chain reaction to cerebrospinal fluid from brain-biopsied patients and correlation with disease. National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. J Infect Dis. 1995;171:857–63.
52. Limaye AP, Kirby KA, Rubenfeld GD, et al. Cytomegalovirus reactivation in critically ill immunocompetent patients. JAMA. 2008;300:413–22.

53. Bhide A, Papageorghiou AT. Managing primary CMV infection in pregnancy. BJOG. 2008;115:805–8.
54. Demmler GJ. Infectious Diseases Society of America and Centers for Disease Control. Summary of a workshop on surveillance for congenital cytomegalovirus disease. Rev Infect Dis. 1991;13:315–29.
55. Fowler KB, McCollister FP, Dahle AJ, et al. Progressive and fluctuating sensorineural hearing loss in children with asymptomatic congenital cytomegalovirus infection. J Pediatr. 1997;130:624–30.
56. Sawyer MH, Webb DE, Balow JE, Straus SE. Acyclovir-induced renal failure. Clinical course and histology. Am J Med. 1988;84:1067–71.
57. Weil AA, Glaser CA, Amad Z, Forghani B. Patients with suspected herpes simplex encephalitis: rethinking an initial negative polymerase chain reaction result. Clin Infect Dis. 2002;34:1154–7.
58. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis. 2004;39:1267–84.
59. Hart J Jr, Tillman G, Kraut MA, et al. West Nile virus neuroinvasive disease: neurological manifestations and prospective longitudinal outcomes. BMC Infect Dis. 2014;14:248.
60. Rayamajhi A, Nightingale S, Bhatta NK, et al. A preliminary randomized double blind placebo-controlled trial of intravenous immunoglobulin for Japanese encephalitis in Nepal. PLoS One. 2015;10:e0122608.
61. Pohl D, Alper G, Van Haren K, et al. Acute disseminated encephalomyelitis: updates on an inflammatory CNS syndrome. Neurology. 2016;87:S38–45.
62. Lee WM, Stravitz RT, Larson AM. Introduction to the revised American Association for the Study of Liver Diseases Position Paper on acute liver failure 2011. Hepatology. 2012;55:965–7.
63. Buhimschi IA, Buhimschi CS, Weiner CP. Protective effect of N-acetylcysteine against fetal death and preterm labor induced by maternal inflammation. Am J Obstet Gynecol. 2003;188(1):203–8.
64. Jenkins DD, Wiest DB, Mulvihill DM, et al. Fetal and neonatal effects of N-acetylcysteine when used for neuroprotection in maternal chorioamnionitis. J Pediatr. 2016;168:67–76.e6.
65. Amin AF, Shaaban OM, Bediawy MA. N-acetyl cysteine for treatment of recurrent unexplained pregnancy loss. Reprod Biomed Online. 2008;17(5):722–6.
66. Jarufe N, Soza A, Perez-Ayuso RM, et al. Successful liver transplantation and delivery in a woman with fulminant hepatic failure occurring during the second trimester of pregnancy. Liver Int. 2006;26:494–7.
67. Vernadakis S, Fouzas I, Kykalos S, et al. Successful salvage delivery and liver transplantation for fulminant hepatic failure in a 34-week pregnant woman: a case report. Transplant Proc. 2012;44:2768–9.
68. Stuurman AL, Marano C, Bunge EM, De Moerlooze L, Shouval D. Impact of universal mass vaccination with monovalent inactivated hepatitis A vaccines—a systematic review. Hum Vaccin Immunother. 2017;13:724–36.
69. Ichai P, Samuel D. Etiology and prognosis of fulminant hepatitis in adults. Liver Transpl. 2008;14(Suppl 2):S67–79.
70. Brohi ZP, Sadaf A, Perveen U. Etiology, clinical features and outcome of fulminant hepatic failure in pregnancy. J Pak Med Assoc. 2013;63:1168–71.
71. Visvanathan K, Dusheiko G, Giles M, et al. Managing HBV in pregnancy. Prevention, prophylaxis, treatment and follow-up: position paper produced by Australian, UK and New Zealand key opinion leaders. Gut. 2016;65:340–50.
72. Society for Maternal-Fetal M, Dionne-Odom J, Tita AT, Silverman NS. #38: hepatitis B in pregnancy screening, treatment, and prevention of vertical transmission. Am J Obstet Gynecol. 2016;214:6–14.
73. Prasad MR, Honegger JR. Hepatitis C virus in pregnancy. Am J Perinatol. 2013;30:149–59.
74. Page CM, Hughes BL, Rhee EHJ, Kuller JA. Hepatitis C in pregnancy: review of current knowledge and updated recommendations for management. Obstet Gynecol Surv. 2017;72:347–55.
75. Jilani N, Das BC, Husain SA, et al. Hepatitis E virus infection and fulminant hepatic failure during pregnancy. J Gastroenterol Hepatol. 2007;22:676–82.
76. Patra S, Kumar A, Trivedi SS, Puri M, Sarin SK. Maternal and fetal outcomes in pregnant women with acute hepatitis E virus infection. Ann Intern Med. 2007;147:28–33.
77. Labrique AB, Sikder SS, Krain LJ, et al. Hepatitis E, a vaccine-preventable cause of maternal deaths. Emerg Infect Dis. 2012;18:1401–4.
78. Jin H, Zhao Y, Zhang X, Wang B, Liu P. Case-fatality risk of pregnant women with acute viral hepatitis type E: a systematic review and meta-analysis. Epidemiol Infect. 2016;144:2098–106.
79. Priyamvada L, Hudson W, Ahmed R, Wrammert J. Humoral cross-reactivity between Zika and dengue viruses: implications for protection and pathology. Emerg Microbes Infect. 2017;6:e33.
80. Miner JJ, Diamond MS. Dengue antibodies, then Zika: a fatal sequence in mice. Immunity. 2017;46:771–3.
81. Abbas Z, Afzal R. Hepatitis E: when to treat and how to treat. Antivir Ther. 2014;19:125–31.
82. Masadeh M, Shen H, Lee Y, et al. A fatal case of herpes simplex virus hepatitis in a pregnant patient. Intractable Rare Dis Res. 2017;6:124–7.
83. Rogers SY, Irving W, Harris A, Russell NH. Visceral varicella zoster infection after bone marrow transplantation without skin involvement and the use of PCR for diagnosis. Bone Marrow Transplant. 1995;15:805–7.
84. Ichai P, Roque Afonso AM, Sebagh M, et al. Herpes simplex virus-associated acute liver failure: a difficult diagnosis with a poor prognosis. Liver Transpl. 2005;11:1550–5.
85. Nienaber JH, McNamara DR, Banerjee R, Pritt BS, Karre T, Sohail MR. Fulminant gestational hepatitis due to primary herpes simplex type 2 infection: use of serum HSV polymerase chain reaction for noninvasive diagnosis. Diagn Microbiol Infect Dis. 2012;72:181–4.

86. Ludvigsson JF, Marschall HU, Hagstrom H, Hoijer J, Stephansson O. Pregnancy outcome in women undergoing liver biopsy during pregnancy: a nationwide population-based Cohort study. Hepatology. 2017;
87. Norvell JP, Blei AT, Jovanovic BD, Levitsky J. Herpes simplex virus hepatitis: an analysis of the published literature and institutional cases. Liver Transpl. 2007;13:1428–34.
88. Herrera CA, Eichelberger KY, Chescheir NC. Antiviral-resistant fulminant herpes hepatitis in pregnancy. AJP Rep. 2013;3:87–90.
89. Siegel JD RE, Jackson M, Chiarello L, and the Healthcare Infection Control Practices Advisory Committee. 2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings (October 2017 update). Accessed online on 20 February 2018 at https://www.cdc.gov/infectioncontrol/guidelines/isolation/index.html
90. Sigfrid L, Reusken C, Eckerle I, et al. Preparing clinicians for (re-)emerging arbovirus infectious diseases in Europe. Clin Microbiol Infect. 2017;
91. Patterson J, Sammon M, Garg M. Dengue, Zika and Chikungunya: emerging arboviruses in the New World. West J Emerg Med. 2016;17:671–9.
92. Simmons CP, Farrar JJ, Nguyen V, Wills B. Dengue N Engl J Med. 2012;366:1423–32.
93. Buchy P, et al. Evaluation of commercially available diagnostic tests for the detection of dengue virus NS1 antigen and anti-dengue virus IgM antibody. PLoS Negl Trop Dis. 2014;8:e3171.
94. Nascimento LBD, Siqueira CM, Coelho GE, Siqueira JB. Dengue in pregnant women: characterization of cases in Brazil, 2007–2015. Dengue em gestantes: caracterização dos casos no Brasil, 2007–2015. Epidemiol Serv Saude. 2017;26(3):433–42.
95. Machado CR, Machado ES, Rohloff RD, et al. Is pregnancy associated with severe dengue? A review of data from the Rio de Janeiro surveillance information system. PLoS Negl Trop Dis. 2013;7(5):e2217.
96. Elling R, Henneke P, Hatz C, Hufnagel M. Dengue fever in children: where are we now? Pediatr Infect Dis J. 2013;32:1020–2.
97. Tan PC, Rajasingam G, Devi S, Omar SZ. Dengue infection in pregnancy: prevalence, vertical transmission, and pregnancy outcome. Obstet Gynecol. 2008;111:1111–7.
98. Pouliot SH, Xiong X, Harville E, et al. Maternal dengue and pregnancy outcomes: a systematic review. Obstet Gynecol Surv. 2010;65:107–18.
99. Paixao ES, Teixeira MG, Costa M, Rodrigues LC. Dengue during pregnancy and adverse fetal outcomes: a systematic review and meta-analysis. Lancet Infect Dis. 2016;16:857–65.
100. de Almeida RR, Paim B, de Oliveira SA, et al. Dengue hemorrhagic fever: a state-of-the-art review focused in pulmonary involvement. Lung. 2017;195:389–95.
101. Khalil MA, Tan J, Khalil MA, Awan S, Rangasami M. Predictors of hospital stay and mortality in dengue virus infection-experience from Aga Khan University Hospital Pakistan. BMC Res Notes. 2014;7:473.
102. ills BA, Nguyen MD, Ha TL, et al. Comparison of three fluid solutions for resuscitation in dengue shock syndrome. N Engl J Med. 2005;353:877–89.
103. Nguyen TH, Nguyen TH, Vu TT, et al. Corticosteroids for dengue—why don't they work? PLoS Negl Trop Dis. 2013;7:e2592.
104. Eppes C, Rac M, Dunn J, et al. Testing for Zika virus infection in pregnancy: key concepts to deal with an emerging epidemic. Am J Obstet Gynecol. 2017;216:209–25.
105. Azevedo RS, Araujo MT, Martins Filho AJ, et al. Zika virus epidemic in Brazil. I. Fatal disease in adults: clinical and laboratorial aspects. J Clin Virol. 2016;85:56–64.
106. de Oliveira WK, Carmo EH, Henriques CM, et al. Zika virus infection and associated neurologic disorders in Brazil. N Engl J Med. 2017;376:1591–3.
107. Dos Santos T, Rodriguez A, Almiron M, et al. Zika virus and the Guillain-Barre syndrome—case series from seven countries. N Engl J Med. 2016;375:1598–601.
108. Shapiro-Mendoza CK, Rice ME, Galang RR, et al. Pregnancy outcomes after maternal Zika virus infection during Pregnancy—U.S. Territories, January 1, 2016-April 25, 2017. MMWR Morb Mortal Wkly Rep. 2017;66:615–21.
109. Cunha AJ, de Magalhaes-Barbosa MC, Lima-Setta F, Medronho RA, Prata-Barbosa A. Microcephaly case fatality rate associated with Zika virus infection in Brazil: current estimates. Pediatr Infect Dis J. 2017;36:528–30.
110. Arroyo-Avila M, Vila LM. Rheumatic manifestations in patients with Chikungunya infection. P R Health Sci J. 2015;34:71–7.
111. Sharp TM, Roth NM, Torres J, et al. Chikungunya cases identified through passive surveillance and household investigations—Puerto Rico, May 5–August 12, 2014. MMWR Morb Mortal Wkly Rep. 2014;63:1121–8.
112. Hoz JM, Bayona B, Viloria S, Accini JL, Juan-Vergara HS, Viasus D. Fatal cases of Chikungunya virus infection in Colombia: diagnostic and treatment challenges. J Clin Virol. 2015;69:27–9.
113. Laoprasopwattana K, Suntharasaj T, Petmanee P, Suddeaugrai O, Geater A. Chikungunya and dengue virus infections during pregnancy: seroprevalence, seroincidence and maternal-fetal transmission, southern Thailand, 2009–2010. Epidemiol Infect. 2016;144:381–8.

Infection during Early Pregnancy and Septic Abortions

18

Orsolya Miskolci, Deirdre Morley, and Ignacio Martin-Loeches

Bullet Points

- Maternal sepsis remains an important cause of death.
- The physiological changes that occur during pregnancy make the early recognition of the critically ill pregnant women challenging.
- The origin of maternal sepsis can be non-obstetric, as immunological changes make pregnant women more susceptible to infection.
- Pneumonia (especially influenza pneumonia) and urinary tract infections are the most common non-obstetric causes of sepsis in early pregnancy, and both may potentially cause critical illness.
- Obstetric causes of early pregnancy sepsis include vaginal tract infection, uterine infection, chorioamnionitis, endomyometritis, and septic abortion.
- Infections may occur following invasive procedures, e.g. amniocentesis, chorionic villus sampling, cervical cerclage, and percutaneous umbilical blood sampling.
- The incidence of sexually transmitted diseases (STDs) has increased in the last decade, being responsible for significant maternal and fetal morbidity.
- Septic abortion remains an important healthcare concern in many countries where termination of pregnancy is illegal.
- Ascending infections after abortion can spread rapidly, potentially leading to critical illness, multi-organ failure, or even death.
- Vaginitis, although common in early pregnancy, rarely requires critical care admission.

18.1 Introduction

In the year 2018, the 200th birthday of Ignaz Semmelweis was celebrated. In the nineteenth century, Semmelweis, the Hungarian physician also known as "mother's saviour", was responsible for a significant decrease in peripartum maternal mortality by introducing and emphasizing the importance of hand hygiene in obstetric care. As

O. Miskolci
St Georges University Hospital, London, UK

D. Morley
Department of Genito Urinary Medicine and Infectious Diseases, St James Hospital, Dublin, Ireland

I. Martin-Loeches (✉)
St James's Hospital, Dublin, Ireland
e-mail: imartinl@tcd.ie

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_18

a result of the work done in the years since Semmelweis, nowadays severe sepsis and septic shock are significantly less common among pregnant women [1].

Between 2003 and 2013, the international maternal mortality ratio decreased by 1.3% per year. This decrease was accompanied by a concurrent decrease in maternal deaths related to sepsis, from 11.6% to 9.7% between 1990 and 2013 [2]. In 2015 there were approximately 303,000 maternal deaths worldwide; 99% occurred in developing countries [3].

In the United Kingdom (UK), the maternal mortality ratio (MMR) decreased significantly by 37% from 2003 to 2005. This was primarily due to a decrease in influenza-related maternal deaths and deaths due to indirect causes of sepsis during pregnancy. The maternal mortality ratio (MMR) between 2012 and 2014 was 8.5/100,000 live births (a total of 200 deaths) and remained comparable at 9.78/100,000 live births (total of 225 deaths) between 2014 and 2016 [4]. Among the reported deaths, pregnancy-related sepsis (genital and urinary tract infection) was responsible for 4.9%, and other infections accounted for 3.6%. Overall, 10% of women who died before 24th weeks' gestation did so because of sepsis [5].

The origin of early infection occurring during pregnancy can be obstetric or non-obstetric (e.g. urinary tract infection, pneumonia, abdominal infections, soft tissue infections, etc.). Obstetric causes include vaginal tract infection, uterine infection, chorioamnionitis, endomyometritis, or septic abortion. Infections can also occur after invasive procedures (e.g. amniocentesis, chorionic villus sampling, cervical cerclage, and percutaneous umbilical blood sampling).

Most septic episodes (47–63%) occur in the postpartum period [6]. The predominant cause of antepartum sepsis is urinary tract infections (33.6%). During the antepartum period, genital tract infections are responsible for 20% and respiratory tract infections for 9% of the cases, and the source is unknown in one third of the cases (30%). *E. coli* is the responsible pathogen for the majority septic episodes in the antepartum period [7].

Importantly, the international definition of maternal sepsis was changed after literature review and expert consultation in 2017. It is now termed "a life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or postpartum period".

In this chapter, we will focus on infections of obstetric origin in the early stage of pregnancy and discuss infections that can lead to critical illness during the early stages of pregnancy.

18.2 Immune Response in Pregnancy

Multiple physiological changes occur in the cardiovascular and respiratory systems during pregnancy, as discussed elsewhere in this book. Some of these are particularly pertinent to the recognition and management of a critically ill pregnant patient.

Pregnancy is typically a state of immune system modulation. On the one hand, survival of the pregnancy is important for conservation of the species. Therefore, to protect the mother and child, the immune system increases recognition, communication, and repair abilities. On the other hand, the maternal body must accommodate the presence of the fetus. This modifies the maternal response to external immune triggers. Generally, a placental infection that elicits maternal production of inflammatory cytokines (e.g. TNFα, INFγ, IL-12) and high levels of IL-6 will also lead to placental damage and abortion or preterm labour [9]. Conversely, an infection that triggers only a mild inflammatory response will not terminate the pregnancy but will likely activate the immune system of both the mother and the fetus. This activation may cause maternal sensitisation to other microorganisms (i.e. an increased risk of secondary infection) and a fetal inflammatory response without infection.

Mild leukocytosis and thrombocytopenia are part of the normal haematological changes seen in pregnancy. However, there is also an increase in the level of the coagulation factors; pregnancy is considered a hypercoagulable state [10]. Leukocyte functionality and certain antibody levels decrease in pregnancy, which may contribute to an increased incidence of infections [11, 12]. There is also a shift from cell-mediated immunity towards humoral immunity [13, 14].

18.3 The Use of Modified Scoring Systems for Sepsis and Septic Shock in Pregnancy

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [15]. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) promoted the use of Sequential Organ Failure Assessment (SOFA) score for diagnosing and grading sepsis in the general population [16]. The SOFA score assesses potential derangements of six organ systems: the respiratory system, expressed as the PaO2/FiO2 (partial pressure of arterial oxygen/fraction of inspired oxygen) ratio; the coagulation system, based on the degree of thrombocytopenia; liver function, via bilirubin level; the cardiovascular system, based on the presence and severity of shock; the central nervous system, expressed as the GCS level; and the renal system, by assessing creatinine level or urine output [17]. At the bedside, the quick SOFA score (qSOFA) can be applied using the respiratory rate, the systolic blood pressure, and the GCS as a description of mental state.

Early identification and prevention of sepsis are crucial in the obstetric population. Retrospective data from large registries suggest that every fourth woman who presents with sepsis will have severe sepsis [18] and that one in every ten women with severe sepsis will have septic shock [19]. However, the changes that result from physiological adaptations to pregnancy can potentially mask the clinical signs of an infection and even development of organ failure despite use of Sequential Organ Failure Assessment (SOFA) criteria. The Society of Obstetric Medicine of Australia and New Zealand suggests using a modified qSOFA score, the omqSOFA score which accepts a lower systolic blood pressure in pregnancy, 90 mmHg instead of the original 100 mmHg [20]. Altough the SOFA score remains a good predictor of mortality in pregnant patients admitted to the ICU [21, 22], modified early warning scores have evolved for obstetric patients in the last decade to better predict clinical deterioration of obstetric patients in ward settings and the potential need for critical care admission. The modified early obstetric warning system (MEOWS) has a good sensitivity and specificity for predicting morbidity in the pregnant patient [23] but is not sepsis-specific. The Sepsis in Obstetrics Score (SOS), proposed in 2013 by Albright et al., showed a sensitivity of 88.9%, specificity of 95.2%, positive predictive value of 16.7%, and negative predictive value of 99.9% for predicting ICU admission for sepsis in an obstetric population [24]. The SOS scores the changes in temperature, systolic blood pressure, heart rate, respiratory rate, oxygen saturation, white blood cell count, and lactate level. The SOS also includes blood lactate levels, an excellent marker of septic shock. However, lactate is unfortunately often unavailable in rural and low income settings. At the time of the writing of this chapter, there is only one retrospective study of the predictive value of lactate in pregnancy [25]. Of the 850 women included, 159 had lactic acid measured. Women with lactic acid measured had more positive blood cultures (16.8 vs. 5.5%, $p = 0.04$), longer hospital stays (median 3 vs. 2 days, $p < 0.01$), and more preterm deliveries (18.3 vs. 10.9%, $p = 0.05$). Elevated lactate levels were positively associated with intensive care or telemetry unit admission: adjusted OR per 1 mmol/L increase in lactic acid 2.34 (95% CI, 1.33–4.12). The Multiple Organ Dysfunction Score (MODS) was shown to be the best predictor of ICU mortality [26].

18.4 Sexually Transmitted Diseases (STD)

18.4.1 Gonorrhoea

The prevalence of sexually transmitted disease is increasing. STDs can be particularly harmful in pregnancy. The Centers for Disease Control and Prevention (CDC) estimated that approximately 820,000 cases of gonorrhoea occur yearly in the United States, with an increasing rate since 2009 [27]. The prevalence of gonorrhoea in pregnancy ranges from 5% to 10% [28, 29].

Infection due to *Neisseria gonorrhoeae* is one of the major causes of pelvic inflammatory disease (PID). PID can lead to serious reproductive problems in women. Examples include tubal infertility, ectopic pregnancy, and chronic pelvic pain [27]. Untreated gonococcal infection in pregnancy has been also linked to miscarriages, premature birth and low birth weight, premature rupture of membranes, and chorioamnionitis [30]. Of particular relevance to the intensive care clinician is the amniotic infection syndrome that occurs after premature rupture of membranes (PROM). This condition is characterized by placental, fetal membrane, and umbilical cord inflammation, neonatal infection and maternal fever. Preterm delivery is common and perinatal morbidity may be significant [31].

Disseminated gonococcal infection (DGI), although rarely seen in developed world, can cause severe multisystem illness. The disease traditionally has two phases. The early stage frequently manifests as petechial or pustular acral skin lesions, chills, and fever. The second, septic arthritis phase, is characterized by a purulent synovial effusion most commonly involving the knees, ankles, and wrists [8, 32]. The infection is occasionally complicated by perihepatitis and rarely by endocarditis or meningitis. The incidence of *Neisseria gonorrhoeae* antibiotic resistance is increasing. When managing a patient with suspected DGI, it is important to culture specimens from all sites including blood, cerebrospinal, urogenital, and joint fluids. The duration of antibiotic treatment depends on the site/s of infection. Meningitis requires parenteral antibiotics for 10–14 days, whereas endocarditis should be treated for at least 4 weeks [33].

Fluoroquinolones, doxycycline, and tetracycline are contraindicated in pregnancy due to teratogenic side effects. In addition, there is worldwide emergence of fluoroquinolone, penicillin-ciprofloxacin, and cefixime resistance. The treatment recommended for gonococcal infection by the British Association for Sexual Health and HIV (BASHH) is single dose intramuscular Ceftriaxone 500 mg with oral Azithromycin 1 g or single dose intramuscular Spectinomycin 2 g with oral Azithromycin 1 g. Azithromycin has a synergistic effect when given with a cephalosporin [34].

When treating meningitis or arthritis, a higher dose of cephalosporin is required: Intramuscular or intravenous Ceftriaxone 1–2 g every 24 hours plus a single dose of Azithromycin 1 g orally.

18.4.2 Chlamydia

C. trachomatis infection is the most common bacterial STD in the United States, with an estimated three million new infections diagnosed annually. In 2015 the incidence was 478.8 cases per 100,000 population [35].

Chlamydial infection is usually asymptomatic during pregnancy, but it can be associated with several adverse pregnancy and neonatal outcomes (e.g. preterm delivery PPROM, low birth weight, neonatal death, increased transmission of HIV infection and neonatal ophthalmia neonatorum, neonatal Chlamydia pneumonia) [36]. If it remains untreated, ascending infection may lead to intra-amniotic infection (IAI). About 5–10% of women with IAI develop bacteremia. Around 50% of patients with bacteremia will show signs of sepsis and 40% of septic cases will progress to septic shock and subsequently multi-organ failure (altered mental state, ARDS, disseminated intravascular coagulation, acute kidney injury).

Treatment should be provided promptly for all persons testing positive for Chlamydia infection. The BASHH guideline recommends oral treatment with Azithromycin 1 g as a single dose or Erythromycin 500 mg four times daily for 7 days or Erythromycin 500 mg twice daily for 14 days or Amoxicillin 500 mg three times a day for 7 days for treatment during pregnancy [37]. Cases progessing to sepsis are likely to require intravenous treatment.

18.4.3 Syphilis

Treponema pallidum is a challenging healthcare issue especially in developing countries [38]. However, some developed countries, such as the United Kingdom, are also witnessing a rising incidence in STD caused by *Treponema pallidum* after decades of remission. In fact, the number of newly diagnosed infected patients has increased nearly threefold in the last 10 years in the United Kingdom [39]. In 2008, the WHO estimated that 1.4 million pregnant women had active syphilis infection worldwide. Over 500,000 adverse pregnancy outcomes were estimated to occur anually, including spontaneous abortion, early fetal or neonatal deaths, stillbirths, preterm or low birth weight infants, and infected newborns [40]. Early diagnosis and treatment are essential for prevention of vertical transmission. In addition, it is important to consider complications of treatment, including the Jarisch-Herxheimer reaction.

After a 3-week incubation period, syphilis has four stages: primary, secondary, latent, and tertiary. In the primary stage, solitary, painless, highly infective ulcers (chancres) appear commonly in the cervix. Untreated disease progresses to the secondary stage, characterized by generalized symptoms (malaise, fever, lymphadenopathy) and dissemination of a maculopapular rash on the palms, soles, and oral mucosae. All these lesions contain treponemes. Neurological signs and symptoms such as headache, signs of meningeal irritation, or abnormal cerebrospinal fluid findings may occur. In the latent stage, patients may become asymptomatic for decades and often for life. Approximately 30% of untreated patients develop tertiary syphilis which is accompanied by cardiovascular and neurological symptoms (neurosyphilis) or gummatous necrotic lesions in internal organs [41].

T. pallidum readily crosses the placenta. Vertical transmission can occur at any stage of the pregnancy and at any disease stage, but particularly in the primary or secondary stage [42]. In most Western countries, pregnant women are checked routinely for syphilis among other STDs during early pregnancy. There is a high rate of co-infection with HIV; therefore all women diagnosed with syphilis should be offered HIV screening.

Treponemal serology tests are used for screening; they detect the presence of syphilis antibodies. Patients remain antibody-positive for life even in case of a treated infection. False positive results are possible with other *Treponema* infections, e.g. yaws or pinta.

After a reactive treponemal test, a non-treponemal test, *VDRL (venereal disease research laboratory) or RPR (rapid plasma reagin),* is required to confirm the activity of the disease [42, 43]. Response to treatment is defined as a four-fold decrease in RPR titer over time or stable or declining test levels of less than or equal to 1:4.

The first-line treatment is intramuscular benzathine penicillin G 2.4 million units (MU). Alternative treatments that are given in cases with penicillin allergy are less effective; Erythromycin and azithromycin are associated with significant treatment failure rates in pregnancy [44]. Therefore in cases with a history of penicillin allergy the details of the allergic response should be revisited and skin testing or an oral graded penicillin dose-challenge may be considered.

In latent or tertiary syphilis, benzathine (procaine penicillin plus probenecid) or benzylpenicillin for 14 days is the first-line treatment.

The Jarisch-Herxheimer reaction (JHR) is a well-known phenomenon associated with initiation of antibiotic therapy for specific types of infection, syphilis included. The JHR

typically occurs within 1–2 h of treatment and usually resolves within 48 h. The main concern in pregnancy is the risk to the fetus as the JHR may provoke uterine contractions and preterm labour. The JHR is reported by 10–50% of patients receiving treatment for syphilis. Symptoms include fever, tachycardia, myalgia, chills, rigours, hypotension, and exacerbation of the skin lesions. It is caused by release of lipoproteins from the *Treponema* bacteria. Symptoms may mimic sepsis or a drug reaction. However, treatment is supportive; often with intravenous fluids and antipyretics alone. Despite the severity of JHR manifestation in some cases, there is no data to support the use of premedication (e.g. corticosteroids) in pregnancy [42].

18.5 Genital Tract Infections

Several factors make pregnant women more susceptible to genital tract infections and as a result to sepsis. Some of these risk factors are of increasing importance as their incidence is increasing in the general and obstetric populations. Notable conditions include obesity, impaired glucose tolerance (or diabetes), impaired immunity (e.g. long-term immunosuppressant medication), and anemia. Pregnancy-related indicators of increased risk include the presence of a vaginal discharge, a clinical history of pelvic infection, a history of *group B streptococcus* or *group A streptococcus* infection, amniocentesis or other invasive procedures, cervical cerclage, vaginal trauma and retained products of conception post miscarriage or postdelivery [45, 46].

18.6 Vaginitis

Infective vaginitis is common in the pregnant population. Very often patients are asymptomatic. If symptoms occur, women typically present with an odorous vaginal discharge and pruritus. Vaginal infections can be associated with low birth weight, preterm delivery, or premature rupture of membranes, but invasive dissemination of the infection requiring critical care admission is rare.

Symptomatic vulvovaginal candidiasis (VVC) affects 15% of pregnant women. The predominant cause of this yeast infection is *Candida albicans*, which is part of the normal vaginal flora in up to 30% of sexually active women. In the obstetric population, hormonal changes (increased level of oestrogen), increased vaginal glycogen production, and suppression of cell-mediated immunity contribute to the higher incidence of infections. Most episodes of symptomatic VVC occur during the second and third trimesters of pregnancy [47]. In the majority of cases, symptoms remain localized. Localized disease is treated with a topical azole for at least 7 days. However, *Candida* can become an opportunistic pathogen in the presence of a compromised host defence mechanisms. Systemic candidiasis is rare and is usually related to other predisposing factors such as preceeding sepsis or malignancy. Systemic candidiasis may cause congenital candidiasis in the fetus, which presents in the first 24 h after birth [8].

Trichomonas vaginalis infection has a prevalence of up to 50% in the pregnant population. Due to controversial results in the literature, routine screening and treatment are currently not recommended; however symptomatic patients should be treated with metronidazole [8].

Bacterial vaginosis (BV) appears in up to 30% of pregnant women. BV results from a change in the balance of *Lactobacillus* to anaerobes, e.g. *G. vaginalis* or *Mycoplasma hominis*. Only symptomatic patients require treatment with metronidazole [8, 48]. BV is associated with late miscarriage, preterm birth and premature rupture of membranes.

18.7 Septic Abortions

A septic abortion is any abortion (spontaneous or induced) complicated by an upper genital tract infection (endometritis, parametritis).

Septic abortion rarely complicates abortions performed under controlled circumstances [49, 50]. Conversely, septic abortions remain a significant healthcare problem in countries where abortion is illegal or where it is used as a method of contraception. Illegal abortions are often carried out by unqualified caregivers, in an environment capable of providing only minimal medical services. A septic conditions and hand hygiene are often not practiced and antibiotic prophylaxis is often not administered [50, 51]. Worldwide 14% of pregnancy-related deaths occur secondary to spontaneous or induced abortions [2]. WHO estimates are that each year 22 million unsafe abortions take place, leading to five million admissions to hospital, 98% of them in developing countries, causing death in approximately 47,000 women and disability in five million women [52]. The possible long-term consequences of a septic abortion include chronic pain, pelvic inflammatory disease, or infertility. The risk of acute complications, such as uterine perforation, increases with the progression of gestation [50, 53].

Any women of childbearing age presenting with the symptoms listed in Table 18.1 should be investigated for septic abortion.

Infection related to abortion can rapidly progress to localized pelvic infection. If left untreated, peritonitis, systemic bacteremia, sepsis, and septic shock may occur. Other complications include pelvic abscess, entero-vaginal fistula and septic pelvic thrombophlebitis [53, 54]. Instrumentation during termination of pregnancy can potentially injure the uterine walls, leading to uterine rupture or bowel injury. Sepsis due to septic abortion carries the risk of multi-organ failure: acute kidney injury, shock, encephalopathy, disseminated intravascular coagulopathy (DIC), ARDS and even death have been described [55].

Table 18.1 Clinical symptoms and signs of septic abortion

Fever
Abdominal pain
Odorous and purulent vaginal discharge
Possible vaginal bleeding
Pelvic tenderness

18.8 Investigation of Pregnant Women with Suspected Sepsis

A detailed history should be taken. If the obstetric history includes a recent pregnancy, the circumstances of the termination should be investigated, including the instruments used, the use of intrauterine solutions and microbiological or histology sample results if such are available. A pregnancy test can confirm the history of a recent pregnancy, as the beta human chorionic gonadotropin (beta HCG) level remains elevated for 6 weeks after termination or loss of pregnancy [53].

Abdominal and pelvic *examination* may reveal tenderness and/or rebound. Tenderness usually starts in the pelvis but extends to the whole abdomen as local inflammation progresses to generalized peritonitis. It is important to assess whether the uterus is enlarged on physical examination and if odorous vaginal discharge is present.

Laboratory tests constitute an important part of the diagnostic process in cases of sepsis. A complete blood count and inflammatory markers should be taken. Laboratory indicators of organ failure need to be monitored.

Cultures (blood, urine, sputum, vaginal) need to be taken early (within an hour) and are crucial in guiding later antibiotic therapy.

Abdominal and vaginal *ultrasound* typically shows dilated, fluid-filled fallopian tubes. Ultrasound may also reveal the presence of remaining tissue in the uterus. Ultrasound can also assist in ruling out the presence of abdominal collections and abscesses [53, 56].

If uterine perforation or bowel injury is suspected, *computed tomography (CT)* is the imag-

ing modality of choice. CT may identify disruption of the uterine wall, visceral perforation, intra-abdominal or retroperitoneal fluid collections and abscesses. In case of Clostridium myometritis, gas bubbles are often apparent within the wall of the uterus. MRI may provide better radiologic resolution for discrimination between soft tissues. MRI also carries a lower risk of radiation exposure and is therefore considered safer in pregnancy. However its availability in an emergency setting is limited [57]. In case of sepsis and especially multi-organ failure, saving the mother's life is an absolute priority over saving the pregnancy. The imaging modality should therefore be chosen based on the aim of achieving diagnosis as fast as possible.

Once the option of septic abortion has been raised, it is important to initiate *broad-spectrum antibiotics* early. The infection present is often polymicrobial, predominantly including pathogens from the vaginal flora: anaerobic species, e.g. *Peptostreptococcus*, *Staphylococcus* spp., *Clostridium* spp., *Group A Streptococcus*, and *Escherichia coli* [56, 58]. The presence of a sexually transmitted pathogen, particularly *Chlamydia*, has been associated with a significant risk for pelvic infection [56, 59]. *Clostridium* spp. may cause severe, potentially fatal, infection [60]. A recent Cochrane review shows no clinically significant difference in outcomes with intravenous clindamycin versus penicillin plus chloramphenicol for the treatment of septic abortions [50].

Any retained product of pregnancy needs to be evacuated urgently. Specimens sent for microbiology testing are useful for guiding antibiotic treatment. In case of visceral or uterine injury, a general surgeon should be involved as laparotomy is needed.

Abdominal collections may be drained radiologically under ultrasound or computer tomography guidance.

Fluid resuscitation needs to start early (within 1 h), as in any case of sepsis. Supportive care is warranted in the presence of organ failure. Patients with sepsis or signs of organ failure need to be supported in a critical care unit.

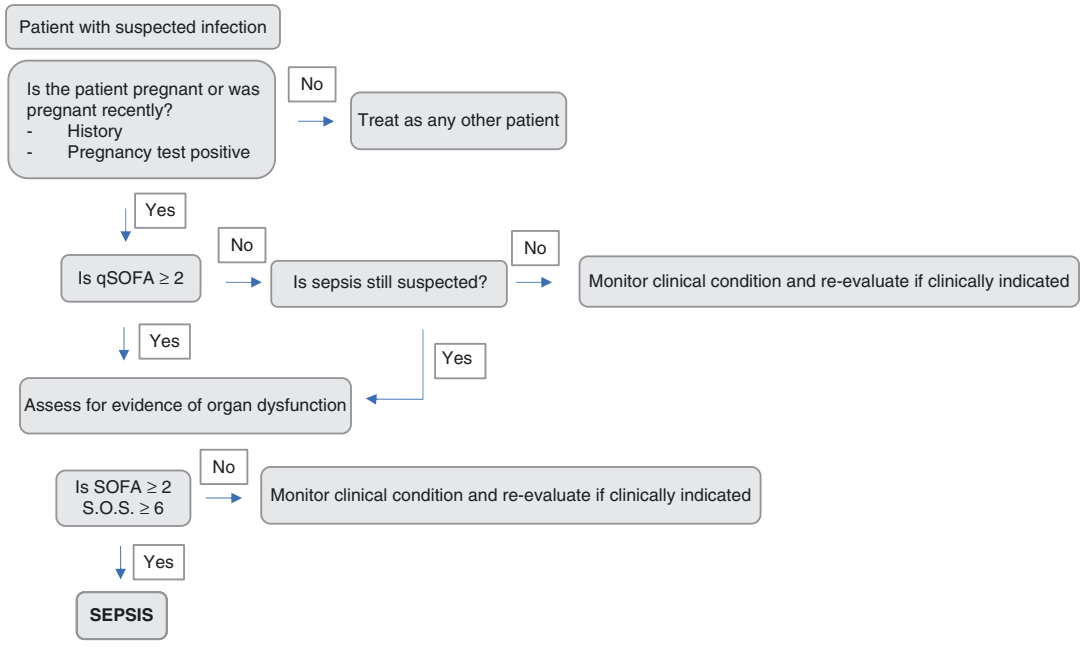
18.9 Summary

Sepsis is a significant cause of maternal mortality worldwide. Early recognition and treatment is essential in the prevention of maternal and fetal harm. Physiological changes during pregnancy are an important consideration as sepsis may manifest atypically. Modified early warning scores such as the MEOWS, SOS, or obstetric modified qSOFA may be useful.

STDs are becoming more prevalent. Disseminated gonococcal disease and ascending chlamydia infection may induce sepsis. Prompt treatment is essential when managing women with a purulent vaginal discharge or abdominal pain, while keeping in mind that some first-line medications are contraindicated in pregnancy. Antibiotic options may also be limited by drug resistance, especially with *Neisseria gonorrhoeae* infection. Syphilis can cause significant fetal harm including death; penicillin should be used as the first line treatment for syphilis unless contraindicated. The Jarisch-Herxheimer reaction is common in pregnant women and should be managed supportively. Infection related to abortion can progress rapidly to life threatening sepsis; early surgical management and targeted antibiotic therapy may be lifesaving.

Finally, non-obstetric infections are prevalent in pregnancy, and urinary tract infection remains the most common cause of sepsis in this particular patient group. Other important causes of antepartum infection are discussed elsewhere including influenza, malaria, toxoplasmosis, and listeria.

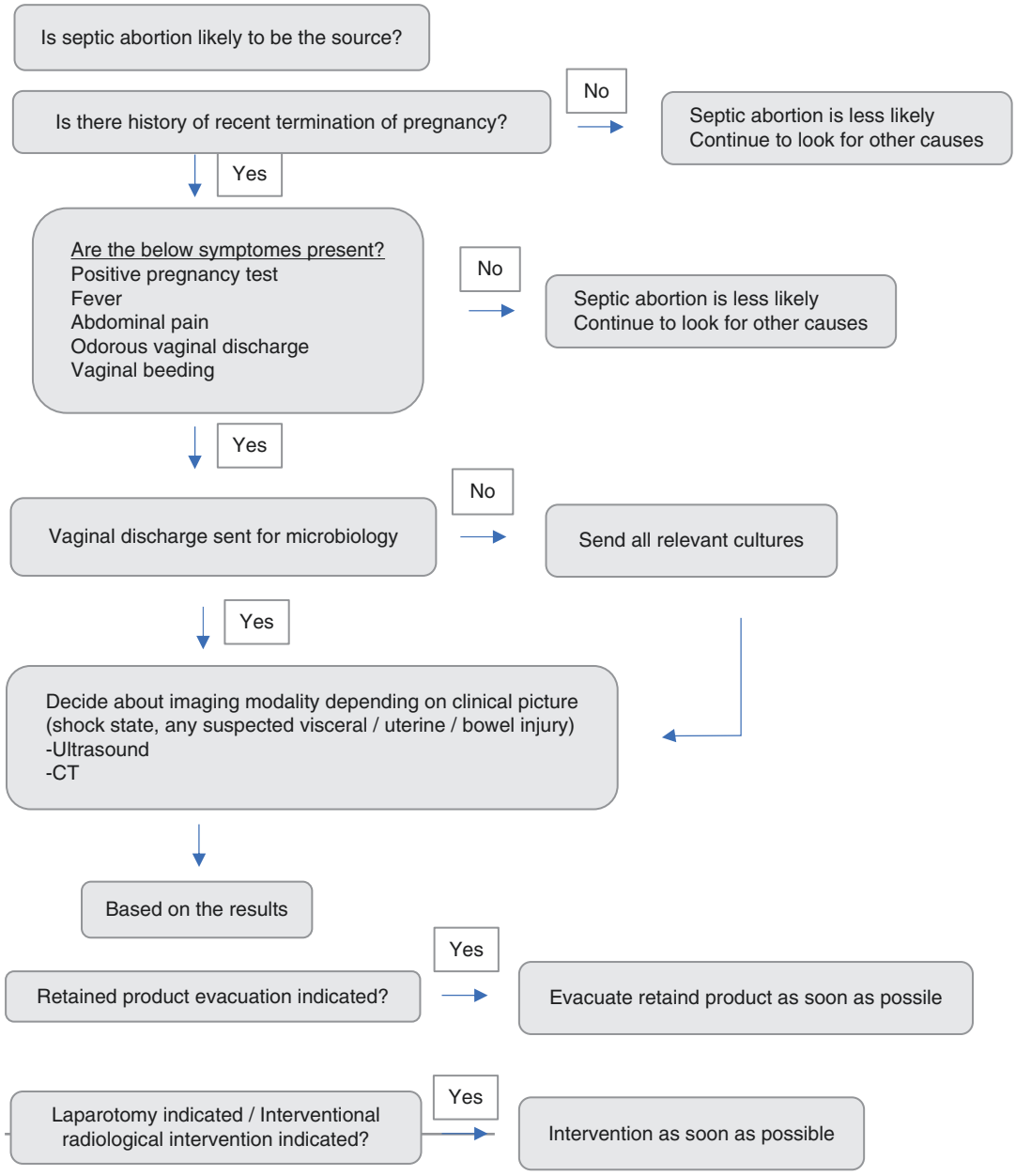
Flow Diagram



Start One hour bundle:
- Measure lactate level
- Take cultures (blood, urine, CSF, sputum, vaginal discharge)
- Start broad spectrum antibiotics
- IV fluids 30 ml/kg if the patient is hypotensive or lactate > 4 mmol/l
- Start vasopressors (Noradrenaline) if remains hypotensive after fluid resuscitation.

Aim for mean arterial pressure (MAP) > 65 mmHg

Imaging according to the most likely source
- X-ray- Radiology
- Ultrasound
- CT - Computed Tomography


Is septic abortion likely to be the source?
Is there history of recent termination of pregnancy?
No
Septic abortion is less likely
Continue to look for other causes
Yes
Are the below symptomes present?
Positive pregnancy test
Fever
Abdominal pain
Odorous vaginal discharge
Vaginal beeding
No
Septic abortion is less likely
Continue to look for other causes
Yes
Vaginal discharge sent for microbiology
No
Send all relevant cultures
Yes
Decide about imaging modality depending on clinical picture
(shock state, any suspected visceral / uterine / bowel injury)
-Ultrasound
-CT
Based on the results
Retained product evacuation indicated?
Yes
Evacuate retaind product as soon as possile
Laparotomy indicated / Interventional radiological intervention indicated?
Yes
Intervention as soon as possible

References

1. Deutschman CS, Neligan PJ, Eid L, Weiss YG. Evidence-based practice of critical care. Evidence-Based Pract Crit Care. 2010; https://doi.org/10.1016/B978-1-4160-5476-4.00073-0.
2. Kassebaum NJN, Bertozzi-Villa A, Coggeshall MSMMS, et al. Global, regional, and national levels and causes of maternal mortality during 1990–2013: a systematic analysis for the global burden of disease study 2013. Lancet. 2014;384:980–1004.
3. WHO (2016) WHO | Maternal mortality. In: WHO. http://www.who.int/mediacentre/factsheets/fs348/en/. Accessed 3 Jun 2017.
4. Knight M, Bunch K, Tuffnell D, Jayakody H, Shakespeare J, Kotnis R, Kenyon S, Kurinczuk JJ, on behalf of MBRRACE-UK. Saving lives, improving mothers' care—lessons learned to inform maternity care from the UK and Ireland confidential enquiries into maternal deaths and morbidity 2014–16. Oxford: National Perinatal Epidemiology Unit, University of Oxford; 2018.
5. Brocklehurs Peter KJJ, KMNMTDKSSJ. Saving lives, improving mothers' care: EMBRRACE UK; 2016. p. 1–100.
6. Knowles SJ, O'Sullivan NP, Meenan AM, Hanniffy R, Robson M. Maternal sepsis incidence, aetiology and outcome for mother and fetus: a prospective study. BJOG. 2015;122:663–71.
7. Acosta CD, Kurinczuk JJ, Lucas DN, Tuffnell DJ, Sellers S, Knight M. Severe maternal sepsis in the UK, 2011–2012: a National Case-Control Study. PLoS Med. 2014;11:e1001672.
8. Creasy RKK, Resnik R, Iams JDD, Greene MF, Iams JDD, Lockwood CJ. Creasy and Resnik's maternal-fetal medicine; principles and practice: Saunders/Elsevier; 2009.
9. Koga K, Cardenas I, Aldo P, Abrahams VM, Peng B, Fill S, Romero R, Mor G. Activation of TLR3 in the trophoblast is associated with preterm delivery. Am J Reprod Immunol. 2009;61:196–212.
10. Sharma SK, Philip J, Wiley J. Thromboelastographic changes in healthy parturients and postpartum women. Anesth Analg. 1997;85:94–8.
11. Baboonian C, Griffiths P. Is pregnancy immunosuppressive? Humoral immunity against viruses. BJOG. 1983;90:1168–75.
12. Krause PJ, Ingardia CJ, Pontius LT, Malech HL, LoBello TM, Maderazo EG. Host defense during pregnancy: neutrophil chemotaxis and adherence. Am J Obstet Gynecol. 1987;157:274–80.
13. Rasmussen SA, Jamieson DJ, Bresee JS. Pandemic influenza and pregnant women. Emerg Infect Dis. 2008;14:95–100.
14. Marzi M, Vigano A, Trabattoni D, Villa ML, Salvaggio A, Clerici E, Clerici M. Characterization of type 1 and type 2 cytokine production profile in physiologic and pathologic human pregnancy. Clin Exp Immunol. 1996;106:127–33.
15. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017;43:304–77.
16. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315:801–10.
17. Ferreira FL, Bota DP, Bross A, Mélot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA. 2001;286:1754–8.
18. Bauer ME, Bateman BT, Bauer ST, Shanks AM, Mhyre JM. Maternal sepsis mortality and morbidity during hospitalization for delivery. Anesth Analg. 2013;117:944–50.
19. Acosta CD, Knight M, Lee HC, Kurinczuk JJ, Gould JB, Lyndon A. The continuum of maternal sepsis severity: incidence and risk factors in a population-based cohort study. PLoS One. 2013;8:e67175.
20. Bowyer L, Robinson HL, Barrett H, et al. SOMANZ guidelines for the investigation and management sepsis in pregnancy. Aust N Z J Obstet Gynaecol. 2017;57:1–12.
21. Jain S, Guleria K, Suneja A, Vaid NB, Ahuja S. Use of the sequential organ failure assessment score for evaluating outcome among obstetric patients admitted to the intensive care unit. Int J Gynecol Obstet. 2016;132:332–6.
22. Oliveira-Neto A, Parpinelli MA, Cecatti JG, Souza JP, Sousa MH. Sequential organ failure assessment score for evaluating organ failure and outcome of severe maternal morbidity in obstetric intensive care. ScientificWorldJournal. 2012;2012:172145.
23. Singh S, McGlennan A, England A, Simons R. A validation study of the CEMACH recommended modified early obstetric warning system (MEOWS). Anaesthesia. 2012;67:12–8.
24. Albright CM, Ali TN, Lopes V, Rouse DJ, Anderson BL. The sepsis in obstetrics score: a model to identify risk of morbidity from sepsis in pregnancy. Am J Obstet Gynecol. 2014;211:39.e1–8.
25. Albright C, Ali T, Lopes V, Rouse D, Anderson B. Lactic acid measurement to identify risk of morbidity from sepsis in pregnancy. Am J Perinatol. 2014;32:481–6.
26. Aarvold ABR, Ryan HM, Magee LA, von Dadelszen P, Fjell C, Walley KR. Multiple organ dysfunction score is superior to the obstetric-specific sepsis in obstetrics score in predicting mortality in septic obstetric patients. Crit Care Med. 2017;45:e49–57.
27. Centers for Disease Control and Prevention. (2017) Sexually Transmitted Disease Surveillance 2015: Gonococcal Isolate Surveillance Project (GISP) Supplement and Profiles.
28. Miller JM, Maupin RT, Mestad RE, Nsuami M. Initial and repeated screening for gonorrhea during pregnancy. Sex Transm Dis. 2003;30:728–30.

29. Berggren EK, Patchen L. Prevalence of Chlamydia trachomatis and Neisseria gonorrhoeae and repeat infection among pregnant urban adolescents. Sex Transm Dis. 2011;38:172–4.
30. Alger LS, Lovchik JC, Hebel JR, Blackmon LR, Crenshaw MC. The association of chlamydia trachomatis, Neisseria gonorrhoeae, and group B streptococci with preterm rupture of the membranes and pregnancy outcome. Am J Obstet Gynecol. 1988;159:397–404.
31. Handsfield HH, Hodson WA, Holmes KK. Neonatal gonococcal infection. I. Orogastric contamination with Neisseria gonorrhoeae. JAMA. 1973;225:697–701.
32. Belkacem A, Caumes E, Ouanich J, Jarlier V, Dellion S, Cazenave B, Goursaud R, Lacassin F, Breuil J, Patey O. Changing patterns of disseminated gonococcal infection in France: cross-sectional data 2009–2011. Sex Transm Infect. 2013;89:613–5.
33. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015;64:1–137.
34. Bignell C, FitzGerald M. UK national guideline for the management of gonorrhoea in adults, 2011. Int J STD AIDS. 2011;22:541–7.
35. Barton J, Braxton J, Davis DW, et al. Sexually transmitted disease surveillance 2015; 2016 https://www.cdc.gov/std/stats16/CDC_2016_STDS_Report-for508WebSep21_2017_1644.pdf. acccesed 20 Nov 2019.
36. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. Sex Transm Infect. 1999;75:3–17.
37. Nwokolo NC, Dragovic B, Patel S, Tong CW, Barker G, Radcliffe K. 2015 UK national guideline for the management of infection with Chlamydia trachomatis. Int J STD AIDS. 2016;27:251–67.
38. Walker DG, Walker GJA. Forgotten but not gone: the continuing scourge of congenital syphilis. Lancet Infect Dis. 2002;2:432–6.
39. Public Health England (PHE). Sexually Transmitted Infections and Chlamydia Screening in England, 2016; 2017.
40. Newman L, Kamb M, Hawkes S, Gomez G, Say L, Seuc A, Broutet N. Global estimates of syphilis in pregnancy and associated adverse outcomes: analysis of multinational antenatal surveillance data. PLoS Med. 2013;10:e1001396.
41. BMJ Best Practice. Syphilis infection. In: BMJ Best Pract; 2016. http://bestpractice.bmj.com/best-practice/monograph/50/diagnosis/step-by-step.html. Accessed 29 Jul 2017.
42. Oswal S, Lyons G. Syphilis in pregnancy. Contin Educ Anaesth Crit Care Pain. 2008;8:224–7.
43. U.S. Department of Health and Human Services. Syphilis in Pregnancy—2015 STD Treatment Guidelines; 2015. https://www.cdc.gov/std/tg2015/syphilis-pregnancy.htm. Accessed 30 Jul 2017.
44. Walker GJ. Antibiotics for syphilis diagnosed during pregnancy. Cochrane Database Syst Rev. 2001:CD001143.
45. Green-top Guideline. Bacterial sepsis in pregnancy. R Coll Obstet Gynacologists. 2012:1–14.
46. Benhamou D, Chassard D, Mercier FJ, Bouvier-Colle M-H. The seventh report of the confidential enquiries into maternal deaths in the United Kingdom: comparison with French data. Ann Fr Anesth Reanim. 2009;28(1):38–43. https://doi.org/10.1016/j.annfar.2008.11.002. Epub 2008 Dec 19.
47. Aguin TJ, Sobel JD. Vulvovaginal candidiasis in pregnancy. Curr Infect Dis Rep. 2015;17:30.
48. National Guideline Clearinghouse (NGC). UK national guideline for the management of bacterial vaginosis 2012. Group 1–15; 2012.
49. Raymond EG, D a G. The comparative safety of legal induced abortion and childbirth in the United States. Obstet Gynecol. 2012;119:1271–2.
50. Udoh A, Effa EE, Oduwole O, Okusanya BO, Okafo O. Antibiotics for treating septic abortion. Cochrane Database Syst Rev. 2016; https://doi.org/10.1002/14651858.CD011528.pub2.
51. Sreelakshmi U, Thejaswini J, Bharathi T. The outcome of septic abortion: a tertiary care hospital experience. J Obstet Gynecol India. 2014;64:265–9.
52. WHO (2015) WHO | Safe abortion: technical and policy guidance for health systems. WHO. doi: https://doi.org/10.1017/CBO9781107415324.004.
53. Stubblefield PPGP, Grimes DA. Septic abortion. N Engl J Med. 1994;331:310–4.
54. Faro S, Pearlman M. Infections and abortion: Elsevier; 1992.
55. Bhattacharya S, Mukherjee G, Mistri P, Pati S. Safe abortion—still a neglected scenario: a study of septic abortions in a tertiary hospital of rural India. Online J Heal Allied Sci. 2010;9:1.
56. Smaill FM, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. Cochrane Database Syst Rev. 2015;8:CD000490.
57. Sherpa D, Johnson BD, Ben-Youssef L, Nagdev A. Diagnosis of septic abortion with point-of-care ultrasound. Clin Pract Cases Emerg Med. 2017;1:268–9.
58. Eschenbach DA. Treating spontaneous and induced septic abortions. Obstet Gynecol. 2015;125:1042–8.
59. Blackwell AL, Thomas PD, Emery SJ, Wareham K. Health gains from screening for infection of the lower genital tract in women attending for termination of pregnancy. Lancet. 1993;342:206–10.
60. Fischer M, Bhatnagar J, Guarner J, et al. Fatal toxic shock syndrome associated with Clostridium sordellii after medical abortion. N Engl J Med. 2005;353:2352–60.

Infections in Late Pregnancy and Puerperium

19

Raghad A. Hussein, Jonathan D. Perez, Joseph L. Smith, and Mary Jane Reed

Key Points

- Compared to the general population, pregnant women are at higher risk of acquiring infections.
- The definition of maternal sepsis has evolved over the years to focus on organ dysfunction, as this facilitates prompt recognition and treatment of potentially deadly infections.
- Chorioamnionitis is inversely related to gestational age and can lead to premature delivery. Non-specific signs and symptoms can make the diagnosis difficult. Timely recognition and administration of appropriately broad antimicrobials decrease maternal and fetal morbidity and mortality.
- Although rare, surgical wound and soft tissue infections from *Staphylococcus pyogenes* and group A streptococci can lead to toxic shock syndrome with subsequent multiorgan failure.
- Maternal obesity and cesarean section are the two most common risk factors for developing surgical site infection. Prophylactic administration of antibiotics significantly reduces the frequency of these complications.
- Necrotizing fasciitis is a fulminant infection which commonly presents as an ambiguous clinical picture that often leads to delayed diagnosis and a relatively high mortality rate. It is a surgical emergency that requires serial debridement and broad-spectrum antibiotics.
- Pregnant women are at increased risk of urinary tract infections. Preventive screening could lead to early recognition and prevention of potentially life-threatening pyelonephritis.
- Listeriosis is a food-borne illness that, if acquired during pregnancy, could be detrimental to maternal and fetal outcomes. Pregnant women are at increased risk of infections and often present with non-specific complaints.
- Malaria is more likely to be severe in primigravida and pregnant women without immunity to *Plasmodium* sp.

R. A. Hussein
Department of Critical Care Medicine, Geisinger Medical Center, Danville, PA, USA
e-mail: rahussein@geisinger.edu

J. D. Perez
Department of Critical Care Medicine, Medical Center Navicent Health, Macon, GA, USA
e-mail: jdplopez@gmail.com

J. L. Smith
Department of Critical Care Medicine and Infectious Disease, Geisinger Medical Center, Danville, PA, USA
e-mail: jol.smith@gmail.com

M. J. Reed (✉)
Department of Critical Care Medicine and Surgery, Geisnger Medical Center, Danville, PA, USA
e-mail: mreed@geisinger.edu

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_19

19.1 Introduction

Sepsis is a potentially preventable condition which consistently remains the third most common cause of direct maternal deaths in low-, middle-, and high-income countries. In the last 25 years, the annual global number of maternal deaths has declined from an estimated 532,000 in 1990 to an estimated 303,000 in 2015 [1]. Nevertheless, approximately 75,000 women and one million neonates, primarily in resource-limited countries, still die every year from maternal sepsis complications. Postpartum bacterial infections alone account for approximately 10–15% of this global burden of maternal deaths [2, 3]. In the United States, the incidence of antepartum and puerperal sepsis has been estimated to be 0.4–0.6 per 1000 deliveries, accounting for 13% of maternal deaths and 5% of intensive care unit (ICU) admissions [4–6]. In addition to the risk of death and short-term complications, puerperal sepsis is associated with long-term morbidities and unique obstetric complications, such as chronic pelvic pain and secondary infertility due to salpingitis and fallopian tube adhesions [6].

Infections in late pregnancy and puerperal sepsis have received less attention than other causes of maternal death such as peripartum hemorrhage and hypertensive diseases of pregnancy. A fundamental strategy to reduce maternal mortality should include prevention, diagnosis, and treatment of peri-partum infections and sepsis.

19.2 The Complexity of Defining Maternal Sepsis

Determining the global incidence of infections occurring in late pregnancy and the peripartum period is difficult. Most of these infections occur in developing countries. Data from these countries are either missing or extrapolated from retrospective studies. Accordingly, the available information reflects the overall burden of infectious disease rather than the actual incidence of infection. Furthermore, in resource-limited countries, most infections remain undiagnosed and unreported due to inadequate access to health care and lack of postnatal follow-up [2, 3]. Another significant factor limiting the accuracy of epidemiological data is inconsistent definitions. Maternal sepsis, genital tract sepsis, puerperal fever, puerperal sepsis, and puerperal infection have all been used interchangeably in the literature, leading to confusion.

Since 1991, sepsis in the non-pregnant population has been defined by the physiological response to infection, i.e., the systemic inflammatory response syndrome (SIRS). However, SIRS criteria overlap with the normal physiologic response to pregnancy and childbirth. This overlap contributes to the difficulty in promptly identifying maternal sepsis, with consequent inadequate or delayed management [7]. An increasing number of clinicians are therefore using early warning scores that have been modified for pregnancy to facilitate identification of maternal deterioration (Chap. 2). Laboratory testing provides little additional information, as pregnancy is accompanied by a physiological increase in white cell counts and a dynamic inflammatory response [8]. The diagnostic accuracy of lactate in maternal infection remains unclear [9, 10].

The World Health Organization (WHO) defines puerperal sepsis as "infection of the genital tract occurring at any time between the onset of the rupture of membranes or labor and the 42nd day postpartum in which fever and one or more of the following are present: pelvic pain, abnormal vaginal discharge, abnormal odor of discharge, or delay in the involution of the uterus." [11, 12] In 2016, in conjunction with the Sepsis-3 consensus, maternal sepsis was redefined as "a life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or the postpartum period." [7, 13]

19.3 Maternal Sepsis

19.3.1 Risk Factors

Pregnancy-induced immunological adaptation is discussed elsewhere in this book (Chap. 15). Pregnant women are particularly susceptible to

certain infections. Typical examples include parasitic diseases such as malaria, bacterial diseases such as listeriosis, and viral infections such as influenza, hepatitis E, and herpes simplex [12].

Known risk factors for puerperal sepsis include cesarean section (CS), which increases the risk fivefold [14, 15]. Other risk factors include obesity, diabetes, prolonged rupture of membranes, repeat vaginal examinations, bacterial vaginosis, carriage of group A streptococcus (GAS), and urinary tract anomalies, including bladder trauma [16, 17].

19.3.1.1 Categories of Infection Occurring during Pregnancy and the Peripartum Period

Infections in pregnant and postpartum women can be categorized as pregnancy-specific, exacerbated during pregnancy or incidental to pregnancy. Pregnancy-specific infections include acute chorioamnionitis, endometritis (with or without retained products of conception), toxic shock syndrome (TSS), wound infections, necrotizing soft tissue infections of the perineum and lactational mastitis. Lactational mastitis rarely causes severe maternal disease that requires ICU admission and will not be discussed in this chapter. Infections exacerbated during pregnancy include urinary tract infections, pneumonia, listeriosis, toxoplasmosis, and viruses (i.e., rubella, influenza, varicella, herpes, parvovirus, cytomegalovirus). Severe maternal viral infections are addressed in detail in Chap. 17. Infections incidental to pregnancy often include human immunodeficiency virus (HIV), sexually transmitted diseases (STDs), tuberculosis, and endocarditis. However, many common infections can cause serious maternal illness, given the right clinical opportunity. These are not discussed in this chapter.

19.3.2 Pregnancy-Specific Infections

19.3.2.1 Chorioamnionitis (CA)

Chorioamnionitis is a primary infection of the chorion and amniotic membranes accompanied by an inflammatory response. It is also termed intrauterine infection (IAI); recently, an expert panel recommended using the term intrauterine infection and inflammation (triple I) [18]. Chorioamnionitis usually results from the compromise of the amniotic sac integrity (spontaneously or iatrogenically), thus exposing the normally sterile intrauterine cavity to the vaginal flora. It may also occur with intact placental membranes due to specific genital tract mycoplasmas or hematogenous spread of bacteria (e.g., listeriosis) [19, 20]. Chorioamnionitis usually occurs from prolonged rupture of the amniotic membranes [21]. Bacterial vaginosis and invasive procedures (e.g., internal fetal monitoring, amniocentesis, chorionic villous sampling) are also associated with risk factors [18]. The infection is often polymicrobial, with *Ureaplasma urealyticum* and *Gardnerella vaginalis* being the two most frequent isolates [22]. Other typical organisms include *Bacteroides* sp., *Mycoplasma hominis*, group B Streptococcus, *Neisseria gonorrhea*, and *Trichomonas vaginalis*. Viruses such as enterovirus, respiratory syncytial virus, Epstein–Barr virus, cytomegalovirus, and adenovirus may also play a role [22].

Chorioamnionitis should be considered in the differential diagnosis when a gravid patient presents with a temperature exceeding 38.0 °C (100.4 °F), maternal tachycardia, fetal tachycardia, chills, and lower abdominal pain, accompanied by purulent vaginal discharge. Symptoms are often nonspecific and may only appear at a late stage of the illness; hence a high index of suspicion is warranted [18, 21].

Broad-spectrum antibiotic coverage should be started immediately, but to date, there is limited evidence regarding the most appropriate antimicrobial regimen and treatment duration [23]. The combination of ampicillin (2gm q6hrs) with gentamycin (1.5 mg/Kg q8 hours or 5 mg/kg/q24 hours) is most commonly used. Less studied but probably equally efficacious alternatives to beta-lactamase penicillins include second- or third-generation cephalosporins or clindamycin (900 mg q8 hours) [24, 25]. Given that streptococcal and staphylococcal species (particularly group B strep and *S. aureus*) have an increasing

rate of resistance to clindamycin, vancomycin is also an alternative. If cesarean delivery is performed in a patient with chorioamnionitis, antibiotics should also include coverage for anaerobes (e.g., clindamycin, metronidazole) [18, 21]. Duration of therapy is through delivery; however, postpartum clinical end points vary in the literature depending on the patient's response and/or complications [18, 22–25].

Amnioinfusion has been proposed as a therapeutic measure for chorioamnionitis. There is no evidence regarding either the effectiveness or the safety of transcervical amnioinfusion for chorioamnionitis. There are no trials studying transabdominal amnioinfusion [26].

A multidisciplinary team including a senior obstetrician, anesthesiologist, intensivist, infectious disease expert, and neonatologist should decide the timing and mode of delivery. This individualized decision depends upon maternal medical and obstetrical history, the clinical response to antibiotic and supportive therapy, current maternal condition, and fetal viability. Cases which may require induction of delivery are those with precipitous maternal deterioration (to save the mother) and those which do not respond clinically to intravenous antibiotic therapy (to save the fetus). After delivery, both maternal and fetal surfaces of the placenta should be cultured [27–29].

The major maternal complications of chorioamnionitis are maternal septic shock, postpartum hemorrhage, premature delivery, and an increase in postpartum hysterectomies [27–29]. Hysterectomy may be performed in an effort to save the mother. The incidence of chorioamnionitis is inversely related to gestational age, occurring in up to 40–70% of preterm deliveries versus 2–4% of term pregnancies [30].

19.3.2.2 Toxic Shock Syndrome

TSS is a rare, life-threatening illness caused by the massive release of inflammatory mediators. This "cytokine storm" is typically triggered by toxins released by *Staphylococcus pyogenes* (TSS toxin-1, enterotoxin B or C) or by the virulent M-protein produced by group A streptococci [31]. Some authors refer to the latter as Streptococcal toxic shock-like syndrome (STSS) [32].

In developed countries, the incidence of TSS is 0.3–0.5:100,000 in women of menstrual age, and that of STSS is 2–4:100,000 cases per the general population [33, 34] Women may acquire these infections during pregnancy and the postpartum period from infected wounds, mastitis, or any deep-seated subcutaneous and soft tissue infections [32, 35].

TSS, best known for its association with the use of high-absorbency tampons, typically manifests in otherwise healthy women. Conversely, STSS is typically associated with a pre-existing painful skin infection. The early manifestations of both TSS and STSS are non-specific, including fever, myalgias, mild confusion, and hypotension. A diffuse rash, which often resembles sunburn, is more typical of TSS. Clinical deterioration to coma and multiorgan failure ensues rapidly (within hours). A list of six criteria for STSS from the CDC can be used to classify either confirmed (fulfill all six criteria) or probable (fulfill five criteria) cases (Fig. 19.1) [36].

The primary infection location must be identified for TSS treatment (e.g., soft tissue, wound) and the source/cause of infection controlled (e.g., surgical debridement, removal of foreign body). Antibiotics should be provided as soon as possible (see Table 19.1). There is limited data on the utility of intravenous immunoglobulin as adjunctive therapy in TSS [36]. All cases with clinical suspicion of TSS or STSS should be admitted immediately to an intensive care unit where supportive care may rapidly be provided for failing organs. The mortality associated with this condition remains high [37].

A less well known but potentially lethal pathogen is *Clostridia sordellii*, which may cause postpartum endometritis with subsequent TSS. This infection is characterized by a robust leukemoid reaction and hemoconcentration. The usual presentation is afebrile and painless. In one case series of TSS caused by *C. sordellii*, the maternal mortality rate was 100% if occurring after childbirth or abortion [38].

Clinical Criteria TSS-other than Streptococcal [37]

An illness with the following clinical manifestations:

- Fever: temperature greater than or equal to 102.0°F (greater than or equal to 38.9°C)
- Rash: diffuse macular erythroderma
- Desquamation: 1-2 weeks after onset of rash
- Hypotension: systolic blood pressure less than or equal to 90 mm Hg for adults or less than fifth percentile by age for children aged less than 16 years
- Multisystem involvement (three or more of the following organ systems):
  - Gastrointestinal: vomiting or diarrhea at onset of illness
  - Muscular: severe myalgia or creatine phosphokinase level at least twice the upper limit of normal
  - Mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia
  - Renal: blood urea nitrogen or creatinine at least twice the upper limit of normal for laboratory or urinary sediment with pyuria (greater than or equal to 5 leukocytes per high-power field) in the absence of urinary tract infection
  - Hepatic: total bilirubin, alanine aminotransferase enzyme, or asparate aminotransferase enzyme levels at least twice the upper limit of normal for laboratory
  - Hematologic: platelets less than 100,000/mm^3
  - Central nervous system: disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent

Laboratory Criteria for Diagnosis

Negative results on the following tests, if obtained:

- Blood or cerebrospinal fluid cultures blood culture may be positive for *Staphylococcus aureus*
- Negative serologies for Rocky Mountain spotted fever, leptospirosis, or measles

Case Classification

Probable

A case which meets the laboratory criteria and in which four of the five clinical criteria described above are present

Confirmed

A case which meets the laboratory criteria and in which all five of the clinical criteria described above are present, including desquamation, unless the patient dies before desquamation occurs

Fig. 19.1 Clinical criteria for TSS

Table 19.1 Antibiotic coverage for TSS and streptococcal toxic shock-like syndrome

Organism	Antibiotic regimen
Streptococcus species	Clindamycin plus carbapenem or penicillin with a beta-lactamase
Staphylococcus species	Clindamycin plus antistaphylococcal antibiotic; vancomycin for MRSA and nafcillin or oxacillin for MSSA

MRSA methicillin-resistant *Staphylococcus aureus, MSAA* methicillin-sensitive *Staphylococcus aureus*

19.3.2.3 Surgical Site Infection and Necrotizing Soft Tissue Infections

Surgical site infection (SSI) is defined as an infection of the skin and subcutaneous tissue surrounding an incision occurring within 30 days of surgery. Diagnosis requires the presence of at least one of the following signs or symptoms: local pain or tenderness, swelling, redness or heat, purulent drainage from the incision (regard-

less of laboratory confirmation of infection), organisms isolated from an aseptically obtained culture from the incision (fluid or tissue), or clinical diagnosis made by a surgeon or attending physician [39].

Administration of prophylactic antibiotic therapy has been shown to significantly decrease maternal SSIs after cesarean delivery [40]. Administration of antibiotics before skin incision rather than after umbilical cord clamping is associated with a 50% reduction in the rate of maternal SSI without affecting neonatal outcomes [41–43]. Despite this, SSI remains one of the more common complications of lower segment cesarean delivery and subsequent maternal sepsis. The CDC US national surveillance study found that 3.2% of the women undergoing cesarean delivery had SSI [44]. In a UK multicenter study of 14 hospitals, 9.6% of women undergoing cesarean delivery developed SSI [45]. The high rate of SSI is of particular concern given the global increase in cesarean delivery rates and maternal obesity, which are associated with almost double the rate of cesarean delivery [46]. Of note, studies of maternal SSI after cesarean delivery are usually not comparable because of their lack of standardization in the definition of SSI, quality of surveillance, heterogeneity of the studied populations, prophylactic antibiotics coverage, aseptic practices, surgical techniques, and routine lengths of maternal hospital stays.

Necrotizing soft tissue infections (NSTIs) are fulminant and often life-threatening infections of the subcutaneous tissues. Some predisposing factors are diabetes mellitus, obesity, hypertension, immunosuppressive conditions including alcoholism and intravenous drug abuse, renal failure, malignancy, trauma, childbirth, and surgery [47, 48]. Post-cesarean delivery or episiotomy incisions and perineal tears are the most commonly affected sites for necrotizing infections in the peripartum patient [49–51]. Importantly, necrotizing soft tissue infections can also occur postpartum in women who are otherwise healthy [48].

The discrepancy between symptoms of NSTI and clinical findings are almost pathognomonic and should raise suspicion when it occurs. NSTI patients typically present with severe local pain without overlying skin changes. This feature commonly leads to delayed disease recognition. When the diagnosis is delayed, loss of sensation may be noted in the infected area, typically followed by the appearance of erythema and edema. At very late stages, purple- grayish bullae appear with subsequent tissue necrosis and sloughing.

Historically, NSTIs have been categorized into four microbiological types (Table 19.2) [52]. Type I is a mixed polymicrobial infection. Streptococcal and staphylococcal species cause type II. Types I and II are more commonly encountered after childbirth [53]. Types III and IV are generally caused by *Vibrio vulnificus*, *Aeromonas* sp., *Candida* sp., and *Zygomycetes* sp. and are generally seen in immunosuppressed patients or, in the case of *Vibrio* and *Aeromonas* infections, in patients with exposure to salt or brackish water, respectively. When seen during pregnancy and the peripartum period, this should raise suspicion of immune suppression [53].

NSTIs are a surgical emergency. Early aggressive therapy is the key to survival and reduced morbidity [49, 50]. Wide and serial surgical debridement along with antibiotics is crucial. Unlike other infections, the resulting tissue loss leads both to disfiguring deformity, which requires reconstruction, and to disability, which requires rehabilitation. The Infectious Diseases Society of America (IDSA) recommends early broad-spectrum empiric coverage to cover the possibility of polymicrobial infection [53]. Regimens include vancomycin (30 mg/kg/day) or linezolid (600 mg IV/PO every 12 h) plus piperacillin-tazobactam (3.37 g IV every 6–8 h) or a carbapenem (1 g IV every 6–8 h) or ceftriaxone (2 g IV every 6 h) and

Table 19.2 Microbiology in necrotizing fasciitis

Type of necrotising fasciitis	Organism(s)
Type I (polymicrobial or mixed)	Aerobic and anaerobic bacteria
Type II	Group A beta-hemolytic streptococcus (GAS) with or without Staphylococcus species
Type III	Gram negative organisms; Klebsiella, Aeromonas, and Vibrio species

metronidazole (500 mg IV/PO every 6 h). In cases with proven group A streptococcal infection, penicillin (2–4 MU every 6–8 h IV) and clindamycin (600–900 mg/kg every 8 h) are recommended. Patients with NSTIs commonly exhibit signs and symptoms of systemic toxicity, and, regardless of care, mortality rates have been reported from 6% to 76% and more recently 25% [47]. Early intensive care unit admission is indicated for monitoring and supportive care [49, 50].

19.3.3 Infections Exacerbated during Pregnancy

19.3.3.1 Urinary Tract Infections

Pregnant women have an increased risk for urinary tract infections between 6 and 24 weeks' gestation [54]. Urinary tract infections are classified as asymptomatic bacteriuria (ASB), acute cystitis, and pyelonephritis. The American College of Obstetrics and Gynecology recommends screening women for ASB during their first pre-natal visit and repeating a urine culture during the last trimester [55]. ASB is defined as $>10^5$ colony-forming units per mL of urine. If it remains undiagnosed, ASB can lead to the development of acute cystitis and pyelonephritis in 30 and 50% of pregnant women, respectively [56, 57]. Pregnant women have a 20–30-fold increase of developing pyelonephritis when diagnosed with ASB in early pregnancy [58]. Acute cystitis is differentiated from asymptomatic cystitis by the presence of dysuria, frequency, and urgency. Pyelonephritis is diagnosed when genitourinary symptoms are accompanied by systemic manifestations such as fever, chills, nausea, vomiting, and flank pain. If left untreated, maternal pyelonephritis can lead to severe maternal sepsis [57, 58].

The organisms commonly causing urinary tract infections in pregnant women are generally similar to those observed in non-pregnant women. *Escherichia coli* is the most common, causing 70–90% of cases [59]. *Proteus mirabilis* and *Klebsiella pneumonia* are also common causes. Gram-positive infections are less common, but group B streptococcus has been isolated in 7–10% of the cases of ASB in pregnancy [60, 61].

In symptomatic women, following urine sampling, antibiotics should be started empirically to cover the more common organisms. Coverage can be narrowed once urine culture results become available. Treatment options include cephalosporins (cephalexin 250 mg PO 2–4 times a day), nitrofurantoin (50–100 mg four times daily), and fosfomycin (one 3 g sachet) [54]. Fluoroquinolones and sulfonamides should be avoided if possible due to potential harm to the fetus and potential emergence of resistant organisms. However, if indicated, maternal care is the priority. Furthermore, growing evidence suggests that these antibiotics are safe for the fetus and can be used if necessary based on antibiotic sensitivities of the causative organism [54, 62–64]. The duration of antibiotic treatment for asymptomatic bacteriuria, acute cystitis, or pyelonephritis has not been determined for pregnant women [65]. Given the ongoing risk of recurrence during pregnancy (4–5%), treatment with oral antibiotics is given for a longer duration than in the general population (i.e., 7–10 days) [54, 59].

Women with pyelonephritis should be managed and followed closely; the patient should defervesce within 24–48 h of initiation of antibiotic therapy. Those who deteriorate clinically, remain febrile, and develop signs of worsening systemic infection should be admitted for intravenous antibiotic therapy and hydration. Women who fail to improve or have recurrent infections should undergo renal imaging (ultrasonography or intravenous pyelogram) to assess for pyelonephritis or other structural abnormalities [66, 67].

Pyelonephritis is the leading cause of septic shock in pregnancy, followed by renal calculi. The latter, however, is a rare phenomenon [67, 68]. The incidence of nephrolithiasis in pregnancy ranges from 1:200 to 1:1500 [68–71]. Mortality from maternal urosepsis is rare. Management consists of adequate volume resuscitation, antibiotics, and rarely, surgical interventions to achieve source control. Most renal stones pass on their own, making the need for ureteroscopy or percutaneous nephrostomy drainage infrequent. Invasive treatment is suggested in cases with unremitting pain, persistent fever, worsening renal function, or septic shock [70, 71].

19.3.3.2 *Listeria Monocytogenes*

Listeria monocytogenes is a facultative aerobic Gram-positive rod which may cause food-borne illness weeks to months after ingestion. Pregnant women are particularly prone to *Listeria* infection, accounting for up to 27% of all listeria infections. Typically they experience only mild flu-like symptoms, malaise with or without a headache, gastroenteritis, or diarrhea which often contributes to missed diagnosis during pregnancy [72, 73]. If left untreated, *Listeria* infection during pregnancy may lead to miscarriage, septic abortion, stillbirth, premature delivery, or life-threatening infection of the newborn [72, 74]. Rarely, the maternal condition may deteriorate to full-blown meningoencephalitis, chorioamnionitis, or, potentially, sepsis [75]. Systemic disease may be accompanied by the appearance of multiple abscesses and granulomas. *Listeria* is associated with high mortality; 20–50% in immunocompromised individuals and, to a lesser extent, in pregnant woman [72, 75].

During a listeria outbreak, pregnant women with a fever of unknown origin should have blood cultures drawn to assess for bacteremia. Pregnant women presenting with diarrhea (regardless of additional symptoms) should also submit stool for listeria cultures. The decision to initiate treatment is based upon clinical judgment. However, the threshold for treatment should be low given the difficulties of diagnosing severe maternal illness and the fact that bacteremia can lead to maternal neurological compromise and sepsis and transplacental fetal infection [76].

Ideally, treatment of listeriosis during pregnancy should be guided by an expert in infectious diseases. In milder cases (e.g., febrile gastroenteritis), the recommended treatment is oral amoxicillin (500 mg three times daily). Treatment of women with severe disease involving CNS involvement or endocarditis should also include the addition of gentamycin (goal peak of 3–5 mcg/mL and a trough less than 1 mcg/mL) for synergy [77]. Listeriosis with bacteremia in pregnancy is treated with intravenous ampicillin (2 gm q4 hours) or intravenous trimethoprim-sulfamethoxazole (10–20 mg/kg daily) in cases of severe penicillin allergy. In extreme cases, the pregnant woman may require desensitization therapy. Sulfonamides are generally not teratogenic [63, 64]; however, trimethoprim is a folic acid antagonist and its use during the first trimester of pregnancy has been associated with neural tube and cardiovascular defects [76]. It has also been suggested to cause kernicterus, but this has not been proven [78]. Women who are unable to receive either of the agents mentioned above can be treated with meropenem (2 g IV every 8 h) and vancomycin. This requires close monitoring of treatment efficacy. The duration of treatment during pregnancy remains unstudied and should be based on the clinical response. In most cases, 2 weeks of treatment is sufficient for bacteremia and 3–4 weeks for CNS infection.

19.3.3.3 Toxoplasmosis

Acute toxoplasmosis infection is caused by the intracellular protozoan *Toxoplasma gondii*. Transmission to humans occurs through ingestion of undercooked meat, contact with oocyte-containing cat faeces, and by vertical transmission. Prevalence rates vary worldwide, with higher rates seen in countries with tropical climates or with a culinary interest in undercooked meat [79, 80]. Universal screening is not recommended in areas of low prevalence [81, 82].

Pregnant women may be asymptomatic and have a flu-like illness or regional lymphadenopathy in acute infection [83]. Immunocompromised women may develop severe manifestations including encephalitis, myocarditis, pneumonitis, or hepatitis.

Diagnosis of acute infection in pregnancy is challenging and usually requires two serological tests 2 weeks apart demonstrating a fourfold increase in IgG antibody titer. Hence, a high index of suspicion is required. Treatment may initially be empirical in cases of critical illness if the clinical story and findings are highly suggestive. If acute infection is suspected, spiramycin should be administered as soon as possible. Treatment with pyrimethamine, sulfadiazine, and folinic acid of women should be administered in women who are at high risk of fetal infection. Pyrimethamine is teratogenic and should be avoided during the first trimester [82].

Fetal infection—Primary maternal infection carries the greatest risk to the fetus, although cases of fetal transmission have been described in immunocompromised women with reactivation of chronic infection [84]. Following infection, the placenta becomes a reservoir for toxoplasmosis with the risk of fetal transmission increasing from approximately 6% in the first trimester to 72% by the third [81]. PCR of amniotic fluid is highly sensitive and specific for diagnosis of fetal infection and should be performed after 18 weeks' gestations or 4 weeks after acute maternal infection. Characteristic fetal ultrasound findings include intracranial calcification, microcephaly, hydrocephalus, hepatosplenomegaly, ascites, and severe intrauterine growth retardation [85].

19.3.4 Malaria

Malaria is caused by infection with *Plasmodium* species. *P. falciparum* and *P. vivax* are the most common causative agents, with most global deaths caused by *P. falciparum* [86]. Malaria is an important cause of maternal and infant morbidity and mortality. It is estimated that 10,000 maternal deaths and upwards of 200,000 newborns die annually from pregnancy-associated malaria. Epidemiologic studies estimate that the overall prevalence of *Plasmodium* infection in highly endemic areas is approximately 25% (1 in 4 women); this proportion is likely underestimated based on diagnostic studies and sensitivity. The prevalence of malaria outside sub-Saharan Africa is estimated to be lower, 1.8–17.4%. However, in this population, both maternal and fetal outcomes are worse; lacking prior exposure to the disease there is less opportunity for immunity [87–89].

The signs of infection are non-specific and vary depending on several factors such as maternal age, the degree of immunity, gravidity (pauci vs. multiparous), endemicity, and species. Some women, especially in endemic areas, are asymptomatic. Others present with fever, chills, nausea, vomiting, diarrhea, abdominal pain, headaches, myalgia, jaundice, and cough [87].

Pregnant women, especially in the first trimester, are more susceptible to malaria. Cell-mediated immunity is decreased as cortisol increases [87, 90], which allows the placenta to form. During this period, *P. falciparum*-infected erythrocytes are sequestered and bind to the vascular endothelium of various organs, which can cause more severe disease, especially in the primigravida patient [87–90]. The sequestration of the parasite-infected erythrocytes is especially high in the placental intervillous spaces.

In high endemic areas, few women present with fevers. Rather, the maternal inflammatory response to this sequestration as the pregnancy progresses causes marked injury and scarring to the placental basement membrane. This interferes with blood flow across the placenta and impedes nutrient supply to the fetus. This placental damage is the main mechanism for miscarriages, intrauterine-growth retardation, preterm birth, and low birth weight [90].

Any patient presenting with fevers in endemic regions or returning from an endemic region should be tested for malaria. Parasitemia should be assessed with a peripheral smear, Giemsa-stained, or rapid diagnostics [87]. A negative peripheral smear doesn't rule out malaria infection or parasitemia, as patients could have low parasitic counts or placental parasites without evidence on peripheral smear. Placental infection can be diagnosed after birth by histological examination [87, 89, 90]. The gold standard for detection of malaria is polymerase chain reaction (PCR), but its utility in high endemic areas is questionable, and its clinical importance in submicroscopic infections is yet to be determined. Therefore its use is not routinely recommended. Rapid diagnostic tests are more commonly used for programs of diagnosis, treatment, and prevention of malaria in high endemic areas [86, 88].

Acute malaria with signs of organ dysfuntion is deemed severe malaria. Severe malaria can present with hypoglycemia, pulmonary edema, respiratory distress, cerebral edema, seizures, and severe anemia [91, 92]. The treatment of severe malaria is mainly supportive; however, expedient treatment with parenteral antimalarial therapy in the gravid patient is essential to affect the outcome [92]. Artesunate IV/IM 2.4 mg/kg should be administered at hours 0,

12, 24, and 48. Subsequently, oral therapy of atovaquone-proguanil, doxycycline (if postpartum), clindamycin, or mefloquine should be administered [91, 92]. If artesunate is not available, artemether IM is preferred to quinine in later pregnancy because of the high risk of hypoglycemia with quinine [92].

Care should be taken during administration of fluids. While there is no literature specifically regarding pregnant women, a study of early fluid administration in critically ill septic children due largely to severe malaria showed worse outcomes in those receiving larger amount of fluids, presumably due to worsening of cerebral edema. For more details regarding fluid administration, see Chap. 7.

19.3.5 Fetal Considerations in Maternal Infections

Maternal infections and sepsis have an increased risk of pre-term delivery. Antenatal corticosteroid therapy (ACS) has shown to improve newborn outcomes when given between 24 and 34 weeks' gestation when delivery is within 7 days [93]. When caring for a gravid patient with overwhelming infection, there may be hesitation in giving an additional immunosuppressive drug. Corticosteroid use during overwhelming infection and sepsis has been debated. Studies over the years have shown conflicted finding as to benefit and harm [94, 95].

In high-income countries, there is little debate over the maternal safety of a single dose of either betamethasone or dexamethasone as ACS therapy in the 24–34-week gestation period. It appears that this single dose does not increase infection even in the presence of prolonged rupture of membranes or sepsis [93, 96]. Betamethasone is considered a weak immunosuppressive with short-term use even though it has a longer half life than dexamethasone [93]. Of note, hydrocortisone does not cross the placenta and therefore does not affect fetal lung maturity [96]. In low- and middle-income countries, however, there is some debate of the benefits of ACS in enviroments where the gestational age estimation is not reliable, the perinatal care is not available, and risks of maternal infections may be higher [97, 98]. Recommended WHO pre-requisites for antenatal corticosterid use include accurate gestational age estimation, no evidence of maternal infection, and adequate peripartum care for both the mother and infant. The WHO recommends not giving ACS to patients with documented chorioaminonitis but relates that the recommendation is based on very low quality evidence [99].

An additional consideration for the fetus at risk for pre term delivery is the administration of magnesium sulfate to the mother which acts as a fetal neuroprotective agent in gestations less than 32 weeks. One dosing regimen is 4gram load IV. Care must be taken in renal insufficency, as magnesium is renally excreted [100].

19.4 Conclusions

Maternal sepsis is the third leading cause of maternal death. The gravid patient is more susceptible to infections both because of the physiologic changes of pregnancy and because of the unique pathology that occurs with pregnancy. Diagnosis of infection and sepsis in the pregnant patient is more difficult as the signs and symptoms of infection and sepsis may be obscured by the physiology of pregnancy. The clinician should have a high index of suspicion and know the expected normal physical and laboratory values at each stage of pregnancy. Coordination with a multidiscinplinary team is invaluable.

References

1. WHO, UNICEF, UNFPA, World Bank Group and the United Nations Population Division. Estimates by WHO, UNICEF, UNFPA, World Bank Group and the United Nations Population Division Trends in maternal mortality: 1990 to 2015. 2015. Last accessed Dec 23, 2018 at http://apps.who.int/iris/bitstream/handle/10665/194254/9789241565141_eng.pdf;jsessionid=2C4F861D72C38CCC194096AE34D0363D?sequence=1
2. van Dillen J, Zwart J, Schutte J, van Roosmalen J. Maternal sepsis: epidemiology, etiology and outcome. Curr Opin Infect Dis. 2010;23:249–54.

3. Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. Lancet. 2006;367:1066–74.
4. Mabie WC, Sibai BM. Treatment in an obstetric intensive care unit. Am J Obstet Gynecol. 1990;162:1–4.
5. Kilpatrick SJ, Matthay MA. Obstetric patients requiring critical care. A five-year review. Chest. 1992;101:1407–12.
6. Monaco TJ Jr, Spielman FJ, Katz VL. Pregnant patients in the intensive care unit: a descriptive analysis. South Med J. 1993;86:414–7.
7. Bonet M, Nogueira Pileggi V, Rijken MJ, et al. Towards a consensus definition of maternal sepsis: results of a systematic review and expert consultation. Reprod Health. 2017;14:67.
8. Abbassi-Ghanavati M, Greer LG, Cunningham FG. Pregnancy and laboratory studies: a reference table for clinicians. Obstet Gynecol. 2009;114:1326–31.
9. Aye IL, Lager S, Ramirez VI, et al. Increasing maternal body mass index is associated with systemic inflammation in the mother and the activation of distinct placental inflammatory pathways. Biol Reprod. 2014;90:129.
10. Graham C, Chooniedass R, Stefura WP, et al. In vivo immune signatures of healthy human pregnancy: inherently inflammatory or anti-inflammatory? PLoS One. 2017;12:e0177813.
11. World Health Organization. Maternal health and safe motherhood programme division of family health. Mother–Baby package: implementing safe motherhood in countries. Geneva: WHO; 1994. Last accessed Dec 12, 2018 at http://apps.who.int/iris/bitstream/handle/10665/63268/WHO_FHE_MSM_94.11_Rev.1.pdf?sequence=1
12. Kourtis AP, Read JS, Jamieson DJ. Pregnancy and infection. N Engl J Med. 2014;370(23):2211–8. https://doi.org/10.1056/NEJMra1213566.
13. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315:801–10.
14. Leth RA, Moller JK, Thomsen RW, Uldbjerg N, Norgaard M. Risk of selected postpartum infections after cesarean section compared with vaginal birth: a five-year cohort study of 32,468 women. Acta Obstet Gynecol Scand. 2009;88:976–83.
15. Declercq E, Barger M, Cabral HJ, et al. Maternal outcomes associated with planned primary cesarean births compared with planned vaginal births. Obstet Gynecol. 2007;109:669–77.
16. Myles TD, Gooch J, Santolaya J. Obesity as an independent risk factor for infectious morbidity in patients who undergo cesarean delivery. Obstet Gynecol. 2002;100(5). Pt 1:959–64.
17. Robinson HE, O'Connell CM, Joseph KS, McLeod NL. Maternal outcomes in pregnancies complicated by obesity. Obstet Gynecol. 2005;106:1357–64.
18. Higgins RD, Saade G, Polin RA, et al. Evaluation and management of women and newborns with a maternal diagnosis of chorioamnionitis: summary of a workshop. Obstet Gynecol. 2016;127(3):426–36.
19. Gibbs RS, Duff P. Progress in pathogenesis and management of clinical intraamniotic infection. Am J Obstet Gynecol. 1991;164(5). Pt 1:1317–26.
20. Eschenbach DA. Ureaplasma urealyticum and premature birth. Clin Infect Dis. 1993;17(Suppl 1):S100–6.
21. Tita ATN, Andrews WW. Diagnosis and management of clinical chorioamnionitis. Clin Perinatol. 2010;37(2):339–54.
22. Hillier SL, Martius J, Krohn M, Kiviat N, Holmes KK, Eschenbach DA. A case-control study of chorioamnionic infection and histologic chorioamnionitis in prematurity. N Engl J Med. 1988;319:972–8.
23. Chapman E, Reveiz L, Illanes E, Bonfill CX. Antibiotic regimens for management of intraamniotic infection. Cochrane Database Syst Rev. 2014;12:CD010976.
24. Fishman SG, Gelber SE. Evidence for the clinical management of chorioamnionitis. Semin Fetal Neonatal Med. 2012;17:46–50.
25. Lyell DJ, Pullen K, Fuh K, et al. Daily compared with 8-hour gentamicin for the treatment of intrapartum chorioamnionitis: a randomized controlled trial. Obstet Gynecol. 2010;115:344–9.
26. Hofmeyr GJ, Kiiza JA. Amnioinfusion for chorioamnionitis. Cochrane Database Syst Rev. 2016;8:CD011622.
27. Bodelon C, Bernabe-Ortiz A, Schiff MA, Reed SD. Factors associated with peripartum hysterectomy. Obstet Gynecol. 2009;114(1):115–23.
28. Hauth JC, Gilstrap LC 3rd, Hankins GD, Connor KD. Term maternal and neonatal complications of acute chorioamnionitis. Obstet Gynecol. 1985;66:59–62.
29. Mark SP, Croughan-Minihane MS, Kilpatrick SJ. Chorioamnionitis and uterine function. Obstet Gynecol. 2000;95(6). Pt 1:909–12.
30. Czikk MJ, McCarthy FP, Murphy KE. Chorioamnionitis: from pathogenesis to treatment. Clin Microbiol Infect. 2011;17(9):1304–11.
31. Brosnahan AJ, Schaefers MM, Amundson WH, et al. Novel toxic shock syndrome Toxin-1 amino acids required for biological activity. Biochemistry. 2008;47(49):12995–3003.
32. Sugiyama T, Kobayashi T, Nagao K, Hatada T, Wada H, Sagawa N. Group a streptococcal toxic shock syndrome with extremely aggressive course in the third trimester. J Obstet Gynaecol Res. 2010;36:852–5.
33. Schlievert PM, Tripp TJ, Peterson ML. Reemergence of staphylococcal toxic shock syndrome in Minneapolis-St. Paul, Minnesota, during the 2000–2003 surveillance period. J Clin Microbiol. 2004;42(6):2875–6.
34. Steer AC, Lamagni T, Curtis N, Carapetis JR. Invasive group a streptococcal disease: epide-

miology, pathogenesis and management. Drugs. 2012;72:1213–27.
35. Crum NF, Chun HM, Gaylord TG, Hale BR. Group A streptococcal toxic shock syndrome developing in the third trimester of pregnancy. Infect Dis Obstet Gynecol. 2002;10(4):209–16.
36. Centers for Disease Control and Prevention Toxic shock syndrome (other than Streptococcal) (TSS) 2011 Case Definition. Last accessed Dec 24, 2018 at www.cdc.gov/nndss/script/casedef.aspx?CondYrID=869&DatePub=1/1/2011%2012:00:00%20AM.
37. Gustafson LW, Blaakær J, Helmig RB. Group A streptococci infection. A systematic clinical review exemplified by cases from an obstetric department. Eur J Obstet Gynecol Reprod Biol. 2017;215:33–40.
38. McGregor JA, Soper DE, Lovell G, Todd JK. Maternal deaths associated with Clostridium sordellii infection. Am J Obstet Gynecol. 1989;161:987–95.
39. Surgical Site Infection (CDC Definition). Last accessed on Dec 24, 2018 at http://www.anzjsurg.com/view/0/surgicalSiteInfectionCDCDef.html
40. Smaill FM, Gyte GM. Antibiotic prophylaxis versus no prophylaxis for preventing infection after cesarean section. Cochrane Database Syst Rev. 2010;(1):CD007482.
41. Young BC, Hacker MR, Dodge LE, Golen TH. Timing of antibiotic administration and infectious morbidity following cesarean delivery: incorporating policy change into workflow. Arch Gynecol Obstet. 2012;285:1219–24.
42. Owens SM, Brozanski BS, Meyn LA, Wiesenfeld HC. Antimicrobial prophylaxis for cesarean delivery before skin incision. Obstet Gynecol. 2009;114:573–9.
43. Mackeen AD, Packard RE, Ota E, Berghella V, Baxter JK. Timing of intravenous prophylactic antibiotics for preventing postpartum infectious morbidity in women undergoing cesarean delivery. Cochrane Database Syst Rev. 2014;(12):CD009516.
44. National Nosocomial Infections Surveillance System. National nosocomial infections surveillance (NNIS) system report, data summary from January 1992 through June 2004, issued October 2004. Am J Infect Control. 2004;32(8):470–85.
45. Wloch C, Wilson J, Lamagni T, Harrington P, Charlett A, Sheridan E. Risk factors for surgical site infection following caesarean section in England: results from a multicentre cohort study. BJOG. 2012;119:1324–33.
46. Poobalan AS, Aucott LS, Gurung T, Smith WC, Bhattacharya S. Obesity as an independent risk factor for elective and emergency caesarean delivery in nulliparous women--systematic review and meta-analysis of cohort studies. Obes Rev. 2009;10:28–35.
47. Hasham S, Matteucci P, Stanley PRW, Hart NB. Necrotising fasciitis. BMJ. 2005;330(7495):830–3.
48. Gupta Y, Chhetry M, Pathak KR, et al. Risk factors for necrotizing fasciitis and its outcome at a tertiary care centre. J Ayub Med Coll Abbottabad. 2016;28(4):680–2.
49. Almarzouqi F, Grieb G, Klink C, et al. Fatal necrotizing fasciitis following episiotomy. Case Rep Surg. 2015;2015:562810.
50. Lynch CM, Pinelli DM, Cruse CW, Spellacy WN, Sinnott JT, Shashy RG. Maternal death from postpartum necrotizing fasciitis arising in an episiotomy: a case report. Infect Dis Obstet Gynecol. 1997;5(5):341–4.
51. Gallup DG, Freedman MA, Meguiar RV, Freedman SN, Nolan TE. Necrotizing fasciitis in gynecologic and obstetric patients: a surgical emergency. Am J Obstet Gynecol. 2002;187:305–10. discussion 310-1
52. Tsai YH, Huang KC, Shen SH, Hsu WH, Peng KT, Huang TJ. Microbiology and surgical indicators of necrotizing fasciitis in a tertiary hospital of Southwest Taiwan. Int J Infect Dis. 2012;16:e159–65.
53. Stevens DL, Bryant AE. Necrotizing soft-tissue infections. N Engl J Med. 2017;377:2253–65.
54. Delzell JE Jr, Lefevre ML. Urinary tract infections during pregnancy. Am Fam Physician. 2000;61(3):713–21.
55. ACOG educational bulletin. Antimicrobial therapy for obstetric patients. Number 245, March 1998 (replaces no. 117, June 1988). American College of Obstetricians and Gynecologists. Int J Gynaecol Obstet. 1998;61(3):299–308.
56. Verma A, Baheti S, Sharma M. Asymptomatic bacteriuria in pregnancy and its relation to perinatal outcome. Int J Reprod Contracept Obstet Gynecol. 2016;5(12):4390–6.
57. Abramson H, Goldmark C Jr, Curnen EC, Dancis J, Eichenwald H, Silverman WA, Kass EH. Maternal infections as affecting the outcome of pregnancy. N Y State J Med. 1962;62:2815–30.
58. Nicolle LE, Bradley S, Colgan R, et al. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. Clin Infect Dis. 2005;40(5):643–54.
59. Matuszkiewicz-Rowińska J, Małyszko J, Wieliczko M. Urinary tract infections in pregnancy: old and new unresolved diagnostic and therapeutic problems. Arch Med Sci. 2015;11(1):67–77.
60. Persson K, Bierre B, Elfström L, Polberger S, Forsgren A. Group B streptococci at delivery: high count in urine increases risk for neonatal colonization. Scand J Infect Dis. 1986;18(6):525–31.
61. Wood EG, Dillon HC Jr. A prospective study of group B streptococcal bacteriuria in pregnancy. Am J Obstet Gynecol. 1981;140(5):515–20.
62. Loebstein R, Addis A, Ho E, et al. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. Antimicrob Agents Chemother. 1998;42(6):1336–9.

63. Lee M, Bozzo P, Einarson A, Koren G. Urinary tract infections in pregnancy. Can Fam Physician. 2008;54(6):853–4.
64. Hansen C, Andrade SE, Freiman H, et al. Trimethoprim-sulfonamide use during the first trimester of pregnancy and the risk of congenital anomalies. Pharmacoepidemiol Drug Saf. 2016;25(2):170–8.
65. Villar J, Lydon-Rochelle MT, Gulmezoglu AM, Roganti A. Duration of treatment for asymptomatic Bacteriuria during pregnancy. Cochrane Database Syst Rev. 2000;2:CD000491.
66. Loughlin KR. Management of urologic problems during pregnancy. Urology. 1994;44:159–69.
67. Galvagno SM, Camann DW. Sepsis and acute renal failure in pregnancy. Anesth Analg. 2009;108(2):572–5.
68. Masselli G, Derme M, Bernieri MG, et al. Stone disease in pregnancy: imaging-guided therapy. Insights Imaging. 2014;5(6):691–6.
69. Mishra VV, Agarwal R, Goraniya N, Choudhary S, Aggarwal R. Successful term pregnancy in a second trimester female with Urosepsis: a case report. J Clin Diagn Res. 2015;9(7):QD03–4.
70. Lewis DF, Robichaux AG 3rd, Jaekle RK, Marcum NG, Stedman CM. Urolithiasis in pregnancy. Diagnosis, management and pregnancy outcome. J Reprod Med 2003;48(1):28–32.
71. Juan YS, Wu WJ, Chuang SM, et al. Management of symptomatic urolithiasis during pregnancy. Kaohsiung J Med Sci. 2007;23(5):241–6.
72. Janakiraman V. Listeriosis in pregnancy: diagnosis, treatment, and prevention. Rev Obstet Gynecol. 2008;1(4):179–85.
73. CDC. Update: multistate outbreak of Listeriosis—United States, 1998–1999. MMWR. 1999;47(51):1117–8.
74. Doganay M. Listeriosis: clinical presentation. FEMS Immunol Med Microbiol. 2003;35(3):173–5.
75. Mateus T, Silva J, Maia RL, Teixeira P. Listeriosis during pregnancy: a public health concern. ISRN Obstet Gynecol. 2013;2013:851712.
76. Matok I, Gorodischer R, Koren G, Landau D, Wiznitzer A, Levy A. Exposure to folic acid antagonists during the first trimester of pregnancy and the risk of major malformations. Br J Clin Pharmacol. 2009;68(6):956–62.
77. Mardis BA, Conley CS, Kyle JA. Listeriosis: An Overview. US Pharm. 2012;37(8):38–41.
78. Thyagarajan B, Deshpande SS. Cotrimoxazole and neonatal kernicterus: a review. Drug Chem Toxicol. 2014;37:121–9.
79. Wilking H, Thamm M, Stark K, Aebischer T, Seeber F. Prevalence, incidence estimations, and risk factors of toxoplasma gondii infection in Germany: a representative, cross-sectional, serological study. Sci Rep. 2016;6:22551.
80. Furtado JM, Smith JR, Belfort R Jr, Gattey D, Winthrop KL. Toxoplasmosis: a global threat. J Glob Infect Dis. 2011;3(3):281–4.
81. Dunn D, Wallon M, Peyron F, Petersen E, Peckham C, Gilbert R. Mother-to-child transmission of toxoplasmosis: risk estimates for clinical counselling. Lancet. 1999;353(9167):1829–33.
82. Paquet C, Yudin MH, Society of Obstetricians and Gynaecologists of Canada. Toxoplasmosis in pregnancy: prevention, screening, and treatment. J Obstet Gynaecol Can. 2013;35(1):78–81.
83. Paquet C, Yudin MH. No. 285- toxoplasmosis in pregnancy: prevention, screening and treatment. J Obstet Gynaecol Can. 2018;40(8):e687–93.
84. Bachmeyer C, Mouchnino G, Thulliez P, Blum L. Congenital toxoplasmosis from an HIV-infected woman as a result of reactivation. J Infect. 2006;52(2):e55–7.
85. Foulon W, Pinon JM, Stray-Pedersen B, et al. Prenatal diagnosis of congenital toxoplasmosis: a multicenter evaluation of different diagnostic parameters. Am J Obstet Gynecol. 1999;181(4):843–7.
86. White NJ, Pukrittayakamee S, Hien TT, Faiz MA, Mokuolu OA, Dondorp AM. Malaria. Lancet. 2014;383(9918):723–35.
87. Manirakiza A, Serdouma E, Ngbalé RN, et al. A brief review on features of falciparum malaria during pregnancy. J Public Health Afr. 2017;8(2):668.
88. Rogerson SJ, Desai M, Mayor A, Sicuri E, Taylor SM, van Eijk AM. Burden, pathology, and costs of malaria in pregnancy: new developments for an old problem. Lancet Infect Dis. 2018;18(4):e107–18.
89. Desai M, ter Kuile FO, Nosten F, et al. Epidemiology and burden of malaria in pregnancy. Lancet Infect Dis. 2007;7(2):93–104.
90. Sharma L, Shukla G. Placental malaria: a new insight into the pathophysiology. Front Med (Lausanne). 2017;4:117.
91. D'Alessandro U, Hill J, Tarning J, et al. Treatment of uncomplicated and severe malaria during pregnancy. Lancet Infect Dis. 2018;18(4):e133–46.
92. World Health Organization. Guidelines for the treatment of malaria. 3rd ed. Geneva: WHO; 2015. Last accessed on Jan 10, 2019 at http://www.who.int/malaria/publications/atoz/9789241549127/en/
93. American College of Obstetricians and Gynecologists' Committee on Obstetric Practice, Society for Maternal–Fetal Medicine. Committee Opinion No. 677: antenatal corticosteroid therapy for Fetal maturation. Obstet Gynecol. 2016;128(4):e187–94.
94. Waljee AK, Rogers MA, Lin P, et al. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. BMJ. 2017;357:j1415.
95. Rygård SL, Butler E, Granholm A, et al. Low-dose corticosteroids for adult patients with septic shock: a systematic review with meta-analysis and trial sequential analysis. Intensive Care Med. 2018;44(7):1003–16.

96. Plante LA. Management of sepsis and septic shock for the obstetrician-gynecologist. Obstet Gynecol Clin N Am. 2016;43(4):659–78.
97. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2017;(3):CD004454.
98. Vogel JP, Oladapo OT, Pileggi-Castro C, et al. Antenatal corticosteroids for women at risk of imminent preterm birth in low-resource countries: the case for equipoise and the need for efficacy trials. BMJ Glob Health. 2017;2(3):e000398.
99. World Health Organization. Recommendations on interventions to improve preterm birth outcomes. Geneva: WHO; 2015. Last accessed Jan 10, 2019 at https://www.who.int/reproductive-health/publications/maternal_perinatal_health/preterm-birth-guideline/en/
100. American College of Obstetricians and Gynecologists Committee on Obstetric Practice, Society for Maternal-Fetal Medicine. Committee opinion no. 455: magnesium sulfate before anticipated preterm birth for neuroprotection. Obstet Gynecol. 2010;115(3):669–71.

Part V

The Respiratory System

20 Physiologic Changes in the Airway and the Respiratory System Affecting Management in Pregnancy

Alexander Izakson, Yitzhak Cohen, and Ruth Landau

Key Points

- Significant anatomic and physiologic adaptations involving the respiratory system occur throughout pregnancy to meet the increased metabolic demands of both the mother and the growing fetus.
- Mechanical changes of the chest wall and the diaphragm occur to accommodate the enlarged uterus.
- There is a significant reduction in functional residual capacity (FRC), with little or no change in total lung capacity (TLC).
- An increase in minute ventilation (V_E) causes a decrease in $PaCO_2$ with a partial compensatory reduction in HCO_3, resulting in a chronic relative respiratory alkalosis.
- There are no significant changes in lung spirometry (although some conflicting data has emerged) and no major changes in diffusing capacity (DL_{CO}).

20.1 Introduction

Pregnancy is associated with significant anatomic and physiologic changes of the respiratory system. These changes affect the ability of a woman to maintain adequate oxygenation at times of respiratory compromise. They may also affect the ability of critical care physicians and anesthesiologists to secure adequate ventilation and oxygenation when endotracheal intubation is deemed necessary.

Historical publications of difficult airway management have highlighted these challenges, with reports of failed endotracheal intubation in the pregnant population being approximately eight times higher than in the nonpregnant population [1]. Difficulty with endotracheal intubation leading to cardiac arrest, cerebral anoxia, or inhalation of stomach contents was reported to

A. Izakson
Department of Anesthesia and Operating Rooms, Ziv Medical Center, Safed, Israel

Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel
e-mail: izaksondoc@gmail.com

Y. Cohen
Post Anesthesia Care Unit, Chaim Sheba Medical Center, Tel Hashomer, Israel

Faculty of Medicine, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv-Yafo, Israel

R. Landau (✉)
Department of Anesthesiology, Columbia University Medical Center, New York, NY, USA
e-mail: rl262@cumc.columbia.edu

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_20

be the major contributing factor to anesthesia-related maternal deaths in the Confidential Enquiries into Maternal Mortality in England and Wales in the 1982–1984 triennium report [2]. The first national study of anesthesia-related maternal mortality in the United States revealed that 52% of deaths resulted from complications of general anesthesia predominantly related to airway management problems [3].

With better approaches to manage the pregnant airway, such as video and optic laryngoscopy, assisted tracheal intubation devices, and application of difficult airway algorithms, outcomes of endotracheal intubation have much improved in recent decades [4]. Nonetheless, due to the acuity of cases and steady increase in the prevalence of high-risk pregnancies, including advanced maternal age, hypertensive diseases, and obesity, challenges persist in maintaining adequate respiratory homeostasis. A recent study reviewing trends of anesthesia-related adverse events demonstrated that general anesthesia for cesarean deliveries still carries a significant maternal risk [5].

An understanding of the respiratory physiologic changes occurring during pregnancy is key for enabling the clinician to distinguish between the common "physiological" dyspnea that occurs during normal pregnancy and critical situations that may occur as a result of acute cardiopulmonary conditions or the deterioration of chronic diseases during pregnancy [6].

This chapter will review the anatomical and physiological changes of the airway and respiratory system and their implications for maternal oxygenation and airway management in pregnant women. Current approaches and algorithms for maternal airway management are presented in Chap. 21.

20.2 Upper Airway Anatomy during Pregnancy

Numerous anatomical changes throughout pregnancy affect the ability of pregnant and peripartum women to breathe and thereby also affect oxygenation. These changes may affect spontaneous breathing and are also clinically meaningful during induction of general anesthesia with endotracheal intubation (Table 20.1).

20.2.1 The Nasal Cavities

While bone or joint changes do not seem to occur in pregnancy, soft tissue changes do occur [7]. Swelling and friability, resulting in edema of the nasopharyngeal and oropharyngeal tissue, occur secondary to capillary engorgement. Capillary engorgement of the larynx and the nasal and oropharyngeal mucosa begins early in the first trimester and increases progressively throughout pregnancy. The effect of estrogen on the nasal mucosa results in rhinitis, which is very common, and nosebleeds [8–10]. Nasal breathing commonly becomes difficult, and epistaxis may occur [11]. Because of the increased risk of epistaxis, a nasopharyngeal approach to airway management should be avoided whenever possible. Extreme caution should be used, and consideration should be given to whether tracheal intubation is indeed required. Nasal obstruction may contribute to snoring and sleep-disordered breathing during pregnancy, which has been associated with hypertension and preeclampsia [12], and even adverse perinatal outcomes [13].

20.2.2 The Larynx

Throughout pregnancy and the postpartum period, changes to the larynx may affect vocal characteristics [14]. Throughout the first and second trimesters, the voice of pregnant women is rounded and well carried with good vibration. During the third trimester, vocal cord fatigue is more prevalent with a decrease in the maximum time of phonation [15].

20.2.3 The Pharynx

Pharyngeal edema, likely due to fluid retention during pregnancy, occurs in many women.

Table 20.1 Changes in airway anatomy during pregnancy

	Anatomical change	Etiology	Implications	Recommendations
Nasal cavities	Edema and vascular engorgement	Hormonal (estrogen) effect on nasal mucosa	• Rhinitis • Difficult nasal breathing • Shortness of breath • Epistaxis	• Avoid nasopharyngeal approach to airway management because of increased risk of epistaxis
Larynx	Edema of the aryepiglottic folds, arytenoids, and false vocal cords	Hormonal (estrogen and progesterone peak during the third trimester) effect on laryngeal mucosa	• Prediction of endotracheal intubation difficulty with Mallampati score is still commonly used but has been shown to have a low positive predictive value • Prolonged labor may worsen the Mallampati score. The largest increase in score occurs between the first and second stages of labor	• Prepare for difficult endotracheal intubation even with a reassuring Mallampati score
Pharynx	Edema	Hormonal (progesterone) effect	• Pharyngeal cross-sectional area may decrease (10%) • Enlargement of the tongue may make it difficult to retract it onto the mandibular space during direct laryngoscopy	• Prepare for difficult endotracheal intubation with adequate positioning (ramp up) and equipment
Trachea	Edema	Hormonal (progesterone) effect	• Subglottic tissue (granuloma) resulting in narrowing of the trachea • Idiopathic subglottic stenosis which may be associated with Wegener's granulomatosis	• Smaller-sized endotracheal tube should be available (from 6.0 up to 8.0) • Supraglottic airway devices should be available as rescue backup
Thoracic cage	Displacement of the diaphragm upward (4 cm). Increase in anteroposterior and lateral chest wall diameter (2 cm)	Hormonal (relaxin) effect on rib attachment. Increased intra-abdominal pressure	• Reduced FRC leading to reduced oxygen reserve and rapid oxygen desaturation if apnea	• Adequate pre-induction preoxygenation • Prepare for rapid sequence induction if endotracheal intubation deemed necessary

FRC functional residual capacity

However pharyngeal edema should always raise some degree of concern as it is considered one of the presenting symptoms in preeclamptic women [16–19].

Pharyngeal swelling may also develop acutely during labor. Labor increases the soft tissue volume surrounding the airway, thereby narrowing the pharyngeal airway. The acoustic reflection method (ARM) longitudinally assesses the cross-sectional area (CSA) of the upper airway from the mouth to the carina noninvasively. ARM has been used to evaluate airway changes during pregnancy. In a longitudinal study conducted on 50 pregnant women, the pharyngeal volume decreased by 10% between the first and third trimesters and returned to normal within 48 h of delivery. No parallel changes were observed in laryngeal and tracheal anatomy [20]. Decreased oral (10–15%) and pharyngeal volumes (10%) were also observed in another study of women during vaginal labor and delivery (n = 21) [21]. The duration of labor and fluid administration during labor did not influence oral and pharyngeal volumes. Oral and pharyngeal volumes were significantly decreased postpartum when compared to pre-labor assessments.

Although tracheal issues are extremely uncommon in pregnancy, exacerbation of subglottic stenosis during pregnancy has been reported in women with Wegener's granulomatosis [22–24] and may require urgent surgical intervention.

20.3 The Mallampati Score in the Peripartum Period

The Mallampati score is commonly used to anticipate whether endotracheal intubation will be easy or difficult. It provides an estimation of the size of the tongue relative to that of the oral cavity [25]. In the 1990s, a Mallampati score of 3 or 4 was found to be significantly associated with a difficult intubation in pregnant women. The relative risk was 7.6 and 11.3, respectively, compared to women with lower scores [26]. Since then, numerous additional studies have established that Mallampati scores increase during pregnancy [27, 28] and during the course of labor and delivery [21, 28–33]. Very few however have evaluated the utility and predictive value of the Mallampati score in clinical practice, since very few women actually require an endotracheal intubation during pregnancy and the peripartum period.

20.3.1 The Mallampati Score in Normal Labor and Delivery

Airway changes during labor and delivery were studied using the conventional Samsoon modification of the Mallampati score (head in neutral position without phonation or extension of the neck). Sixty one women were assessed by means of direct photography during and after labor, and 21 were assessed with acoustic reflectometry software for the components of upper airway, oral volume, and pharyngeal volume [21]. Significant changes were found after delivery in 23/61 women who had delivered vaginally (with Valsalva maneuvers during the second stage of labor). The Mallampati score increased by 1 grade in 20 women (33%) and by ≥2 grades in 3 women (5%). At the end of labor, eight women had a Mallampati score of 4, and 30 women had a score of 3 or 4. As noted above, the duration of labor and the fluids administered during labor did not correlate with the severity of airway changes.

In another longitudinal study, 87 women were evaluated at 8 months (T = 1), upon placement of labor epidural analgesia (T = 2), 20 min after delivery (T = 3) and 48 h postpartum (T = 4), using the Samsoon modified Mallampati test [28]. A Mallampati score of 3 or 4 was found in 10% of women initially (T = 1), in 37% of women after labor epidural placement (T = 2), in 52% immediately postpartum (T = 3), and in 21% of women at 48 h (T = 4). None of the evaluated factors (gestational weight gain, duration of first or second stage of labor, intrapartum intravenous fluid administration) predicted the magnitude of upper airway change. There was a 3.5-fold increase in women with Mallampati score of 3 or 4 during labor compared to before labor, and alterations were not fully reversed by 48 h.

In a study specifically designed to evaluate the effect of labor epidural analgesia on upper airway changes (n = 190 women), it revealed that epidural analgesia had no effect on the Mallampati score. Direct photography did however show an increase in the Mallampati score of 32% of women, a decrease in 10% and no change in 58% of women [31].

The effect of Valsalva maneuvers during the second stage of labor was studied in women undergoing elective cesarean delivery (n = 90) and vaginal delivery (n = 86). Upper airway anatomical parameters were assessed before labor and up to 24 h postpartum [33]. Maternal efforts during vaginal delivery were associated with changes in the Mallampati score immediately after delivery. However, intravenous administration of a greater amount of fluids during scheduled cesarean delivery was associated with increased Mallampati scores even 6–24 h postpartum [33].

20.3.2 The Mallampati Score with Hypertensive Disease of Pregnancy

The impact of hypertensive diseases during pregnancy on airway anatomy has been evaluated in two studies [29, 31]. One study compared Mallampati scores during the course of labor among 30 normotensive and 30 hypertensive women. This study revealed that women with hypertension had higher Mallampati scores in early labor and also had a twofold higher likelihood of increase in the Mallampati score during the course of labor and delivery [32]. These findings were corroborated in another study evaluating airway anatomy during and after labor in women with and without preeclampsia with severe features [34]. The Mallampati score and ultrasound measures of tongue thickness, anterior neck soft tissue at the level of the hyoid bone and the vocal cords, thyromental distance, and neck circumference were recorded before active labor, within 1 h of delivery and 24–48 h postpartum. The Mallampati score increased during the course of labor in both preeclamptic and normotensive women. There was a significant difference in tissue thickness at the hyoid level in preeclamptic versus normotensive patients at all times but no difference in thyromental distance or neck circumference between groups at any time. Prolonged duration of labor was associated with increased Mallampati score, regardless of the presence of hypertensive disease [31]. Such study findings confirm the premise that general anesthesia should be avoided whenever possible in women with hypertensive disorders of pregnancy. If general anesthesia is unavoidable, then preparedness for a difficult intubation should be maximized.

20.3.3 Correlating Mallampati Score and Actual Intubation Difficulty during Cesarean Delivery

As mentioned, few studies were actually able to correlate findings from preoperative bedside tests and actual intubation difficulty in women who underwent cesarean delivery under general anesthesia [35–38].

One such evaluation studied 239 women and assessed five bedside predictors: Mallampati score, sterno-mental distance, thyromental distance, inter-incisor gap, and atlanto-occipital extension. The Cormack-Lehane classification grades the views obtained by direct laryngoscopy based on the structures observed. [39] Before emergency cesarean delivery under general anesthesia, 5.8% of women (n = 14) had a Cormack and Lehane laryngoscopic view ≥3 [only epiglottis seen but none of the glottis (grade 3) or neither glottis nor epiglottis seen (grade 4)]. Age, height, weight, BMI, and weight gain were not associated with a difficult intubation. The five predictors combined had a sensitivity of 0.21 and specificity of 0.92 to predict a difficult intubation. The positive predictive value of a Cormack and Lehane classification of ≥3 was 0.15 and the negative predictive value was 0.95, indicating that 79% of difficult intubations would likely be missed [35].

Another study conducted on an even larger cohort of obese women undergoing cesarean

delivery under general anesthesia (n = 570) also showed that the neck circumference, sternomental distance, and modified Mallampati test had limited value in predicting a difficult intubation [36].

The ratio of height to thyromental distance is another measure used to predict difficult laryngoscopy and intubation prior to cesarean delivery under general anesthesia. [38] The same authors studied this measure in a series of women undergoing cesarean delivery under general anesthesia (n = 757). Difficult larynx visualization was reported in 8.6% of women, and this was associated not only with the ratio of height to thyromental distance but also with neck circumference and the ratio of neck circumference and thyromental distance [37].

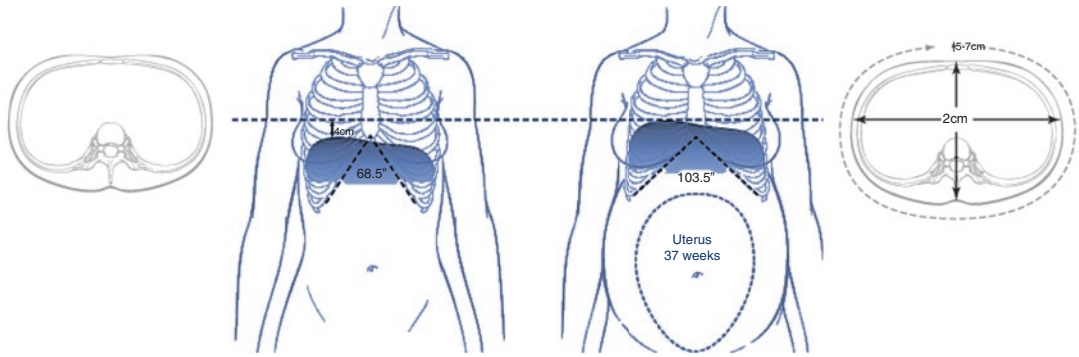
20.4 Respiratory Anatomical and Physiological Changes during Pregnancy

The increase in the size of the pregnant uterus becomes significant in terms of respiratory physiology from the end of the first trimester. At this time it begins to affect intra-abdominal pressure, which increases in parallel [40]. Concomitantly, under the effect of relaxin, relaxation of the ligamentous attachments of the lower ribs occurs [41]. The geometry of the thorax changes due to the increased flexibility of the chest wall resulting from these changes. Also affecting a geometrical change is the increasing upward pressure of the abdominal contents resulting from uterine enlargement during the second and third trimesters (Fig. 20.1) [42].

20.4.1 Chest Wall Configuration

The anteroposterior and transverse diameters of the chest wall increase steadily throughout pregnancy by about 2 cm. The resultant increase of 5–7 cm in the circumference of the lower rib cage creates a quasi-horizontal rib position (Fig. 20.1) [42]. The subcostal angle increases by about 55% (from 70.7 to about 107 degrees). While the thoracic diameter and circumference return to prepregnancy values after delivery, a 20% increase in costal angle remains even 24 weeks after delivery (Fig. 20.1) [42].

Increased intra-abdominal pressure displaces the diaphragm upward by approximately 4 cm. This change repositions the diaphragm in a manner that increases intrathoracic volume during contraction. Diaphragmatic displacement is increased by 2 cm during inspiration when



1. The subcostal angle of the ribs increases.
2. The antero-posterior and transverse diameters of the chest wall also increase, which result in an overall increase of the circumference of the chest wall
3. These changes compensate for the 4-cm elevation of the diaphragm

→ There is minimal or no change in total lung capacity (TLC)

Fig. 20.1 Anatomical changes of the chest wall during pregnancy (modified from Hegewald et al.)

compared with the nonpregnant state. This change increases respiratory tidal volume during pregnancy (Fig. 20.1).

20.4.2 Static Lung Function during Pregnancy

Despite the significant changes in rib cage and diaphragm configuration, respiratory muscle function (as evidenced by maximal inspiratory and expiratory pressures) remains unchanged during pregnancy [43]. As the upward movement of the diaphragm is compensated by the increase in the lateral and anteroposterior chest dimensions, total lung capacity (TLC) remains essentially unchanged or only minimally reduced (−5%) during pregnancy (Fig. 20.2) [44, 45].

However, lung volumes do undergo significant changes during pregnancy. Functional residual capacity (FRC) is markedly reduced (by 20–30%), and tidal volume (TV) is significantly increased (by 30–50%). Starting at about 12 weeks of gestation, FRC in the upright position decreases by about 20% (400–600 mL) from pre-pregnancy values (Fig. 20.2) [45]. FRC further decreases in the supine position, which can exacerbate oxygen desaturation. Placing a supine parturient in a 30° head-up position may increase FRC by up to 10% (approximately 200 mL) [46]. This simple maneuver will significantly improve maternal oxygen reserve in some cases. Tidal volume (TV) is increased by 30–50% with at least half the change occurring during the first trimester [44]. Inspiratory capacity (IC) increases by 5–10% during the second and third trimesters (Fig. 20.2). Causes are the increase in TV and possibly also an increase in inspiratory reserve volume (IRV). Lung volumes return to pre-pregnancy values several months after delivery.

Respiratory rate remains essentially unchanged or slightly increased during pregnancy. The increase in thoracic diameter and volume (thoracic breathing) appears to play a larger role during ventilation than do the descent of the diaphragm and the dynamics of abdominal girth (abdominal breathing). However, there is significant variability in the changes observed between pregnant women, and variability may be found at different stages of the third trimester even in the same parturient.

20.4.3 Dynamic Respiratory Parameters during Pregnancy

In contrast to the significant and unrefuted findings in lung volume changes occurring during

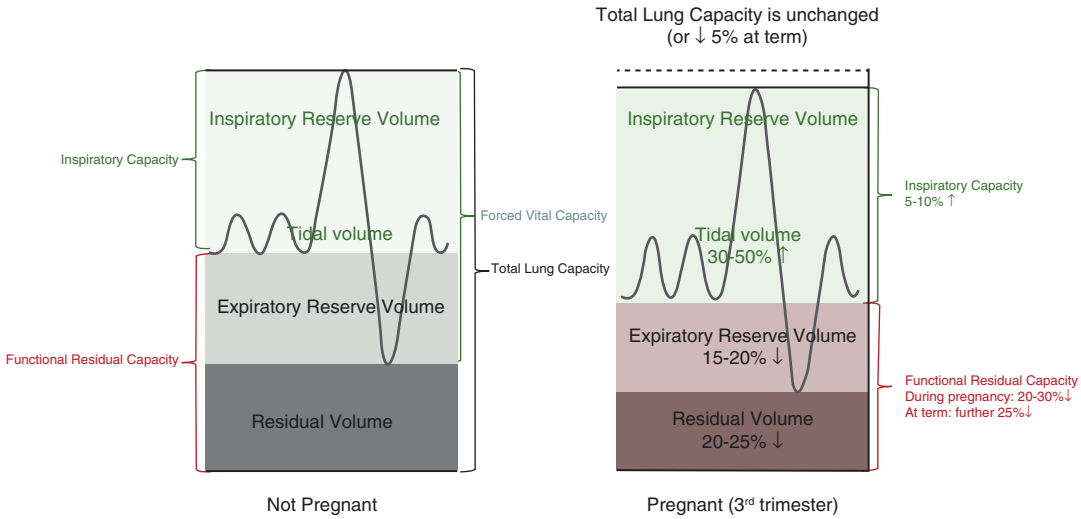


Fig. 20.2 Changes in lung volumes during pregnancy and at term (modified from Hegewald et al.)

pregnancy, dynamic respiratory parameters are generally considered overall unchanged throughout pregnancy. However, this topic remains controversial. Possible reasons for differing results include sample size variability (most studies have been conducted in small cohorts), ethnic dissimilarities, use of medications concurrent to conduction of measurements, the type of spirometer used for measurement, and positioning during measurements (i.e., standing, sitting, or supine). If changes in pulmonary function do exist, they are likely to be relatively minor.

This issue is particularly pertinent to the effect of pregnancy on asthma. The symptoms of asthma improve during pregnancy in one third of women and remain unchanged in another third. Symptoms are most likely to worsen among women experiencing severe asthma before pregnancy [47].

20.4.4 Peak Expiratory Flow, Forced Expiratory Volume, and Forced Vital Capacity

Numerous longitudinal studies have assessed peak expiratory flow (PEF) rate, forced expiratory volume (FEV), and FEV in 1 s (FEV1), as well as the forced vital capacity (FVC) during pregnancy and postpartum. The results of these studies are conflicting.

In one study healthy women with no history of pulmonary disease evaluated at each trimester and postpartum (n = 57) showed no change in PEF rate with advancing gestation. [48] In another study, healthy women evaluated in different positions (standing, sitting, and supine) at 4-week intervals from the first trimester until 6 weeks postpartum (n = 38) showed a gradual decline in PEF throughout pregnancy in all positions which had not resolved by 6 weeks postpartum. The decline was most prominent in the supine position, and PEF returned to only 72% of its value in early pregnancy (first trimester measurement) [49]. The findings of the latter study were questioned because measurements were not normalized to age and height (PEF index) [50]. However, another study which evaluated lung function in the first and third trimesters in a mixed-parity cohort (n = 120) also reported significant decreases in FVC and FEV1 values in the third trimester, which were more pronounced among multiparous women and those who smoke [51].

There are studies that show different results. In one such study, healthy women evaluated four times during pregnancy and 6 months postpartum (n = 87) showed a gradual increase in PEF rate and FVC after week 23 and up to 6 months postpartum, while FEV remained unchanged. Differences between nulliparous and multiparous women were also identified, with multiparous women found to have an overall higher FVC predicted for age and height (4.4% increase) than nulliparous women. These findings suggest that the change in FVC that occurs during pregnancy persists well beyond delivery [52].

The take-home message from these studies is that if pregnancy is indeed associated with increased PEF rates and FVCs persisting well into the postpartum period, spirometric tests in pregnant women with suspected impairment of lung function should be interpreted with caution; "normal" test results may in fact not be so good. Furthermore, in pregnancies associated with a reduction of FVC and FEV1, interpretation of tests intended to determine whether respiratory function is deteriorating should ideally lean on the personal trajectory of the individual being studied.

20.4.5 Pulmonary Function Tests in Women with Asthma

Longitudinal evaluation throughout pregnancy (at 8–20 weeks, 21–28 weeks, and 29–40 weeks) of women with (n = 20) and without (n = 20) asthma identified similar changes in pulmonary function in both groups. In early pregnancy, no significant difference in pulmonary function was observed between the groups. Pulmonary function also declined during the second trimester and then improved in the final weeks of pregnancy in both groups. However, more significant changes (reduction in FEV1 and FEV6, followed

by forced vital capacity (FVC)) were found in women with asthma [53].

20.4.6 Pulmonary Function Tests in Women with Preeclampsia

Several studies suggest that preeclampsia impairs the respiratory function of pregnant and peripartum women [54–57]. However, this observation is confounded by the lack of an early pregnancy comparator (no study evaluated pulmonary function in these women before diagnosis of preeclampsia) and by a high prevalence of cesarean delivery which may in itself lead to significant fluid shifts, increased airway and pulmonary edema, and consequently alterations in PFTs.

In one case-control study, women with preeclampsia ($n = 37$) and controls matched for gestational age ($n = 37$) were evaluated once in the third trimester (between 33 and 38 weeks of gestation) to identify whether minute ventilation (V_E; L/min) changes with preeclampsia [56]. The body mass index was slightly higher in the preeclampsia group (31 ± 4 versus 28 ± 5, respectively; $p = 0.01$), and 21/37 women in the preeclampsia group met criteria for severe preeclampsia as defined at the time (based on 2000 criteria [58]); of note these criteria have since changed. [59] V_E was higher, and FVC was lower in the group of women with preeclampsia compared to controls. Other parameters were similar. The 6-min walking distance was also significantly shorter in women with preeclampsia group compared to controls, suggesting a resultant lower tolerance to exercise.

20.4.7 Pulmonary Function Tests in Women with Multiple Gestation (Twins)

In a cross-sectional study performed in 68 women with twin pregnancies ($n = 17$ in the first trimester, $n = 35$ in the second trimester, $n = 16$ in the third trimester), 140 women with singleton pregnancies, and 22 nonpregnant women, respiratory function was evaluated once (between 7 and 40 weeks of gestation) [60]. Compared with nonpregnant women, women with singleton or twin pregnancies had an increased mean V_E in each trimester and a reduced FRC and ERV assessment in the third trimester. No significant differences were demonstrated in the respiratory function of healthy women with twin compared to singleton pregnancies.

20.5 Diffusing Capacity

Gas transfer in the lungs can be assessed by the diffusing capacity for carbon monoxide (DL_{CO}). The single breath method was used to determine the DL_{CO} throughout pregnancy in a cohort of healthy women [61]; DL_{CO} was not consistently reduced throughout pregnancy. DL_{CO} has been shown to increase with exercise in pregnancy, suggesting that pregnancy does not impair the ability of a healthy pulmonary capillary bed to be recruited during exercise [62]. However, the global measurement of DL_{CO} only provides an indication of whether gas exchange is normal or not. It does not identify how this gas exchange is related to changes in hemoglobin concentration, the pulmonary capillary blood volume, or the alveolar-capillary membrane. To this end concurrent measurement of both DL_{CO} and DL_{NO} has been proposed. [63] NO combines with hemoglobin faster than CO does and is independent of either pulmonary capillary blood volume or hemoglobin concentration. Measurements of DL_{CO} and DL_{NO} in pregnancy may therefore better serve to predict aerobic capacity, identify pulmonary hypertension, and identify pulmonary vascular diseases in general [64, 65].

20.6 Ventilation and Gas Exchange

Minute ventilation (V_E) is significantly increased at rest during pregnancy compared to the nonpregnant state. [44, 54] Chemosensitivity to CO_2 is also increased as a result of the increased respiratory drive. At term, V_E is increased by 20–50%, which is associated with a 30–50% increase in

tidal volume (TV) and possibly a slight increase in respiratory rate [44]. Because neither inspiratory time nor the duration of the respiratory cycle is altered, this suggests that inspiratory flow is increased. There is conflicting data regarding whether dead space ventilation is also increased.

Pregnancy hyperventilation is mediated by progesterone and occurs in response to the increased metabolic rate and increased CO_2 production. Dyspnea is therefore a common complaint in a majority of pregnant women by the third trimester. It is considered a "physiologic" symptom possibly related to an awareness of this increased drive [66–70].

20.6.1 Oxygen Consumption and Carbon Dioxide Production

Oxygen consumption (VO_2) is increased during pregnancy due to the increased metabolic demands imposed by the growing fetus, placenta, and uterus. Maternal weight gain during pregnancy also increases VO_2 at rest. Resting VO2 values are 20% higher at term compared to postpartum values. Exercise VO_2 values increase to a lesser extent, by only 15% from the end of the first trimester to term [71, 72].

Carbon dioxide production (VCO_2) is even more increased than oxygen consumption. Pregnant women have VCO2 values that are approximately 35% higher than nonpregnant values. [71] Because the increase in V_E exceeds the increases in VO_2 and VCO_2, the alveolar and arterial partial pressures of O_2 (PAO2 and PaO2) increase and those of CO_2 ($PACO_2$ and $PaCO_2$) decrease during pregnancy.

20.6.2 The Partial Pressure of Oxygen in Arterial Blood (PaO_2)

Current recommendations for preoxygenation of pregnant women in urgent situations are for eight deep breaths over 60 s. This has been shown to result in adequate denitrogenation as measured by end-tidal fractional oxygen concentration (F_{ETO2}) [73] (see Chap. 21). However, the increase in oxygen consumption and decrease in functional residual capacity that occur during pregnancy lead to more rapid onset of hypoxemia during episodes of apnea even with careful preoxygenation in pregnant women when compared to their nonpregnant counterparts. Following preoxygenation, the time to hypoxemia during apnea was shorter in both the supine position and a 45-degree head-up position in pregnant women compared to nonpregnant women (156 and 173 s compared to 243 and 331 s, respectively) [74, 75].

An additional practical effect of the increased V_E and reduced FRC of pregnancy on anesthetic care results from the facilitated gas exchange at the alveolar level. This rapid exchange increases the rate of uptake of inhalation agents, leading to faster changes in the depth of anesthesia in response to anesthetic gas administration.

20.6.3 Partial Pressure of Arterial Carbon Dioxide ($PaCO_2$)

Starting from the first trimester, hyperventilation drives the arterial partial pressure of carbon dioxide ($PaCO_2$) down during pregnancy. Some studies have reported a gradual decrease, while others show an early initial reduction that remains stable [76].

During unmedicated labor, pain will result in exaggerated hyperventilation (both V_E and TV increase) with a further decrease in $PaCO_2$ with each contraction. This phenomenon resolves postpartum. [77] With labor epidural analgesia, both V_E and TV decrease to pre-labor values, resulting in a significant increase in the arterial PCO_2 and a decrease in both alveolar and arterial oxygen tensions (see Chap. 39). The mean arterial PO_2 was comparable in women with labor epidural analgesia to the predicted value for this age group. [77]

Hyperventilation and its resultant respiratory alkalosis are accompanied by renal compensation with increasing bicarbonate (HCO_3) excretion, reaching the lowest values of 18–22 mEq/L in late third trimester [78]. Maternal arterial pH is therefore maintained at 7.42–7.46 at term [79]. Chronic

alkalosis increases 2,3-diphosphoglycerate (2,3-DPG) content in maternal erythrocytes [80, 81], which shifts the oxyhemoglobin dissociation curve to the right. This shift maintains hemoglobin-oxygen affinity (p50) unchanged during pregnancy despite respiratory alkalosis, thereby facilitating transplacental oxygen delivery to the fetus [82].

In summary, arterial blood gases and acid-base parameters significantly change in pregnancy: pH increases, $PaCO_2$ decreases, PaO_2 increases, HCO_3^- decreases, maternal 2,3-DPG increases, and p50 remains the same because of alkalosis [83]. Interpretation of blood gas values of pregnant women should take into account these physiological changes and in particular that of $PaCO_2$ and HCO_3. A $PaCO_2$ value of 40 mmHg in a pregnant woman that appears compensated may in fact suggest imminent respiratory decompensation.

20.7 Conclusions

Pregnancy-induced anatomical and physiological changes result in an array of issues that may impair maternal spontaneous breathing, oxygenation, and ventilation. These may lead to devastating consequences in women with respiratory decompensation at this time. Indeed, the constellation of increased airway edema and congestion and greater tendency for airway bleeding, combined with an increased oxygen demand and reduced lung volumes, impair the ability to maintain adequate oxygenation and ventilation and result in early onset desaturation and hypoxemia in the event of emergency endotracheal intubation.

References

1. Samsoon GL, Young JR. Difficult tracheal intubation: a retrospective study. Anaesthesia. 1987;42(5):487–90.
2. Davies JM, Weeks S, Crone LA, Pavlin E. Difficult intubation in the parturient. Can J Anaesth. 1989;36(6):668–74.
3. Hawkins JL, Koonin LM, Palmer SK, Gibbs CP. Anesthesia-related deaths during obstetric delivery in the United States, 1979-1990. Anesthesiology. 1997;86(2):277–84.
4. Hawkins JL, Chang J, Palmer SK, Gibbs CP, Callaghan WM. Anesthesia-related maternal mortality in the United States: 1979–2002. Obstet Gynecol. 2011;117(1):69–74.
5. Guglielminotti J, Wong CA, Landau R, Li G. Temporal trends in Anesthesia-related adverse events in Cesarean deliveries, New York state, 2003–2012. Anesthesiology. 2015;123(5):1013–23.
6. Lapinsky SE. Management of acute respiratory failure in pregnancy. Semin Respir Crit Care Med. 2017;38(2):201–7.
7. Demir UL, Demir BC, Oztosun E, Uyaniklar OO, Ocakoglu G. The effects of pregnancy on nasal physiology. Int Forum Allergy Rhinol. 2015;5(2):162–6.
8. Bende M, Hallgarde M, Sjogren U. Uvnas-Moberg K. Nasal congestion during pregnancy. Clin Otolaryngol Allied Sci. 1989;14(5):385–7.
9. Dzieciolowska-Baran E, Teul-Swiniarska I, Gawlikowska-Sroka A, Poziomkowska-Gesicka I, Zietek Z. Rhinitis as a cause of respiratory disorders during pregnancy. Adv Exp Med Biol. 2013;755:213–20.
10. Ellegard EK. Clinical and pathogenetic characteristics of pregnancy rhinitis. Clin Rev Allergy Immunol. 2004;26(3):149–59.
11. Kumar R, Hayhurst KL, Robson AK. Ear, nose, and throat manifestations during pregnancy. Otolaryngol Head Neck Surg. 2011;145(2):188–98.
12. Dominguez JE, Habib AS, Krystal AD. A review of the associations between obstructive sleep apnea and hypertensive disorders of pregnancy and possible mechanisms of disease. Sleep Med Rev. 2018;42:37.
13. Li L, Zhao K, Hua J, Li S. Association between sleep-disordered breathing during pregnancy and maternal and Fetal outcomes: an updated systematic review and meta-analysis. Front Neurol. 2018;9:91.
14. Cassiraga VL, Castellano AV, Abasolo J, Abin EN, Izbizky GH. Pregnancy and voice: changes during the third trimester. J Voice. 2012;26(5):584–6.
15. Hamdan AL, Mahfoud L, Sibai A, Seoud M. Effect of pregnancy on the speaking voice. J Voice. 2009;23(4):490–3.
16. Brimacombe J. Acute pharyngolaryngeal oedema and pre-eclamptic toxaemia. Anaesth Intensive Care. 1992;20(1):97–8.
17. Heller PJ, Scheider EP, Marx GF. Pharyngolaryngeal edema as a presenting symptom in preeclampsia. Obstet Gynecol. 1983;62(4):523–5.
18. Perlow JH, Kirz DS. Severe preeclampsia presenting as dysphonia secondary to uvular edema. A case report. J Reprod Med. 1990;35(11):1059–62.
19. Pritchard JA. Severe preeclampsia with pharyngolaryngeal edema. Obstet Gynecol. 1984;64(1):146–7.
20. Leboulanger N, Louvet N, Rigouzzo A, et al. Pregnancy is associated with a decrease in pharyngeal but not tracheal or laryngeal cross-sectional area: a pilot study using the acoustic reflection method. Int J Obstet Anesth. 2014;23(1):35–9.

21. Kodali BS, Chandrasekhar S, Bulich LN, Topulos GP, Datta S. Airway changes during labor and delivery. Anesthesiology. 2008;108(3):357–62.
22. Scholz A, Srinivas K, Stacey MR, Clyburn P. Subglottic stenosis in pregnancy. Br J Anaesth. 2008;100(3):385–8.
23. Rumbak M, Dryer J, Padhya T, Camporesi E, Karlnoski R, Mangar D. Successful management of subglottic stenosis during the third trimester of pregnancy. J Bronchology Interv Pulmonol. 2010;17(4):342–4.
24. Engel NM, Gramke HF, Peeters L, Marcus MA. Combined spinal-epidural anaesthesia for a woman with Wegener's granulomatosis with subglottic stenosis. Int J Obstet Anesth. 2011;20(1):94–5.
25. Mallampati SR, Gatt SP, Gugino LD, et al. A clinical sign to predict difficult tracheal intubation: a prospective study. Can Anaesth Soc J. 1985;32(4):429–34.
26. Rocke DA, Murray WB, Rout CC, Gouws E. Relative risk analysis of factors associated with difficult intubation in obstetric anesthesia. Anesthesiology. 1992;77(1):67–73.
27. Pilkington S, Carli F, Dakin MJ, et al. Increase in Mallampati score during pregnancy. Br J Anaesth. 1995;74(6):638–42.
28. Boutonnet M, Faitot V, Katz A, Salomon L, Keita H. Mallampati class changes during pregnancy, labour, and after delivery: can these be predicted? Br J Anaesth. 2010;104(1):67–70.
29. Farcon EL, Kim MH, Marx GF. Changing Mallampati score during labour. Can J Anaesth. 1994;41(1):50–1.
30. Isono S. Mallampati classification, an estimate of upper airway anatomical balance, can change rapidly during labor. Anesthesiology. 2008;108(3):347–9.
31. Guru R, Carere MD, Diwan S, Morau EL, Saunders J, Shorten GD. Effect of epidural analgesia on change in Mallampati class during labour. Anaesthesia. 2013;68(7):765–9.
32. Raza D, Ismail S. Change in Mallampati class during labor: hypertensive versus normotensive parturients. Acta Anaesthesiol Scand. 2018;62:1086–91.
33. Hu J, Huang S, Tian F, Sun S, Li N, Xie Y. A comparison of upper airway parameters in postpartum patients: vaginal delivery vs. caesarean section. Int J Clin Exp Med. 2014;7(12):5491–7.
34. Ahuja P, Jain D, Bhardwaj N, Jain K, Gainder S, Kang M. Airway changes following labor and delivery in preeclamptic parturients: a prospective case control study. Int J Obstet Anesth. 2018;33:17–22.
35. Basaranoglu G, Columb M, Lyons G. Failure to predict difficult tracheal intubation for emergency caesarean section. Eur J Anaesthesiol. 2010;27(11):947–9.
36. Eiamcharoenwit J, Itthisompaiboon N, Limpawattana P, Suwanpratheep A, Siriussawakul A. The performance of neck circumference and other airway assessment tests for the prediction of difficult intubation in obese parturients undergoing cesarean delivery. Int J Obstet Anesth. 2017;31:45–50.
37. Hirmanpour A, Safavi M, Honarmand A, Jabalameli M, Banisadr G. The predictive value of the ratio of neck circumference to thyromental distance in comparison with four predictive tests for difficult laryngoscopy in obstetric patients scheduled for caesarean delivery. Adv Biomed Res. 2014;3:200.
38. Honarmand A, Safavi MR. Prediction of difficult laryngoscopy in obstetric patients scheduled for caesarean delivery. Eur J Anaesthesiol. 2008;25(9):714–20.
39. Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. Anaesthesia. 1984;39(11):1105–11.
40. Paramore RH. The intra-abdominal pressure in pregnancy. Proc R Soc Med. 1913;6(Obstet Gynaecol Sect):291–334.
41. Goldsmith LT, Weiss G, Steinetz BG. Relaxin and its role in pregnancy. Endocrinol Metab Clin N Am. 1995;24(1):171–86.
42. Gilroy RJ, Mangura BT, Lavietes MH. Rib cage and abdominal volume displacements during breathing in pregnancy. Am Rev Respir Dis. 1988;137(3):668–72.
43. Contreras G, Gutierrez M, Beroiza T, et al. Ventilatory drive and respiratory muscle function in pregnancy. Am Rev Respir Dis. 1991;144(4):837–41.
44. Hegewald MJ, Crapo RO. Respiratory physiology in pregnancy. Clin Chest Med. 2011;32(1):1–13.
45. LoMauro A, Aliverti A. Respiratory physiology of pregnancy: physiology masterclass. Breathe (Sheff). 2015;11(4):297–301.
46. Hignett R, Fernando R, McGlennan A, et al. A randomized crossover study to determine the effect of a 30 degrees head-up versus a supine position on the functional residual capacity of term parturients. Anesth Analg. 2011;113(5):1098–102.
47. Dombrowski MP, Schatz M. Bulletins-obstetrics ACoP. ACOG practice bulletin: clinical management guidelines for obstetrician-gynecologists number 90, February 2008: asthma in pregnancy. Obstet Gynecol. 2008;111(2 Pt 1):457–64.
48. Brancazio LR, Laifer SA, Schwartz T. Peak expiratory flow rate in normal pregnancy. Obstet Gynecol. 1997;89(3):383–6.
49. Harirah HM, Donia SE, Nasrallah FK, Saade GR, Belfort MA. Effect of gestational age and position on peak expiratory flow rate: a longitudinal study. Obstet Gynecol. 2005;105(2):372–6.
50. Brancazio LR. Effect of gestational age and position on peak expiratory flow rate: a longitudinal study. Obstet Gynecol. 2005;106(1):199.
51. Pastro LDM, Lemos M, Fernandes FLA, et al. Longitudinal study of lung function in pregnant women: influence of parity and smoking. Clinics (Sao Paulo). 2017;72(10):595–9.
52. Grindheim G, Toska K, Estensen ME, Rosseland LA. Changes in pulmonary function during pregnancy: a longitudinal cohort study. BJOG. 2012;119(1):94–101.
53. Zairina E, Abramson MJ, McDonald CF, et al. A prospective cohort study of pulmonary function during pregnancy in women with and without asthma. J Asthma. 2016;53(2):155–63.
54. Rees GB, Broughton Pipkin F, Symonds EM, Patrick JM. A longitudinal study of respiratory changes in normal human pregnancy with cross-sectional data on

subjects with pregnancy-induced hypertension. Am J Obstet Gynecol. 1990;162(3):826–30.
55. Roopnarinesingh R, Collins C, McKenna P. Pre-eclampsia affects pulmonary function in pregnancy. J Obstet Gynaecol. 2007;27(7):672–5.
56. da Silva EG, de Godoy I, de Oliveira Antunes LC, da Silva EG, Peracoli JC. Respiratory parameters and exercise functional capacity in preeclampsia. Hypertens Pregnancy. 2010;29(3):301–9.
57. Viana MC, Araujo Junior E, Santana EF, Lima JW, Costa Fda S. Analysis of pulmonary function in high-risk pregnancies: a case-control study. J Matern Fetal Neonatal Med. 2015;28(9):994–9.
58. Report of the National High Blood Pressure Education Program Working Group on high blood pressure in pregnancy. Am J Obstet Gynecol. 2000;183(1):S1–S22.
59. ACOG Practice Bulletin No. 202: gestational hypertension and preeclampsia. Obstet Gynecol. 2019;133(1):e1–e25.
60. McAuliffe F, Kametas N, Costello J, Rafferty GF, Greenough A, Nicolaides K. Respiratory function in singleton and twin pregnancy. BJOG. 2002;109(7):765–9.
61. Milne JA, Mills RJ, Coutts JR, Macnaughton MC, Moran F, Pack AI. The effect of human pregnancy on the pulmonary transfer factor for carbon monoxide as measured by the single-breath method. Clin Sci Mol Med. 1977;53(3):271–6.
62. Bedell GN, Adams RW. Pulmonary diffusing capacity during rest and exercise. A study of normal persons and persons with atrial Septal defect, pregnancy, and pulmonary disease. J Clin Invest. 1962;41(10):1908–14.
63. Zavorsky GS, Blood AB, Power GG, Longo LD, Artal R, Vlastos EJ. CO and NO pulmonary diffusing capacity during pregnancy: safety and diagnostic potential. Respir Physiol Neurobiol. 2010;170(3):215–25.
64. Zavorsky GS, van der Lee I. Can the measurement of pulmonary diffusing capacity for nitric oxide replace the measurement of pulmonary diffusing capacity for carbon monoxide? Respir Physiol Neurobiol. 2017;241:9–16.
65. Zavorsky GS, Hsia CC, Hughes JM, et al. Standardisation and application of the single-breath determination of nitric oxide uptake in the lung. Eur Respir J. 2017;49(2):1600962.
66. Gilbert R, Epifano L, Auchincloss JH Jr. Dyspnea of pregnancy. A syndrome of altered respiratory control. JAMA. 1962;182:1073–7.
67. Gilbert R, Auchincloss JH Jr. Dyspnea of pregnancy. Clinical and physiological observations. Am J Med Sci. 1966;252(3):270–6.
68. Gee JB, Packer BS, Millen JE, Robin ED. Pulmonary mechanics during pregnancy. J Clin Invest. 1967;46(6):945–52.
69. Milne JA, Howie AD, Pack AI. Dyspnoea during normal pregnancy. Br J Obstet Gynaecol. 1978;85(4):260–3.
70. Milne JA. The respiratory response to pregnancy. Postgrad Med J. 1979;55(643):318–24.
71. Pernoll ML, Metcalfe J, Kovach PA, Wachtel R, Dunham MJ. Ventilation during rest and exercise in pregnancy and postpartum. Respir Physiol. 1975;25(3):295–310.
72. Pernoll ML, Metcalfe J, Schlenker TL, Welch JE, Matsumoto JA. Oxygen consumption at rest and during exercise in pregnancy. Respir Physiol. 1975;25(3):285–93.
73. Chiron B, Laffon M, Ferrandiere M, Pittet JF, Marret H, Mercier C. Standard preoxygenation technique versus two rapid techniques in pregnant patients. Int J Obstet Anesth. 2004;13(1):11–4.
74. Baraka AS, Hanna MT, Jabbour SI, et al. Preoxygenation of pregnant and nonpregnant women in the head-up versus supine position. Anesth Analg. 1992;75(5):757–9.
75. Baraka AS. Preoxygenation during pregnancy in the head-up versus the supine position. Anesthesiology. 2006;104(2):380. author reply 381
76. Templeton A, Kelman GR. Maternal blood-gases, PAo2–Pao2, hysiological shunt and VD/VT in normal pregnancy. Br J Anaesth. 1976;48(10):1001–4.
77. Fisher A, Prys-Roberts C. Maternal pulmonary gas exchange. A study during normal labour and extradural blockade. Anaesthesia. 1968;23(3):350–6.
78. Lucius H, Gahlenbeck H, Kleine HO, Fabel H, Bartels H. Respiratory functions, buffer system, and electrolyte concentrations of blood during human pregnancy. Respir Physiol. 1970;9(3):311–7.
79. Fadel HE, Northrop G, Misenhimer HR, Harp RJ. Normal pregnancy: a model of sustained respiratory alkalosis. J Perinat Med. 1979;7(4):195–201.
80. Madsen H, Ditzel J. Red cell 2,3-diphosphoglycerate and hemoglobin–oxygen affinity during normal pregnancy. Acta Obstet Gynecol Scand. 1984;63(5):399–402.
81. Tsai CH, de Leeuw NK. Correlation between 2,3-diphosphoglycerate and red cell mass in the third trimester of pregnancy. Acta Obstet Gynecol Scand. 1985;64(4):303–5.
82. Bard H, Teasdale F. Red cell oxygen affinity, hemoglobin type, 2,3-diphosphoglycerate, and pH as a function of fetal development. Pediatrics. 1979;64(4):483–7.
83. Awe RJ, Nicotra MB, Newsom TD, Viles R. Arterial oxygenation and alveolar-arterial gradients in term pregnancy. Obstet Gynecol. 1979;53(2):182–6.

21 Airway Management during Pregnancy and the Peripartum Period

Wendy H. Teoh

Bullet Points

- Factors contributing to the challenges of the pregnant airway are airway edema, respiratory and metabolic changes, weight gain and obesity, breast enlargement, gastroesophageal changes, and increased aspiration risk.
- Readiness is crucial for every unit caring for obstetric patients, and a difficult airway cart with adequate and sufficient equipment is essential.
- Preoxygenation prolongs the safe apnea time and can be assessed by measuring the end-tidal oxygen concentration (achieved when above 90%), which denotes successful denitrogenation.
- Waveform capnography confirms that the endotracheal tube is in the trachea and remains the gold standard of confirmation; it should be routinely used in intubated patients in critical care units.
- Advanced techniques include waveform capnography, direct laryngoscopy, or videolaryngoscopy confirming endotracheal tube in the vocal cords, or flexible scope visualization of the tracheal lumen.
- Awake intubation carries the advantage of maintaining airway patency and spontaneous ventilation; it may be performed via a flexible optical scope, videolaryngoscopy, intubation with second-generation supraglottic airways, tracheostomy, cricothyroidotomy, and by retrograde intubation.

21.1 Incidence of Difficult Airway and Failed Intubation in Obstetrics

Failed tracheal intubation in the pregnant patient is a dramatic situation as the presence of fetus (es) means that more than one life could potentially be compromised if severe hypoxia occurred during difficult airway management.

The incidence of failed intubation in the obstetric population is eight times higher than that in the general population. It has remained unchanged over the past four decades at 1:390 for general anesthesia (GA) in the obstetric population and 1:443 for cesarean deliveries [1]. In busy

W. H. Teoh (✉)
Private Anaesthesia Practice, Wendy Teoh Pte. Ltd., Singapore

College of Anaesthesiologists Singapore, Singapore

Singapore Society of Anaesthesiologist's Airway Special Interest Group, Singapore
e-mail: teohwendy@yahoo.com

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_21

tertiary obstetric centers with higher GA rates for cesarean deliveries with 24/7 specialist coverage, the failed intubation incidence may actually be lower (1:462) [2].

The Fourth National Audit Project (NAP4) of the Royal College of Anaesthetists and Difficult Airway Society (DAS) report from 2011 identified the maternal mortality rate from failed intubations to be approximately 2.3 per 100,000 GAs for cesarean delivery (1 death per 90–102 failed intubations) compared to 1:180,000 GAs for the general population [3]. Key learning points gleaned from this report were that physiological changes in pregnancy, active labor, and the often remote and isolated location of labor and cesarean delivery rooms increase the complexity of management of airway complications when they occur, and the presence of fetus(es) further complicates management.

Compared to the early 1980s when a high number of cases of difficult, failed intubation and/or failed ventilation used to regularly feature in the Reports on Confidential Enquiries into Maternal Deaths, fueling clinician's worries about managing the obstetric airway, it is encouraging that such incidences have reduced considerably over the years due to the greater use of neuraxial anesthesia in obstetrics and in part due to better training, staffing, equipment, and facilities. However, the potential for a failed intubation remains. There is also concern that changes in anesthetic training in the United Kingdom and the United States, as well as reduced number of GAs for cesarean deliveries, have led to reduced exposure of trainees to practice the skills necessary for obstetric airway management [4, 5].

In the 2006–2008 Center for Maternal and Child Enquiries (CMACE) report, two of the seven anesthesia-related deaths resulted from failure to ventilate, leading to a recommendation that because effective management of failed tracheal intubation is a core anesthetic skill, it should be taught and rehearsed regularly, with the use of simulation for teaching and rehearsing failed intubation strongly recommended [6]. Indeed, recent data has corroborated this, with data collected between 2008 and 2010 using the UK Obstetric Surveillance System reporting an incidence of failed intubation of 1:224 [7] and data collected between 2006 and 2013 in a US academic center reporting a 1:232 incidence [8], with only 3 failed intubations out of 695 GAs, all successfully managed with a laryngeal mask airway with no adverse maternal or fetal outcomes directly related to failed intubation. Advances in adjunct airway equipment, availability of an experienced anesthesiologist, and simulation-based teaching of failed airway management in obstetrics were contributory factors to the improved maternal outcomes in these patients. It is timely that the recent publication of the Obstetric Anaesthetists' Association (OAA) and DAS guidelines for the management of difficult and failed tracheal intubation in obstetrics includes an algorithm for "Safe obstetric general anesthetic" which is designed to be used as a teaching tool to update and standardize the conduct of GA for pregnant women [9].

21.2 Maternal Airway Challenges

Airway management in pregnancy is more challenging than in the nonpregnant state due to several factors:

21.2.1 Maternal Anatomic and Physiologic Factors

21.2.1.1 Airway Edema

Increased maternal blood volume and higher estrogen levels result in mucosal edema, capillary engorgement, and increased tissue friability. Hence intubation, insertion of nasal airways, orogastric, or nasogastric tubes, is associated with increased bleeding tendency. Epistaxis and soft palate hematoma can occur even after little or minimal unprovoked trauma [10]. Edema distorts laryngeal anatomy, narrowing apertures and mandates intubation with smaller sized diameter tracheal tubes. In addition, specific pregnancy-associated comorbidities such as preeclampsia, more frequent respiratory tract infections, and

oxytocin augmentation of labor with resultant water retention, over-zealous fluid administration, combined effects of prolonged Valsalva efforts, and maternal pushing during the second stage of labor can significantly worsen the airway edema. Pre-labor Mallampati classifications worsen during labor and evaluations should be repeated prior to intubation; [11, 12] these changes extend to 48 h after delivery [13]. A high Mallampati score (class 3 or 4) was thought to strongly associate with difficult intubation, with historical data reporting increased relative risks of 7.6 and 11.3, respectively [14], but recent studies were not able to correlate findings from preoperative bedside tests and actual intubation difficulty in women who underwent cesarean delivery under GA (see Chap. 20).

21.2.1.2 Respiratory, Metabolic Changes, and Denitrogenation

The enlarging gravid uterus pushes the diaphragm cephalad causing 15–30% reduced expiratory reserve volumes and decreased functional residual capacity (FRC). Early airway closure can occur at normal tidal volume breathing exacerbated in supine, Trendelenburg, and pregnant women with high body mass index (BMI). Increased oxygen consumption, the pain and stress of labor, potentiates rapid hypoxemia necessitating denitrogenation (administration of a maximal fraction of inspired oxygen ($Fi0_2$) with tight fitting mask) prior to rapid sequence induction (RSI) to achieve the longest apneic duration before desaturation. This is best achieved by elevating the head of the bed 25 degrees [15]. The standard technique for preoxygenation is to breathe 100% oxygen for 3–5 mins of tidal volume; [16] however given the emergent nature of GA in obstetrics, eight deep breaths over 60 s have been shown to provide adequate denitrogenation as measured by end-tidal fractional oxygen concentration (F_{ETO2}) [17].

21.2.1.3 Obesity and Weight Gain

By 2025, the global obesity prevalence will surpass 21% in women [18]. The Centers for Disease Control and Prevention (CDC) reported that 34.9% of adults in the United States had a BMI above 30 in 2011–2012 [19], with this figure projected to be 50% by 2025 [20]. The average weight gain during pregnancy in women with a BMI between 25 and 29.9 is 15.3 ± 6.8 kg [21], due to increased fat deposition, blood and interstitial fluid volume, uterus, and the enlarging fetus. Obese patients have a threefold increased risk of difficult intubation [22], and high BMI is a risk factor on univariate analysis for both difficult/impossible mask ventilation and difficult endotracheal intubation [23]. Obesity results in greater reduction in FRC, higher metabolic demands, increased oxygen consumption, and more rapid desaturation during apnea. Using a computational simulator, preoxygenation with 100% oxygen was followed by simulated RSI, a laboring parturient with a BMI of 50 demonstrated the fastest desaturation, defined as the time taken for arterial oxygen saturation (SaO_2) to decline below 90% (98 versus 292 s in a non-obese pregnant case) [24]. Morbidly obese pregnant patients are also at increased risk of postpartum hemorrhage, cephalopelvic disproportion resulting in higher rates of emergency cesarean deliveries and instrumental deliveries. Delayed childbearing and increased use of assisted reproduction techniques result in an older and more obese obstetric population [25], with higher risk of emergency cesarean deliveries, failed epidural anesthesia, pulmonary aspiration of gastric contents, and maternal death from airway complications [26, 27]. Comorbid preeclampsia, hypertension, and gestational diabetes in older pregnant women can potentiate and exacerbate the effects of hypoxemia, hypercarbia, and acidosis during a delayed or failed intubation.

Severely obese parturients have an increased "can't intubate, can't oxygenate" (CICO) risk. The cricothyroid membrane (CTM) is the last portal of escape for emergency oxygenation and definitive management for front-of-neck access (FONA) and cricothyrotomy when a failed intubation scenario arises. However, attempted FONA can fail because computerized tomography (CT) studies have shown that the CTM is not necessarily a superficial structure in women of

childbearing age [28]. The cricothyroid membrane is indeed a deep structure, especially in the morbidly obese (BMI > 45) where it may be difficult to palpate and identify [29]. Clinicians poorly identify the cricothyroid membrane by digital palpation, succeeding in only 39% (11/28) of obese compared to 71% (20/28) of non-obese pregnant patients [30]. Hence, point-of-care ultrasonography (POCUS) of the upper airway [31] is currently the best modality to provide useful information about the cricothyroid membrane's location and depth to aid FONA in obesity [32–34], with ultrasound being a natural choice and superior to CT scans as it avoids ionizing radiation to both mother and fetus(es) (see Chap. 35).

21.2.1.4 Breast Enlargement

Mammomegaly in supine pregnant women often impedes the insertion and manipulation of the laryngoscope to achieve good glottic visualization. The "head-ramped" position (where the external auditory meatus is aligned horizontally with the sternal notch) is advocated [35]. This semi-upright position achieved by placing blankets, pads, or other commercially available positioning devices under the shoulders, neck, and occiput significantly improves the laryngeal view and is superior to the "sniffing position" when intubating obese pregnant women (Fig. 21.1)

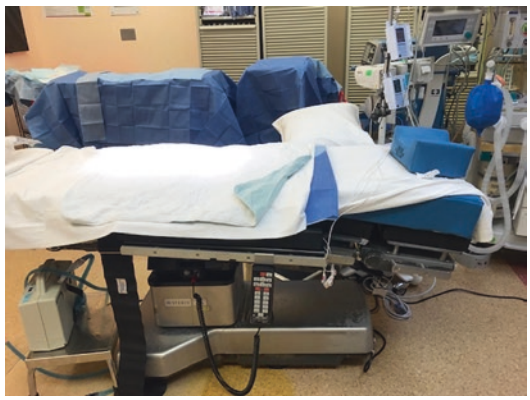


Fig. 21.1 Troop pillow illustrated here in an obstetric operating room, allowing safe ramping up in case of urgent or emergent general anesthesia with endotracheal intubation (here shown with back of the table in 'ramped down') position

[36]. Using a short-handled laryngoscope [37], getting an assistant to push the breasts caudally and detaching the laryngoscope handle from the blade then inserting the blade first into the mouth before reattachment are other strategies to minimize the difficulty in positioning the laryngoscope.

21.2.1.5 Gastroesophageal Changes and Aspiration Risk

Although maternal mortality from pulmonary aspiration of gastric contents has declined to negligible rates in the last three decades [6, 38–41], due to increased neuraxial analgesic/anesthetic techniques for cesarean delivery, pregnant women remain at risk for regurgitation and aspiration of gastric contents due to hormonal changes (increased gastrin, decreased motilin, and progesterone-induced relaxation of gastrointestinal smooth muscle decreasing lower esophageal sphincter tone). The relative risk of aspiration in pregnant versus nonpregnant women is best estimated from comparisons within single-study populations. Historical data identified a threefold higher aspiration risk in women undergoing cesarean delivery, with an overall incidence of aspiration of 1:2131 in the general population undergoing anesthesia versus 1:661 in parturients [42].

Labor and neuraxial opioids were historically believed to delay gastric emptying [43], although recent work on ultrasonographic quantification of gastric antrum volumes in laboring women suggests that gastric motility is preserved under epidural anesthesia [44, 45]. In third trimester gestation, an antral cross-sectional area of 9.6 cm^2 in the semi-recumbent right lateral position discriminated for high gastric volumes $\geq$1.5 mL kg^{-1}, demonstrating potentially increased aspiration risk [46, 47]. The recent 2016 "Practice Guidelines for Obstetric Anesthesia: An Updated Report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia and the Society for Obstetric Anesthesia and Perinatology" recommend timely administration of nonparticulate antacids, H2-receptor antagonists, and/or metoclopramide for aspiration prophylaxis before surgical proce-

dures such as cesarean delivery or postpartum tubal ligation [48].

21.2.2 Environmental/Situational and Anesthetic Factors

Situational urgency and time pressure to deliver the baby have typically resulted in suboptimal decision-making and fixation error by clinicians during critical situations. Similarly, in situations when a critically ill pregnant woman needs to be intubated, the emergency of the situation, in the presence of fetus(es) (that may or may not yet be delivered), requires adequate education of all involved in the procedure itself and readiness of the environment and staff. Training issues prevail due to reduced clinical experience of anesthetic trainees and assistants related to the low exposure to GA for cesarean deliveries and dwindling use of GA, as well as the rarity of circumstances of a critically ill pregnant woman requiring an intubation in the ICU. These are key educational elements for the success of an emergent intubation under these unique circumstances.

21.3 Safe General Anesthesia for Healthy Pregnant Patients

The OAA/DAS Obstetric Difficult Airway Guidelines proposed an updated conduct for safe obstetric GA (Algorithm 1; Fig. 21.2) [9]. Planning and preparation are emphasized with airway assessment, fasting whenever possible,

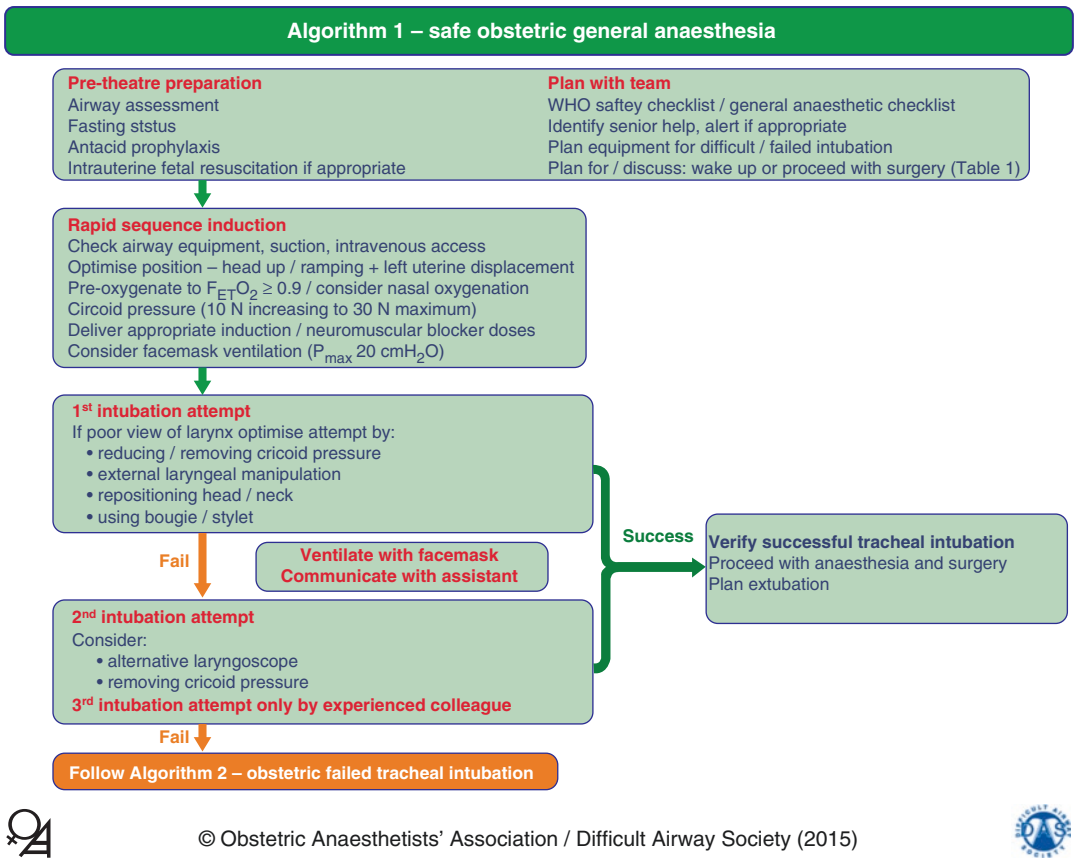


Fig. 21.2 Algorithm 1—safe obstetric general anaesthesia of the OAA/DAS Obstetric Difficult Airway Guidelines (Reproduced with permission)

antacid prophylaxis, and intra-uterine fetal resuscitation where appropriate. If the GA is provided with the intent of delivering the fetus (cesarean delivery), there should be concurrent team discussion whether to wake the mother or proceed with anesthesia without endotracheal tube in the event of failed intubation. This decision is influenced by several presenting factors related to the woman, fetus, anesthesiologists' experience, and clinical situation, as outlined in the OAA/DAS Obstetric Difficult Airway Guidelines (Table 21.1; Fig. 21.3).

The fifth National Audit Project of the RCoA (NAP5) [49] found a higher incidence of awareness in obstetric GAs and in patients with unanticipated difficult airway. It is therefore recommended that additional induction agent should always be available and be administered should a difficult airway be encountered. There is no consensus whether short-acting opiates should be used routinely in obstetrics instead of only reserving their use in specific situations such as preeclampsia or in patients with cardiac disease.

Table 21.1 Suggested equipment and drugs for a difficult airway cart

Basic airway equipment	Face masks Oral airways 2 working laryngoscope handles Macintosh blades size 3 and 4 6.5–7.0 mm endotracheal tubes with stylet Empty 10 ml syringe to inflate the pilot balloon Backup endotracheal tubes in a range of sizes Gum elastic bougie Second-generation supraglottic airways (SGA) A working suction apparatus
Secondary intubation equipment	Other direct laryngoscopes (McCoy blade, Miller blade) Videolaryngoscopes Optical stylets or intubation conduits Fiberoptic bronchoscope Surgical airway kit
Drugs for intubation	Propofol, midazolam, etomidate, ketamine Succinylcholine Rocuronium, sugammadex

21.3.1 Algorithms for Management of Difficult Intubation

The OAA/DAS obstetric guidelines propose an obstetric failed tracheal intubation algorithm (Algorithm 2; Fig. 21.4) [9]. When first attempt at endotracheal intubation fails, face mask ventilation should be performed while communicating with the team. The second intubation attempt should be done by the most experienced anesthesiologist present using a different laryngoscope and with the cricoid pressure removed. Only two attempts are recommended, and a third attempt should only rarely be done (and this must be done by the most skilled, different anesthesiologist) as airway swelling can develop very rapidly, converting a "can oxygenate, can't intubate situation" to a CICO. Three failed optimal laryngoscopy attempts should invoke the failed intubation drill with early call for help. Here, oxygenation and ventilation should take priority over intubation, using either a face mask or second-generation supraglottic airway (SGA). If face mask was found to be difficult prior to the intubation attempt and if the preinduction team decision was to proceed with surgery, then immediate insertion of the SGA is the preferred airway rescue strategy. If oxygenation or ventilation is impossible at any point of the algorithm, then a CICO scenario (Algorithm 3; Fig. 21.5) is declared, and surgical rescue airway is indicated [9]. Failed oxygenation resulting in maternal cardiac arrest mandates a perimortem cesarean delivery within 4–5 min of the arrest to optimize the effectiveness of chest compressions for maternal resuscitation [50].

21.4 Airway Management of the Critically ill Pregnant Patient

21.4.1 Hazards of ICU Airway Management

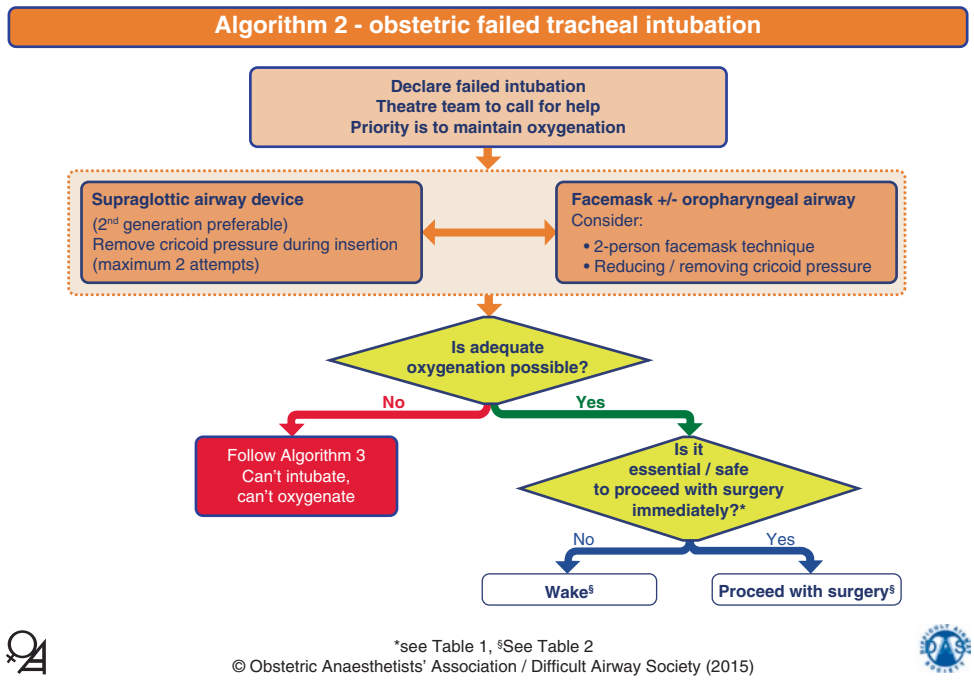
ICU patients' airways are extremely demanding with significantly greater incidence of airway-related mortality and severe morbidity than that

Table 1 – proceed with surgery?

	Factors to consider	WAKE			PROCEED
Before induction	Maternal condition	• No compromise	• Mild acute compromise	• Haemorrhage responsive to resuscitation	• Hypovolaemia requiring corrective surgery • Critical cardiac or respiratory compromise, cardiac arrest
	Fetal condition	• No compromise	• Compromise corrected with intrauterine resuscitation, pH < 7.2 but > 7.15	• Continuing fetal heart rate abnormality despite intrauterine resuscitatiom, pH < 7.15	• Sustained bradycardia • Fetal haemorrhage • Suspected uterine rupture
	Anaesthetist	• Novice	• Junior trainee	• Senior trainee	• Consultant / specialist
	Obesity	• Supermorbid	• Morbid	• Obese	• Normal
	Surgical factors	• Complex surgery or major haemorrhage anticipated	• Multiple uterine scars • Some surgical difficulties expected	• Single uterine scar	• No risk factors
	Aspiration risk	• Recent food	• No recent food • In labour • Opioids given • Antacids not given	• No recent food • In labour • Opioids not given • Antacids given	• Fasted • Not in labour • Antacids given
	Alternative anaesthesia • regional • securing airway awake	• No anticipated difficulty	• Predicted difficulty	• Relatively contraindicated	• Absolutely contraindicated or has faild • Sugery started
After failed intubation	Airway device / ventilation	• Difficult facemask ventilation • Front-of-neck	• Adequate facemask ventilation	• First generation supraglottic airway device	• Second generation supraglottic airway device
	Airway hazards	• Laryngeal oedema • Stridor	• Bleeding • Trauma	• Secretions	• None evident

Criteria to be used in the decision to wake or proceed following failed intubation. In any individul paitient, some factors may suggest waking and others proceeding. The final decision will depend on the anaethetist's clinical judgement.

Fig. 21.3 Factors involved in the decision-making about whether to proceed or wake up a patient following failed intubation (Reproduced with permission)



*see Table 1, §See Table 2

Fig. 21.4 Algorithm 2—failed intubation algorithm

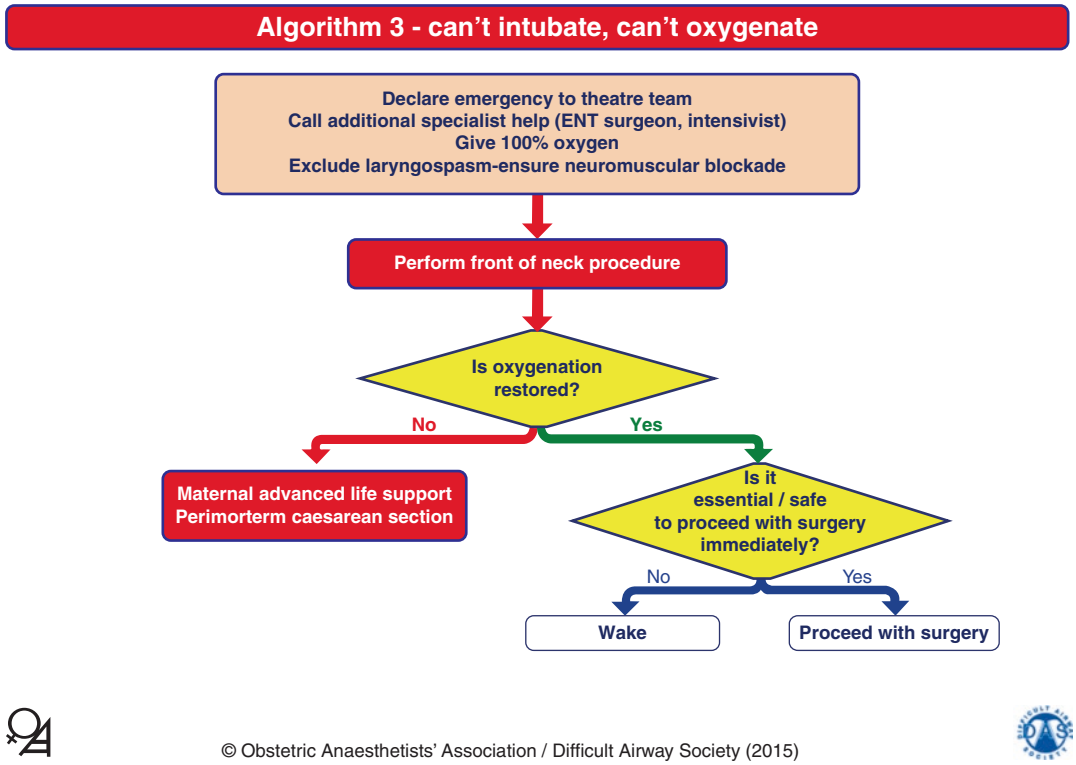


Fig. 21.5 Algorithm 3- can't intubate, can't oxygenate (CICO) scenario

encountered in general operating room (OR) practice [3]. Studies quantifying airway difficulties per se in the ICU are scarce, but a report on 3423 nonoperating room emergent endotracheal intubations performed by anesthesia residents was reviewed, with 60% occurring in the ICU [51]. The NAP4 of the Royal College of Anaesthetists was a nationwide, prospective observational 1-year audit in the United Kingdom that collated data from the OR, emergency department (ED), and ICU. They studied airway-related mortality, brain damage, emergent surgical access, ICU admission, or prolongation of ICU stay [3]. NAP4 found 38 airway-related deaths: 16 in the OR, 4 in the ED, and 18 in the ICU. With a denominator of 2.9 million anesthetics performed in the OR, 20,000 endotracheal intubations in the ED, and 58,000 episodes of advanced respiratory support in ICU, airway-related death was found to be 58 times more common per patient in the ICU than in the OR [3]. Death or brain damage rates were 61% when difficult airways were encountered in the ICU compared to 14% in the OR. This translates to airway-related mortality rates of 1 in 2700 ICU patients versus 1 in 180,000 in the OR [52].

ICU patients are physiologically compromised, having significant ventilation–perfusion (VQ) scan abnormalities and lower functional residual capacities: preoxygenation is less effective and apnea tolerated poorly. Patients are frequently unfasted or have delayed gastric emptying. The intubation is often urgent, with little time for assessment or preparation. Airway assessment in the critically ill is problematic, so difficulty is often unanticipated. Ideal airway intervention must therefore be prompt and smooth, as the critically ill simply do not tolerate poor airway management, what more a pregnant patient with two lives at stake when faced with the need to intubate a deteriorating eclamptic, or parturient with significant respiratory disease [53], pneumonia, hypoxemic respiratory failure,

hemodynamic instability, impaired consciousness, angioedema, Ludwig's angina, acute epiglottitis, sepsis, or multi organ failure.

Thorough preoxygenation, the competent use of videolaryngoscopes, and an intubation checklist incorporating RSI are key management strategies. However, the hazards of airway management in the ICU only begin once the tube is inserted. An intubated patient care bundle including capnography needs to be instituted to exclude esophageal intubation, with continued vigilance for partially displaced tubes and displaced airways especially in the obese, agitated, and during patient transfers to imaging facilities. Successful airway management requires training and a well-formulated airway plan that is shared with the entire team and that uses equipment with which team members are proficient. Difficult extubation, endotracheal tube exchange techniques, tracheostomy insertion, and care are unique to ICU airway management (beyond the scope of this chapter), and proficiency in dealing with tracheostomy emergencies, bleeding, obstruction, partially displaced tubes is a core ICU skill.

21.4.2 Equipment and Readiness

A well-stocked portable difficult airway cart is essential for every unit caring for obstetric patients. Airway carts throughout the hospital should be standardized including in the OR, ED, and ICU. Equipment should be purchased with the least experienced potential user in mind. Suggested equipment are listed (Table 21.1) [54, 55].

21.4.2.1 Drugs

ICU patients are often hypovolemic, septic, and/or in hemodynamic shock. A third of all severe complications of ICU endotracheal intubation are hemodynamic [56], and this affects the choice of pharmacological agent to facilitate intubation. Etomidate or ketamine is the most commonly used induction agents in shocked patients, but etomidate's use has been questioned because of its suppression of 11β-hydroxylase, which causes relative adrenal insufficiency and purportedly increases mortality, with some authorities asking to abandon its use [57, 58]. Ketamine is an excellent induction agent for ICU patients; it provides dissociative sedation and preserves spontaneous respiration with intact airway reflexes. The primary concern regarding ketamine is its elevation of intracranial pressure, but its positive effect on arterial blood pressure also results in increased cerebral perfusion pressure, so its use is increasingly prevalent in trauma and head-injured patients so long the patient is adequately ventilated [59–61]. Propofol remains a popular induction agent to facilitate endotracheal intubation by anesthesiologists, but its use in the ICU patient can exacerbate hypotension. Nonetheless, experience in using a particular drug can have excellent outcomes, as demonstrated by critical care doctors in Scotland (national study of 794 intubations over 4 months, 70% occurring in ICU and 18% ED) [62]. Their first-time intubation success rate was 91%; no patient required more than three attempts at intubation, with three-quarters of intubations performed by doctors who had undergone >24 months formal anesthetic training, with routine supervision of junior trainees. Generally, the dose of sedative agents can be decreased 30% to 50% in ICU patients. Using neuromuscular blocking agents (NMBAs) allows further reductions in induction dose [63]. Succinylcholine is the traditional NMBA used in the ICU. A recent 2015 Cochrane review found intubating conditions of rocuronium 1.2 mg/kg and succinylcholine 1 mg/kg to be equivocal; however succinylcholine was clinically superior due to its shorter duration of action [64]. When intubating hemodynamically unstable ICU patients, one must bear in mind that the speed of onset of rocuronium is dependent on cardiac output [65]. Anaphylaxis occurrence with succinylcholine and rocuronium is similar [66]. Sugammadex (16 mg/kg) must be immediately available to effectively reverse an RSI dose in less than 10 min [67]. Succinylcholine fasciculation raises oxygen consumption and precipitates earlier desaturation of 116 s compared to

rocuronium [68]. Succinylcholine-induced hyperkalemia from development of extrajunctional acetylcholine receptors with prolonged immobility is a dangerous concern. There is no clear guidance as to the duration of immobilization that puts patients at highest risk, with many clinicians using 10–14 days as a cutoff [69, 70].

21.4.3 Airway Assessment

Assessing the maternal airway for features of a difficult airway allows anticipation of equipment needs and backup B and C plans should plan A fail. If the plan is for an imminent cesarean delivery, and the GA is not needed for other indications (respiratory support), prevention of airway problems is best achieved by early placement of an epidural catheter (particularly in the morbidly obese or preeclamptic parturient) [48]. Cormack and Lehane's four laryngeal grades of structures visualized on direct laryngoscopy [71] are significantly correlated with the Mallampati class [72]. A higher Mallampati score (of III and IV), presence of a short neck, protruding incisors, or a receding mandible, is known to increase the relative risk of intubation difficulty in pregnancy [14]. Other multivariate tools to assess airway difficulty are the Wilson Risk Sum index [73] and the el-Ganzouri index [74]. The latter's seven criteria of mouth opening, thyromental distance, neck movement, mandibular protrusion, body weight, Mallampati class, and history of difficult intubation are independent predictors of difficult intubation (see Chap. 20). However, emergent ICU intubation precludes detailed assessment and is often fraught with problems (hypoxic uncooperative patient, eclamptic, secretions, blood, vomit in airway, cervical spine collars in place precluding cervical spine mobility assessment).

De Jong developed the MACOCHA score which is the only ICU-specific assessment tool to evaluate risk factors for difficult intubation [75]. It comprises seven items (factors related to patients: Mallampati 3 or 4, obstructive sleep apnea syndrome, reduced cervical spine mobility, limited mouth opening <3 cm; or factors related to pathology: coma, severe hypoxemia <80%; or factor related to operator: non-anesthesiologist) coded from 0 to 12, where 0 = easy and 12 = very difficult. A score of 3 or greater is the cutoff value denoting difficult intubation with a high discriminant value [76]. The MACOCHA predictive score is unique as it scores operator experience: specifically, anesthesia training of at least 24 months, and includes two ICU-specific criteria: hypoxemia and coma before intervention, important because hypoxia permits less time for preparation, leads to quicker desaturation, and may increase operator stress; coma makes assessment more difficult and is associated with greater laryngeal contamination. If there is a history suggestive of upper airway obstruction, flexible nasal endoscopy is a valuable tool [77]. Predictors of difficult mask ventilation and supraglottic airway ventilation have been described but not validated in the ICU setting [78–81].

21.4.4 Rapid Sequence Induction and Intubation (RSI)

Technique: The definition of RSI varies but certainly includes preoxygenation and an induction dose of IV hypnotic followed by a rapid-onset neuromuscular blocking agent. ICU patients are rarely fasted and have functional ileus and at high risk of regurgitation and pulmonary aspiration when given sedatives to allow endotracheal intubation. All critical care physicians should learn to perform RSI and adopt it as the standard mode of intubation for critically ill patients [81, 82]. The RSI technique is part of the only intubation bundle seen to reduce complications of ICU endotracheal intubation, the ICU intubation bundle management protocol, in which ten components have been delineated and proposed [82].

Before intubation:

1. Presence of two operators.
2. Fluid loading (in the absence of cardiogenic pulmonary edema).
3. Preparation of long-term sedation.
4. Preoxygenation with noninvasive positive-pressure ventilation.

During intubation:

1. Rapid sequence induction.
2. Cricoid pressure.

After intubation:

1. Immediate confirmation of tube placement by capnography.
2. Vasopressor use if needed.
3. Early administration of sedation.
4. Initial "protective ventilation" (tidal volume 6–8 mL/kg of ideal body weight, PEEP <5 cm H_2O, respiratory rate between 10 and 20 cycles/min).

Adapted from this initial work [82], an ICU RSI intubation care bundle was developed which incorporates checklists and lists personnel responsible for which task and is an approach amenable to ongoing teamwork and simulation training (Table 21.2) [83].

Cricoid Pressure: In the classic RSI, cricoid pressure is applied, and no face mask ventilation occurs between induction and endotracheal intubation; however, gentle face mask ventilation during cricoid pressure application is acceptable. Gentle face mask ventilation is often necessary to prolong the time to desaturation in critically ill patients who are at greater risk of hypoxemia from primary lung pathology, high metabolic demands, anemia, insufficient respiratory drive, and inability to protect their airway against aspiration [84]. Debate continues as to the efficacy of cricoid pressure in preventing regurgitation [85]. Cricoid pressure-associated complications include airway obstruction leading to interference with manual ventilation, laryngeal visualization, tracheal intubation, placement of supraglottic devices, and relaxation of the lower esophageal sphincter [86]. If used, cricoid pressure should be applied by trained staff (ideally) and released if interfering with mask ventilation, SGA placement, laryngoscopy, or intubation.

Table 21.2 Intensive care unit rapid sequence intubation care bundle

1.	**Preintubation: Assemble airway team**	**Who?**
1.1	Lead nurse (runs preprocedure checklist): Team coordinator	N1
1.2	First operator (physician)	O1
1.3	Second operator (senior physician who may administer initial drugs)	O2
1.4	Cricoid operator (staff nurse; also monitors vital signs on monitor)	N2
1.5	Intubator's assistant (second staff nurse)	N3
1.6	Manual in-line stabilization operator (additional team member, as appropriate)	M1
2.	**Preintubation preparation**	
Checklist commences (lead by N1 with all team present)		N1/O2
This must be read aloud to entire team		
2.1	Reliable intravenous access; time for arterial line?	O1/O2
2.2	Capnography on ($EtCO_2$); ensure self-check has completed before induction	N1/O1
2.3	Apply full monitoring, if not already	N2/N3
2.4	Sit patient 20–25 degree head-up or ramp as appropriate (unless contraindicated)	N2/N3
2.5	Chart/bedhead signage/handover communication reviewed: DA or allergy?	O1/TEAM
2.6	Assess airway	O1/O2
2.7	Aspirate gastric tube	N2/N3
2.8	Administer oxygen via nasal cannula	N2/N3
2.9	Start preoxygenation with NIPPV (FiO_2 = 1.0; PEEP = 5–8 cm H_2O; PS to V_T of 6 to 8 mL/kg; good mask fit)	N1/N2/N3
2.10	Commence 500 mL fluid bolus (unless contraindicated); optimize inotropes	O1/O2
2.11	Confirm waters circuit or Ambu bag available for bag-valve-mask ventilation	N1
2.12	Yankauer suction working	N1

(continued)

Table 21.2 (continued)

2.13	Ensure intubation cart with difficult airway equipment is at bedside. If flexible bronchoscope is not on cart, is it immediately available?	N1/O1
2.14	Prepare intubation drugs: Hypnotic, relaxant, atropine, bolus pressor/inotrope	O2/O1
2.15	Prepare continuous sedation drugs	N2/N3
2.16	Confirm sugammadex 16 mg/kg immediately available, if appropriate	N1/TEAM
2.17	DECISION: If intubation fails, can patient be woken up?	O2
3.	**Verbal confirmations**	
Team coordinator asks		
3.1	Operator 2 states intubation plan	O2
3.2	Does anyone have any concerns? Opportunity for team to clarify plan	TEAM
3.3	Has patient been preoxygenated for 3 min?	O1
3.4	$EtCO_2$ working?	O1
3.5	$EtO_2 > 0.9$	O2
3.6	Can patient be optimized further before induction?	O2
Team coordinator states checklist complete		N1
4.	**Intubation attempt**	
4.1	Optimize head neck: Sniffing position with face parallel to ceiling if possible	O1/O2
4.2	Push induction drugs: ketamine 2 mg/kg, rocuronium 1.2 mg/kg, (check no contraindication to succinylcholine, if used)	O2
4.3	Cricoid pressure	N2
4.4	As face mask removed, ensure nasal cannula flow 15 L/min	N3
4.5	Bag ventilation	O1
4.6	Intubation	O1
4.7	Confirm intubation with waveform $EtCo_2$	O1/O2
4.8	Auscultate both lungs	O1/O2
4.9	Cuff pressure 20–25 cm H_2O	N2
5.	**Post-intubation care**	
5.1	Pressor for MAP <70 mm Hg	O1/O2
5.2	Initiate sedation	N2
5.3	Initiate invasive ventilation: V_T 6–8 mL/kg ideal body weight; PEEP 5 cm H_2O; RR 10–20; FiO_2 1.0; Plateau pressure < 30 cm H_2O, as appropriate	N2
5.4	Recruitment maneuver if stable (CPAP 30 to 40 cm H_2O for 30 to 40 sec)	O2
5.5	Chest radiograph and annotate intubation details in medical record	O1/O2
5.6	Note tube depth on chart	N2
5.7	Arterial blood gas	N2
5.8	Titrate FiO_2 down to target PaO_2 and V_E to target $PaCO_2$	N2
5.9	Complete intubation audit documentation	N1/O2

DA difficult airway, *$EtCO_2$* end-tidal carbon dioxide, *EtO_2* end-tidal oxygen, *NIPPV* noninvasive positive-pressure ventilation, *PEEP* positive end-expiratory pressure, *PS* pressure support, *RR* respiratory rate, V_E minute ventilation; V_T tidal volume

Use of Neuromuscular Blocking Agents (NMBA): Studies of difficult intubations in ICU typically reveal low usage of neuromuscular blockade. However, recent guidelines from the United Kingdom, United States, and Canada for the management of unanticipated difficult airway state unequivocally that if airway management or endotracheal intubation is difficult, further attempts should not proceed without administration of NMBA to abolish laryngeal reflexes, increase chest compliance, and facilitate mask ventilation [87–89]. A recent 2017 Cochrane review reinforces the recommendation for use of neuromuscular

blocking agents to improve tracheal intubation conditions [90].

21.4.5 Optimizing Oxygenation Preintubation

Critically ill patients are prone to a profound drop in peripheral capillary oxygen saturation (SpO_2) due to a combination of intrapulmonary shunt, low mixed venous saturation (as a result of low cardiac output, anemia, and hypermetabolic states), and apnea/hypoventilation [91]. A tight fitting anesthetic-type full face mask must be used for preoxygenation. Beware of leaks around the face mask, evidenced by lack of $EtCO_2$ tracing which is the commonest cause of preoxygenation failure. Correct mask sizing, and using two hands minimizes leaks. Standard non-rebreather face masks only achieve FiO_2 of 70% and should not be used. If there is unavoidable leak, the efficacy of mask preoxygenation can be improved by apnoeic oxygenation via nasal cannula at 15 L/min during preoxygenation [92], or as high-flow humidified oxygen (up to 60 L min^{-1}) [93] to prolong the safe apnea period. If the SpO_2 remains low after 4 min of preoxygenation, this is diagnostic of intrapulmonary shunt [94]. Shunt fractions of 30% cause patients to be highly refractory to simple preoxygenation [95]. Positive end-expiratory pressure (PEEP of 5–10 cm H_2O) during preoxygenation is recommended to recruit alveoli [82] but should not exceed the esophageal sphincter pressure (20–25 cm H_2O) to avoid gastric distension. Computed tomography studies show that PEEP of 10 cm H_2O during preoxygenation reduces atelectasis from 10% to 2% [96]. The supine position facilitates dorsal lung collapse, so patients should be preoxygenated in the semi-recumbent position or sitting head-up 20 degrees [97]. In critically ill pregnant women, left uterine displacement can prevent aortocaval compression, aid venous return, preserve cardiac output, and maintain uteroplacental blood flow.

21.4.6 Videolaryngoscopy

Videolaryngoscopy is increasingly becoming standard of care in the ICU as it definitely improves laryngeal view [98, 99]. Videolaryngoscopes generally provide glottic visualization without the need to align the three oropharyngolaryngeal axes due to placement of a camera in the distal third of its blade [100]. This widens the users "eye," enhancing the view from a conventional 15° to a wider 80° viewing angle, allowing intubators a "look around the corner" which is ideal to aid intubation in the anterior or grade 3–4 larynx encountered not infrequently in obstetrics [101]. A meta-analysis of nine trials of videolaryngoscopy in the ICU showed that it reduced the risk of difficult intubation, the incidence of Cormack and Lehane grade 3 and 4 views, and esophageal intubation and did increase first-pass success [102]. Other advantages include possible reduction of cervical spine movement during intubation [103] and performing an awake intubation with videolaryngoscopy [104], although uncommon. It also allows suctioning of vomitus, blood, and secretions in the airway under direct vision and allows members of the ICU team to view the intubation process and aids communication, allowing adjustment of any misapplication of cricoid pressure and more directed assistance by optimizing backward-upright-right-pressure (BURP) maneuvers without relying on verbal directions from a potentially task-fixated operator during a stressful intubation. A recent Cochrane review however found no evidence that videolaryngoscopy use reduces the number of intubation attempts or the incidence of hypoxia or respiratory complications and may take longer to intubate [105]. This is because device-specific proficiency needs to be gained with each videolaryngoscope; there are channeled and non-channeled videolaryngoscopes with their own subtleties, conventional Macintosh-shaped blades, and angulated blades that need a pre-styletted endotracheal tube in a J-hockey stick shape [106, 107]. Proficiency gained with one device may not be wholly transferable to another, and this impacts the ICU rotational trainee, and

even senior supervising doctors who may not have trained in an era of prevalent videolaryngoscopy. Universal adoption of videolaryngoscopy can lead to decay in intubating skills with a direct laryngoscope; one way to counter this is to train using a videolaryngoscope with a conventional Macintosh-shaped blade, and then the device can be used as a direct laryngoscope and the video component used when a direct line of sight is not possible. In summary, videolaryngoscopes should be available in the ICU, and all intensivists should be proficient in their use. If a difficult intubation is suspected, videolaryngoscopy should be used from the outset in keeping with the 2013 guidelines from the American Society of Anesthesiologists (ASA) Task Force on Management of the Difficult Airway [87]. The device should have a screen visible to all team members. It is complementary to direct laryngoscopy (not a replacement) because failed videolaryngoscopy may be rescued with direct laryngoscopy in some instances [108].

21.4.7 Confirmation of Tracheal Intubation

Post-intubation, initial confirmation of correct endotracheal tube (ETT) position, involves clinical assessment with a usual insertion depth of 21 cm for females and chest radiography where the ETT tip should be about 5 cm above the carina between the clavicular heads. Waveform capnography confirms that the ETT is in the trachea and remains the gold standard of confirmation and should be routinely used in intubated patients in ICU [82]. The practice of daily chest radiographs should be abandoned and performed only when indicated, the process of obtaining a chest radiograph risks dislodging the ETT, and complications are not reduced by daily films. In the ensuing ICU stay, clinical signs such as chest wall excursion, auscultation, condensation in the endotracheal tube, and Spo_2 are unreliable and cannot be used without confirmation by an advanced technique [89]. Advanced techniques include waveform capnography, direct laryngoscopy or videolaryngoscopy confirming ETT in the vocal cords, or flexible scope visualization of the tracheal lumen. The gold standard remains continuous waveform capnography. The NAP4 study in ICU patients [3] revealed that capnography ($EtCO_2$) was not used in 75% to 100% of unrecognized esophageal intubations with most of these patients dying and that lack of capnography materially contributed to 77% of all ICU deaths, including tube displacements. In some cases, when waveform capnography was used, the tracing was misinterpreted, resulting in death [3].

21.4.8 Awake Intubation

Awake intubation has advantages of maintaining airway patency and spontaneous ventilation. Awake intubation can be performed via a flexible optical scope, videolaryngoscopy, intubation via an SGA, tracheostomy, cricothyroidotomy, and by retrograde intubation [109]. Its role may be limited in critically ill parturients who need immediate intubation and who may be uncooperative from hypoxia, pulmonary edema, and raised intracranial pressure; all these in itself represent contraindications to awake intubation, including that of an inexperienced operator and absolute patient refusal. Intensivists should beware the significant risk of nasal bleeding if awake nasal intubation is carried out in pregnant patients due to increased vascularity. It is generally recommended to avoid using cocaine as a nasal decongestant as it may interfere with placental blood flow and the systemic effects of vasoconstrictors are potentially hazardous in preeclampsia.

21.4.9 Failed Intubation

Airway carts throughout the hospital should be standardized including in the OR, ED, and ICU. Equipment should be purchased with the least experienced potential user in mind, and ICUs must have immediate access to a flexible intubation scope. Should the initial intubation plan fail, the emphasis must be on oxygenating

the critically ill parturient. They risk critical hypoxemia, impacting both mother and fetus, with further deterioration of the airway, risk aspiration, and a CICO situation. Declaration of a failed intubation is critical, so the team recognizes this crisis phase and refocuses efforts on how best to assist the airway operator. Human non-technical factors come into play. Pathologic thought processes often occur during airway crises where the operator becomes task-fixated on endotracheal intubation, neglects oxygenation, and loses situational awareness. This hinders them mentally from progressing through the difficult airway algorithms in a timely manner as they fail to appreciate the urgency while endeavoring to intubate the trachea repeatedly.

When intubation attempts fail, nasal high-flow oxygen should continue, and ventilation using a face mask or SGA attempted [87]. Inexperienced ICU residents are better able to oxygenate using SGAs rather than face masks, as this frees up the hands and is less tiring. No more than three SGA insertion attempts should be undertaken to avoid further iatrogenic airway trauma, bleeding, and edema [88]. Second-generation SGAs (with a gastric drain port) are advocated as patient safety is enhanced [110]: they possess higher oropharyngeal seal pressures, thus allowing PEEP and positive pressure ventilation [111]; the improved esophageal seal makes regurgitation of gastric contents less likely; and passing an orogastric tube via the drain tube of the second-generation SGA to empty the stomach and suck out its contents reduces the risk of aspiration [112, 113]. Since the introduction of the LMA ProSeal (considered the first prototype second-generation SGA), others on the market are the LMA Supreme, I-gel, LMA Protector, AES Guardian CPV, LaryngoSeal, Totaltrack VLM, Ambu AuraGain, and air-Q Blocker [114]. In a majority of cases, the SGA provides effective rescue ventilation and oxygenation after failed intubation [115]. If oxygenation through a SGA is successful, then one can either allow the patient to wake up and breathe spontaneously (rarely possible in ICU patients), intubate the trachea through the SGA, or perform invasive tracheal access.

The Intubating Laryngeal Mask Airway (ILMA; LMA North America, San Diego, CA), known as the LMA Fastrach, is an SGA specifically designed to facilitate intubation [116, 117]. However, when faced with a failed intubation, the SGA initially used for rescue is usually one the operator is most familiar with and usually not an ILMA nor one of the newer devices that are also designed to allow guided tracheal intubation, eg. LMA Protector, AMBU AuraGain, I gel, and TotalTrack VLM. Removal of an SGA which is adequately oxygenating an ICU patient during a failed intubation and replacing it with an ILMA is a difficult judgment call and unlikely to occur given the heterogeneity in difficult airway cart devices, lack of availability, or operator inexperience. Most operators would elect to intubate via the working device rather than swap to another with which they are inevitably less familiar.

An extremely useful technique in emergency failed endotracheal intubation is the low-skill fiberoptic intubation [118], or "Laryngeal Mask Airway-Aintree Catheter-Fiberoptic bronchoscope" technique for difficult intubation [119]. An Aintree intubation catheter (AIC; Cook Medical, Bloomington, IN) is mounted on a flexible fiberscope which is then passed through the SGA into the trachea under visualization (minimizing trauma). The flexible fiberscope and SGA are then removed leaving only the AIC in the trachea, after which an endotracheal tube is railroaded in place over the AIC. It proved useful in 128 patients with a 93% success rate; most had Cormack-Lehane grade 3 or 4 views, and some could not be ventilated via face mask [119]. If intubation is impossible and critical hypoxia develops, it is possible to oxygenate via the AIC provided there is a path for air to escape, but barotrauma is a real risk [120].

21.4.10 Emergency Invasive Airway Access

We should be mindful that not every CICO situation occurs out of nowhere. A prompt decision to perform emergency invasive airway access needs to be made and determines outcomes because the

natural evolution of an airway crisis is first difficulty, trauma, swelling, and bleeding/aspiration progressing to complete obstruction (all largely iatrogenic). Emergency airway access can be achieved by one of three techniques: surgical incision with a scalpel, narrow cannula-over-needle, or large bore cannula (usually ≥4 mm) over a wire or trocars [121]. A small bore/needle technique is a temporary airway with a high failure rate, prone to kinking and displacement, whereas a simple surgical technique has a high success rate and results in a cuffed tube in the trachea that allows the continuation of ventilator treatment. A surgical technique must be mastered by all emergency airway providers and should be considered the default technique [121, 122].

21.5 Conclusion

The anatomic and physiological changes of pregnancy make management of the airway in obstetric patients particularly treacherous. Critically ill pregnant women with cardiopulmonary or hemodynamic compromises, with the fetus(es) that may or may not be imminently delivered, are further physiologically compromised. They have significant V/Q abnormalities and lower FRCs: preoxygenation is less effective, and apnea is poorly tolerated. Pregnant patients are frequently unfasted, have delayed gastric emptying, and may require urgent intubation without time for assessment or preparation. Dedicated guidelines on tracheal intubation in critically ill adults were recently published in 2018 and provide welcome direction and comprehensive management strategies [122]. Thorough preoxygenation, use of videolaryngoscopes, an intubation checklist incorporating a modified RSI, and post-intubation continuous waveform capnography are key.

Successful airway management requires training of a well-formulated airway plan, known to the entire team, using equipment familiar to the team members. The first intubation attempt is always the best; attention should be paid to denitrogenation of the lungs, patient positioning (head ramped), left uterine displacement, skilled assistance, using neuromuscular blocking agents, and the release of cricoid pressure if it impedes glottic exposure when performing a rapid sequence endotracheal intubation. Failed intubation after three optimal laryngoscopy attempts should invoke the failed intubation drill, remembering that oxygenation and ventilation takes priority over intubation. A SGA with gastric access port is recommended as the preferred rescue airway strategy. A CICO situation calls for early rescue by cricothyrotomy/surgical airway. No singular airway device improves outcomes: the emphasis is on adequate training, supervision, and experience in airway management; good assessment and backup planning; using RSI intubation bundles, checklists, and standards of practice to minimize procedural difficulty; using airway equipment with which the doctor has practiced and is familiar with, with the immediate availability of appropriate rescue devices and deployment of the most appropriate rescue techniques when airway management fails; these strategies are amenable to ongoing training and simulation drills to optimize human factors and enhance teamwork for improving care of the critically ill parturient.

References

1. Kinsella SM, Winton AL, Mushambi MC, et al. Failed tracheal intubation during obstetric general anaesthesia: a literature review. Int J Obstet Anesth. 2015;24:356–74.
2. Teoh WH, Yeoh SB, Ithnin F, Sia AT. Incidence of difficult & failed intubations during obstetric general anaesthesia in a tertiary referral center. Br J Anaesth. 2012;108. Suppl(2):ii212.
3. Cook TM, Woodall N, Frerk C, Fourth National Audit P. Major complications of airway management in the UK: results of the fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 1: anaesthesia. Br J Anaesth. 2011;106:617–31.
4. Palanisamy A, Mitani AA, Tsen LC. General anesthesia for cesarean delivery at a tertiary care hospital from 2000 to 2005: a retrospective analysis and 10-year update. Int J Obstet Anesth. 2011;20:10–6.
5. Tsen LC, Camann W. Training in obstetric general anaesthesia: a vanishing art. Anaesthesia. 2000;55:712–3.
6. Cantwell R, Clutton-Brock T, Cooper G, et al. Saving Mothers' lives: reviewing maternal deaths to make

motherhood safer: 2006–2008. The eighth report of the confidential enquiries into maternal deaths in the United Kingdom. BJOG. 2011;118. Suppl:1:1–203.
7. Quinn AC, Milne D, Columb M, Gorton H, Knight M. Failed tracheal intubation in obstetric anaesthesia: 2 yr national case-control study in the UK. Br J Anaesth. 2013;110:74–80.
8. Rajagopalan S, Suresh M, Clark SL, Serratos B, Chandrasekhar S. Airway management for cesarean delivery performed under general anesthesia. Int J Obstet Anesth. 2017;29:64–9.
9. Mushambi MC, Kinsella SM, Popat M, et al. Obstetric anaesthetists' association and difficult airway society guidelines for the management of difficult and failed tracheal intubation in obstetrics. Anaesthesia. 2015;70:1286–306.
10. Teoh WH, Yeoh SB, Tan HK. Airway management of an expanding soft palate haematoma in a parturient. Anaesth Intensive Care. 2013;41:680–1.
11. Kodali BS, Chandrasekhar S, Bulich LN, Topulos GP, Datta S. Airway changes during labor and delivery. Anesthesiology. 2008;108:357–62.
12. Pilkington S, Carli F, Dakin MJ, et al. Increase in Mallampati score during pregnancy. Br J Anaesth. 1995;74:638–42.
13. Boutonnet M, Faitot V, Katz A, Salomon L, Keita H. Mallampati class changes during pregnancy, labour, and after delivery: can these be predicted? Br J Anaesth. 2010;104:67–70.
14. Rocke DA, Murray WB, Rout CC, Gouws E. Relative risk analysis of factors associated with difficult intubation in obstetric anesthesia. Anesthesiology. 1992;77:67–73.
15. Dixon BJ, Dixon JB, Carden JR, et al. Preoxygenation is more effective in the 25 degrees head-up position than in the supine position in severely obese patients: a randomized controlled study. Anesthesiology. 2005;102:1110–5. discussion 5A.
16. Tanoubi I, Drolet P, Donati F. Optimizing preoxygenation in adults. Can J Anaesth. 2009;56:449–66.
17. Chiron B, Laffon M, Ferrandiere M, Pittet JF, Marret H, Mercier C. Standard preoxygenation technique versus two rapid techniques in pregnant patients. Int J Obstet Anesth. 2004;13:11–4.
18. Collaboration NCDRF. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet. 2016;387:1377–96.
19. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011–2012. JAMA. 2014;311:806–14.
20. https://iuns.org/resources/the-global-challenge-of-obesity-and-the-international-obesity-task-force/.
21. Hutcheon JA, Platt RW, Abrams B, Himes KP, Simhan HN, Bodnar LM. Pregnancy weight gain charts for obese and overweight women. Obesity (Silver Spring). 2015;23:532–5.
22. Shiga T, Wajima Z, Inoue T, Sakamoto A. Predicting difficult intubation in apparently normal patients: a meta-analysis of bedside screening test performance. Anesthesiology. 2005;103:429–37.
23. Kheterpal S, Han R, Tremper KK, et al. Incidence and predictors of difficult and impossible mask ventilation. Anesthesiology. 2006;105:885–91.
24. McClelland SH, Bogod DG, Hardman JG. Preoxygenation and apnoea in pregnancy: changes during labour and with obstetric morbidity in a computational simulation. Anaesthesia. 2009;64:371–7.
25. McKeen DM, George RB, O'Connell CM, et al. Difficult and failed intubation: incident rates and maternal, obstetrical, and anesthetic predictors. Can J Anaesth. 2011;58:514–24.
26. Hood DD, Dewan DM. Anesthetic and obstetric outcome in morbidly obese parturients. Anesthesiology. 1993;79:1210–8.
27. Vallejo MC. Anesthetic management of the morbidly obese parturient. Curr Opin Anaesthesiol. 2007;20:175–80.
28. Long N, Ng S, Donnelly G, et al. Anatomical characterisation of the cricothyroid membrane in females of childbearing age using computed tomography. Int J Obstet Anesth. 2014;23:29–34.
29. Gadd K, Wills K, Harle R, Terblanche N. Relationship between severe obesity and depth to the cricothyroid membrane in third-trimester non-labouring parturients: a prospective observational study. Br J Anaesth. 2018;120:1033–9.
30. You-Ten KE, Desai D, Postonogova T, Siddiqui N. Accuracy of conventional digital palpation and ultrasound of the cricothyroid membrane in obese women in labour. Anaesthesia. 2015;70:1230–4.
31. You-Ten KE, Siddiqui N, Teoh WH, Kristensen MS. Point-of-care ultrasound (POCUS) of the upper airway. Can J Anaesth. 2018;65:473–84.
32. Kristensen MS, Teoh WH, Graumann O, Laursen CB. Ultrasonography for clinical decision-making and intervention in airway management: from the mouth to the lungs and pleurae. Insights Imaging. 2014;5:253–79.
33. Kristensen MS, Teoh WH, Rudolph SS. Ultrasonographic identification of the cricothyroid membrane: best evidence, techniques, and clinical impact. Br J Anaesth. 2016;117(Suppl 1):i39–48.
34. Kristensen MS, Teoh WH, Rudolph SS, et al. Structured approach to ultrasound-guided identification of the cricothyroid membrane: a randomized comparison with the palpation method in the morbidly obese. Br J Anaesth. 2015;114:1003–4.
35. El-Orbany M, Woehlck H, Salem MR. Head and neck position for direct laryngoscopy. Anesth Analg. 2011;113:103–9.
36. Collins JS, Lemmens HJ, Brodsky JB, Brock-Utne JG, Levitan RM. Laryngoscopy and morbid obesity: a comparison of the "sniff" and "ramped" positions. Obes Surg. 2004;14:1171–5.
37. Datta S, Briwa J. Modified laryngoscope for endotracheal intubation of obese patients. Anesth Analg. 1981;60:120–1.

38. Thomas TA, Cooper GM, Editorial Board of the Confidential Enquiries into Maternal Deaths in the United K. Maternal deaths from anaesthesia. An extract from why mothers die 1997–1999, the confidential enquiries into maternal deaths in the United Kingdom. Br J Anaesth. 2002;89:499–508.
39. Cooper GM, McClure JH. Maternal deaths from anaesthesia. An extract from why mothers die 2000–2002, the confidential enquiries into maternal deaths in the United Kingdom: chapter 9: anaesthesia. Br J Anaesth. 2005;94:417–23.
40. Cooper GM, McClure JH. Anaesthesia chapter from saving mothers' lives; reviewing maternal deaths to make pregnancy safer. Br J Anaesth. 2008;100:17–22.
41. Heath M. CEMACH report: oesophageal intubation. Br J Anaesth. 2005;95:426.
42. Olsson GL, Hallen B, Hambraeus-Jonzon K. Aspiration during anaesthesia: a computer-aided study of 185,358 anaesthetics. Acta Anaesthesiol Scand. 1986;30:84–92.
43. Kelly MC, Carabine UA, Hill DA, Mirakhur RK. A comparison of the effect of intrathecal and extradural fentanyl on gastric emptying in laboring women. Anesth Analg. 1997;85:834–8.
44. Arzola C, Perlas A, Siddiqui NT, Carvalho JC. Bedside gastric ultrasonography in term pregnant women before elective Cesarean delivery: a prospective cohort study. Anesth Analg. 2015;121:752–8.
45. Bataille A, Rousset J, Marret E, Bonnet F. Ultrasonographic evaluation of gastric content during labour under epidural analgesia: a prospective cohort study. Br J Anaesth. 2014;112:703–7.
46. Arzola C, Perlas A, Siddiqui NT, Downey K, Ye XY, Carvalho JC. Gastric ultrasound in the third trimester of pregnancy: a randomised controlled trial to develop a predictive model of volume assessment. Anaesthesia. 2018;73:295–303.
47. Perlas A, Arzola C, Van de Putte P. Point-of-care gastric ultrasound and aspiration risk assessment: a narrative review. Can J Anaesth. 2018;65:437–48.
48. Practice Guidelines for Obstetric Anesthesia. An updated report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia and the Society for Obstetric Anesthesia and Perinatology. Anesthesiology. 2016;124:270–300.
49. Pandit JJ, Andrade J, Bogod DG, et al. 5th National Audit Project (NAP5) on accidental awareness during general anaesthesia: summary of main findings and risk factors. Br J Anaesth. 2014;113:549–59.
50. Katz VL. Perimortem cesarean delivery: its role in maternal mortality. Semin Perinatol. 2012;36:68–72.
51. Martin LD, Mhyre JM, Shanks AM, Tremper KK, Kheterpal S. 3,423 emergency tracheal intubations at a university hospital: airway outcomes and complications. Anesthesiology. 2011;114:42–8.
52. Health and Social Care Information Centre: Critical Care data 2008–09. https://digitalnhsuk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics.
53. Teoh WH. Respiratory diseases in pregnancy. In: Clark V, Van de Velde M, Fernando R, editors. Oxford textbook of obstetric anaesthesia: Oxford University Press; 2016. p. 659–75. ISBN: 978-0-19-871333-3.
54. Mhyre JM, Healy D. The unanticipated difficult intubation in obstetrics. Anesth Analg. 2011;112:648–52.
55. Baker PA, Flanagan BT, Greenland KB, et al. Equipment to manage a difficult airway during anaesthesia. Anaesth Intensive Care. 2011;39:16–34.
56. Perbet S, De Jong A, Delmas J, et al. Incidence of and risk factors for severe cardiovascular collapse after endotracheal intubation in the ICU: a multicenter observational study. Crit Care. 2015;19:257.
57. Cuthbertson BH, Sprung CL, Annane D, et al. The effects of etomidate on adrenal responsiveness and mortality in patients with septic shock. Intensive Care Med. 2009;35:1868–76.
58. Bruder EA, Ball IM, Ridi S, Pickett W, Hohl C. Single induction dose of etomidate versus other induction agents for endotracheal intubation in critically ill patients. Cochrane Database Syst Rev. 2015;(1):CD010225.
59. Beckers SK, Brokmann JC, Rossaint R. Airway and ventilator management in trauma patients. Curr Opin Crit Care. 2014;20:626–31.
60. Bernhard M, Matthes G, Kanz KG, et al. Emergency anesthesia, airway management and ventilation in major trauma. Background and key messages of the interdisciplinary S3 guidelines for major trauma patients. Anaesthesist. 2011;60:1027–40.
61. Morris C, Perris A, Klein J, Mahoney P. Anaesthesia in haemodynamically compromised emergency patients: does ketamine represent the best choice of induction agent? Anaesthesia. 2009;64:532–9.
62. Simpson GD, Ross MJ, McKeown DW, Ray DC. Tracheal intubation in the critically ill: a multicentre national study of practice and complications. Br J Anaesth. 2012;108:792–9.
63. Griesdale DE, Henderson WR, Green RS. Airway management in critically ill patients. Lung. 2011;189:181–92.
64. Tran DT, Newton EK, Mount VA, Lee JS, Wells GA, Perry JJ. Rocuronium versus succinylcholine for rapid sequence induction intubation. Cochrane Database Syst Rev. 2015:CD002788.
65. Dong J, Gao L, Lu W, Xu Z, Zheng J. Pharmacological interventions for acceleration of the onset time of rocuronium: a meta-analysis. PLoS One. 2014;9:e114231.
66. Laxenaire MC, Mertes PM. Groupe d'Etudes des reactions Anaphylactoides P. Anaphylaxis during anaesthesia. Results of a two-year survey in France. Br J Anaesth. 2001;87:549–58.
67. Girard T. Pro: rocuronium should replace succinylcholine for rapid sequence induction. Eur J Anaesthesiol. 2013;30:585–9.
68. Taha SK, El-Khatib MF, Baraka AS, et al. Effect of suxamethonium vs rocuronium on onset of oxygen desaturation during apnoea following rapid sequence induction. Anaesthesia. 2010;65:358–61.

69. Booij LH. Is succinylcholine appropriate or obsolete in the intensive care unit? Crit Care. 2001;5:245–6.
70. Frederiksen B, Steensen M, Carl P. Fatal succinylcholine-induced hyperkalemia in an intensive care unit. Ugeskr Laeger. 2011;173:2704–5.
71. Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. Anaesthesia. 1984;39:1105–11.
72. Mallampati SR, Gatt SP, Gugino LD, et al. A clinical sign to predict difficult tracheal intubation: a prospective study. Can Anaesth Soc J. 1985;32:429–34.
73. Wilson ME, Spiegelhalter D, Robertson JA, Lesser P. Predicting difficult intubation. Br J Anaesth. 1988;61:211–6.
74. el-Ganzouri AR, McCarthy RJ, Tuman KJ, Tanck EN, Ivankovich AD. Preoperative airway assessment: predictive value of a multivariate risk index. Anesth Analg. 1996;82:1197–204.
75. De Jong A, Molinari N, Terzi N, et al. Early identification of patients at risk for difficult intubation in the intensive care unit: development and validation of the MACOCHA score in a multicenter cohort study. Am J Respir Crit Care Med. 2013;187:832–9.
76. De Jong A, Jung B, Jaber S. Intubation in the ICU: we could improve our practice. Crit Care. 2014;18:209.
77. Rosenblatt W, Ianus AI, Sukhupragarn W, Fickenscher A, Sasaki C. Preoperative endoscopic airway examination (PEAE) provides superior airway information and may reduce the use of unnecessary awake intubation. Anesth Analg. 2011;112:602–7.
78. Kheterpal S, Martin L, Shanks AM, Tremper KK. Prediction and outcomes of impossible mask ventilation: a review of 50,000 anesthetics. Anesthesiology. 2009;110:891–7.
79. Law JA, Broemling N, Cooper RM, et al. The difficult airway with recommendations for management—part 2—the anticipated difficult airway. Can J Anaesth. 2013;60:1119–38.
80. Mechlin MW, Hurford WE. Emergency tracheal intubation: techniques and outcomes. Respir Care. 2014;59:881–92. discussion 892-4.
81. Reynolds SF, Heffner J. Airway management of the critically ill patient: rapid-sequence intubation. Chest. 2005;127:1397–412.
82. Jaber S, Jung B, Corne P, et al. An intervention to decrease complications related to endotracheal intubation in the intensive care unit: a prospective, multiple-center study. Intensive Care Med. 2010;36:248–55.
83. Higgs A. Airway management in intensive care medicine. In: Hagberg CA, Artime CA, Aziz MF (eds). Hagberg and Benumof's Airway Management 4th ed. Philadelphia, PA: Elsevier; 2018. p. 754–80. ISBN:978-0-323-42881-1.
84. Weingart SD, Levitan RM. Preoxygenation and prevention of desaturation during emergency airway management. Ann Emerg Med. 2012;59:165–75. e1
85. Algie CM, Mahar RK, Tan HB, Wilson G, Mahar PD, Wasiak J. Effectiveness and risks of cricoid pressure during rapid sequence induction for endotracheal intubation. Cochrane Database Syst Rev. 2015:CD011656.
86. Salem MR, Khorasani A, Zeidan A, Crystal GJ. Cricoid pressure controversies: narrative review. Anesthesiology. 2017;126:738–52.
87. Apfelbaum JL, Hagberg CA, Caplan RA, et al. Practice guidelines for management of the difficult airway: an updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Anesthesiology. 2013;118:251–70.
88. Frerk C, Mitchell VS, McNarry AF, et al. Difficult Airway Society 2015 guidelines for management of unanticipated difficult intubation in adults. Br J Anaesth. 2015;115:827–48.
89. Law JA, Broemling N, Cooper RM, et al. The difficult airway with recommendations for management—part 1—difficult tracheal intubation encountered in an unconscious/induced patient. Can J Anaesth. 2013;60:1089–118.
90. Lundstrom LH, Duez CH, Norskov AK, et al. Avoidance versus use of neuromuscular blocking agents for improving conditions during tracheal intubation or direct laryngoscopy in adults and adolescents. Cochrane Database Syst Rev. 2017;5:CD009237.
91. Bhatia PK, Bhandari SC, Tulsiani KL, Kumar Y. End-tidal oxygraphy and safe duration of apnoea in young adults and elderly patients. Anaesthesia. 1997;52:175–8.
92. Hayes-Bradley C, Lewis A, Burns B, Miller M. Efficacy of nasal cannula oxygen as a preoxygenation adjunct in emergency airway management. Ann Emerg Med. 2016;68:174–80.
93. Patel A, Nouraei SA. Transnasal humidified rapid-insufflation ventilatory exchange (THRIVE): a physiological method of increasing apnoea time in patients with difficult airways. Anaesthesia. 2015;70:323–9.
94. Nunn JF: Oxygen stores and the steady state. In Nunn JF(ed): Applied respiratory physiology, 4th ed. Oxford, Butterworth-Heinemann,1995. p156–197.
95. Leibowitz AB. Persistent preoxygenation efforts before tracheal intubation in the intensive care unit are of no use: who would have guessed? Crit Care Med. 2009;37:335–6.
96. Coussa M, Proietti S, Schnyder P, et al. Prevention of atelectasis formation during the induction of general anesthesia in morbidly obese patients. Anesth Analg. 2004;98:1491–5.
97. Ramkumar V, Umesh G, Philip FA. Preoxygenation with 20 degree head-up tilt provides longer duration of non-hypoxic apnea than conventional preoxygenation in non-obese healthy adults. J Anesth. 2011;25:189–94.
98. Griesdale DE, Chau A, Isac G, et al. Videolaryngoscopy versus direct laryngoscopy in critically ill patients: a pilot randomized trial. Can J Anaesth. 2012;59:1032–9.

99. Mort TC. Video laryngoscopy improves intubation success and reduces esophageal intubations compared with direct laryngoscopy in the medical intensive care unit. Crit Care. 2013;17:1019.
100. Thong SY, Teoh WH. Videolaryngoscopy & Indirect Intubating Aids in Airway Management. In: Khan Z.H (ed) Airway Management. DOI: https://doi.org/10.1007/978-3-319-08578-4_3, Springer International Publishing Switzerland 2014.
101. Teoh WH. Airway Management & General Anesthesia for Lower Segment Cesarean Section. In: Baheti DK, Parikh K, Pandya S, Kodali BS, (eds). World Clinics on Anaesthesia, Critical Care & Pain: Analgesia and Anesthesia for Labour & Delivery. Jaypee Brothers Medical Publishers New Delhi, 2013;1(2):420–40.
102. De Jong A, Molinari N, Conseil M, et al. Video laryngoscopy versus direct laryngoscopy for orotracheal intubation in the intensive care unit: a systematic review and meta-analysis. Intensive Care Med. 2014;40:629–39.
103. Kill C, Risse J, Wallot P, Seidl P, Steinfeldt T, Wulf H. Videolaryngoscopy with glidescope reduces cervical spine movement in patients with unsecured cervical spine. J Emerg Med. 2013;44:750–6.
104. Moore AR, Schricker T, Court O. Awake videolaryngoscopy-assisted tracheal intubation of the morbidly obese. Anaesthesia. 2012;67:232–5.
105. Lewis SR, Butler AR, Parker J, Cook TM, Smith AF. Videolaryngoscopy versus direct laryngoscopy for adult patients requiring tracheal intubation. Cochrane Database Syst Rev. 2016;(11):CD011136.
106. Greenland KB, Segal R, Acott C, Edwards MJ, Teoh WH, Bradley WP. Observations on the assessment and optimal use of videolaryngoscopes. Anaesth Intensive Care. 2012;40:622–30.
107. Teoh WH, Saxena S, Shah MK, Sia AT. Comparison of three videolaryngoscopes: Pentax Airway Scope, C-MAC, Glidescope vs the Macintosh laryngoscope for tracheal intubation. Anaesthesia. 2010;65:1126–32.
108. Aziz MF, Healy D, Kheterpal S, Fu RF, Dillman D, Brambrink AM. Routine clinical practice effectiveness of the Glidescope in difficult airway management: an analysis of 2,004 Glidescope intubations, complications, and failures from two institutions. Anesthesiology. 2011;114:34–41.
109. Law JA, Morris IR, Brousseau PA, de la Ronde S, Milne AD. The incidence, success rate, and complications of awake tracheal intubation in 1,554 patients over 12 years: an historical cohort study. Can J Anaesth. 2015;62:736–44.
110. Cook TM, Kelly FE. Time to abandon the 'vintage' laryngeal mask airway and adopt second-generation supraglottic airway devices as first choice. Br J Anaesth. 2015;115:497–9.
111. Teoh WH, Lee KM, Suhitharan T, Yahaya Z, Teo MM, Sia AT. Comparison of the LMA supreme vs the i-gel in paralysed patients undergoing gynaecological laparoscopic surgery with controlled ventilation. Anaesthesia. 2010;65:1173–9.
112. Kristensen MS, Teoh WH, Asai T. Which supraglottic airway will serve my patient best? Anaesthesia. 2014;69:1189–92.
113. Shariffuddin II, Teoh WH, Tang E, Hashim N, Loh PS. Ambu(R) AuraGain versus LMA supreme second seal: a randomised controlled trial comparing oropharyngeal leak pressures and gastric drain functionality in spontaneously breathing patients. Anaesth Intensive Care. 2017;45:244–50.
114. Lindsay HA, Cook TM, Russo SG, Hagberg CA. Supraglottic airway techniques:laryngeal mask airways. In: Hagberg CA, Artime CA, Aziz MF (eds). Hagberg and Benumof's Airway Management. 4th ed. Philadelphia, PA: Elsevier; 2018. p. 328–48. ISBN: 978-0-323-42881-1.
115. Parmet JL, Colonna-Romano P, Horrow JC, Miller F, Gonzales J, Rosenberg H. The laryngeal mask airway reliably provides rescue ventilation in cases of unanticipated difficult tracheal intubation along with difficult mask ventilation. Anesth Analg. 1998;87:661–5.
116. Fun WL, Lim Y, Teoh WH. Comparison of the GlideScope video laryngoscope vs. the intubating laryngeal mask for females with normal airways. Eur J Anaesthesiol. 2007;24:486–91.
117. Teoh WH, Lim Y. Comparison of the single use and reusable intubating laryngeal mask airway. Anaesthesia. 2007;62:381–4.
118. Higgs A, Clark E, Premraj K. Low-skill fibreoptic intubation: use of the Aintree catheter with the classic LMA. Anaesthesia. 2005;60:915–20.
119. Berkow LC, Schwartz JM, Kan K, Corridore M, Heitmiller ES. Use of the laryngeal mask airway-Aintree intubating catheter-fiberoptic bronchoscope technique for difficult intubation. J Clin Anesth. 2011;23:534–9.
120. Duggan LV, Law JA, Murphy MF. Brief review: supplementing oxygen through an airway exchange catheter: efficacy, complications, and recommendations. Can J Anaesth. 2011;58:560–8.
121. Kristensen MS, Teoh WH, Baker PA. Percutaneous emergency airway access; prevention, preparation, technique and training. Br J Anaesth. 2015;114:357–61.
122. Higgs A, McGrath BA, Goddard C, et al. DAS guidelines on the airway management of critically ill patients. Anaesthesia. 2018;73:1035–6.

Introduction to Lung Ultrasound Techniques and Diagnosis in the Seriously Ill Pregnant Woman

22

Arvind Kalyan Sundaram, Robert Strony, Laurent Zieleskiewicz, and Mary Jane Reed

Bullet Points

- Lung ultrasound is a simple yet powerful tool in detecting acute respiratory pathologies.
- Lung ultrasound works on the principle of acoustic impedance, which is resistance to the sound wave propagation.
- The micro-convex probe is the preferred probe for lung ultrasound, but linear, phased assay and curvilinear probe can also be used.
- Lung examination using ultrasound probe is performed by dividing the lung into segments and using standardized points to identify lung pathology.
- There are 11 important signs and artifacts used for diagnosing different lung pathologies.
- Cardiogenic and non-cardiogenic pulmonary edema, pneumonia, pneumothorax, and pulmonary embolism are some of the commonest lung diseases that cause respiratory failure in pregnancy.
- The BLUE protocol is one of the several protocols used in lung ultrasound that can identify up to 97% of the lung pathologies that can cause respiratory failure.

A. K. Sundaram
Department of Clinical Science (Education), Geisinger Commonwealth School of Medicine, Geisinger Medical Center, Danville, PA, USA

R. Strony
Geisinger Commonwealth School of Medicine, Danville, PA, USA

Lewis Katz School of Medicine Temple University, Philadelphia, PA, USA

Geisinger Health System, Danville, PA, USA

L. Zieleskiewicz
Department of Anesthesiology and Intensive Care Medicine, Aix Marseille Université, Assistance Publique Hôpitaux de Marseille, North Hospital, Marseille, France
e-mail: Laurent.ZIELESKIEWICZ@ap-hm.fr

M. J. Reed (✉)
Department of Critical Care Medicine and Surgery, Geisnger Medical Center, Danville, PA, USA
e-mail: mreed@geisinger.edu

22.1 Introduction

Lung ultrasound (LUS) was first championed by Dr. Daniel A. Lichtenstein in French intensive care units (ICUs) during the 1980s. Ultrasonography has emerged as an important diagnostic tool for specific acute lung pathologies in the ICU and emergency departments. A recent study has suggested that the LUS patterns observed in pregnant women and non-obstetric patients are similar, and hence LUS is a useful safe diagnostic tool during pregnancy [1].

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_22

22.2 Physiological Changes to Respiratory System during Pregnancy

Pregnancy involves anatomical, physiological, and biochemical changes which occur in response to the presence of the developing fetus. Pathology of cardiopulmonary system is often the most immediate concern for health-care providers. The upper airway, chest wall, respiratory muscles, and the lung volumes change throughout pregnancy. Elevated levels of progesterone during pregnancy cause venous engorgement and hyperemia of the mucosal surface of the airway which leads to nasal congestion and rarely epistaxis. Progesterone stimulates the brain respiratory center and increases the slope of the curve of ventilatory response to changes in alveolar $PaCo_2$ which is responsible for causing the dyspnea in pregnancy [2]. Pregnancy also contributes to the 45% rise in minute ventilation by increasing the tidal volume of each breath without causing tachypnea. Pregnant women demonstrate a chronic metabolic alkalosis which is compensated by loss of renal bicarbonate [3]. During later trimesters, increased minute ventilation is driven by increasing CO_2 across the placenta from the fetal circulation in addition to the progesterone [4]. As the minute ventilation increases, there is associated increase in oxygen consumption of up to 20%. Pregnancy is also associated with decreases in total lung capacity by 5%, functional residual capacity (FRC) by 20%, and residual volume (RV)—due to increase in the anteroposterior and transverse dimensions of ribcage along with upward displacement of the diaphragm by the gravid uterus. The combination of decreased FRC and increased oxygen consumption predisposes pregnant women to precipitous desaturation during intubation [5].

22.3 Role of Lung Ultrasound in Pregnancy

Less than 2% of pregnant women are admitted to the intensive care unit during the peripartum period. Among these women, the incidence of acute respiratory failure ranges from 0.1% to 0.3% [6]. Common causes of respiratory failure in pregnancy are cardiogenic and non-cardiogenic pulmonary edema, pneumonia, asthma exacerbations, pulmonary embolism, and rarely acute respiratory distress syndrome [7]. Although safe in pregnancy (see Chap. 35), radiation exposures from imaging studies in pregnant women are associated with higher level of anxiety to the patients and the health-care providers [8]. Lung ultrasound has been shown to be a powerful tool in diagnosing the causes of acute respiratory failure in more than 90% of the cases [9]. Despite the significant role of LUS in diagnosing acute respiratory failure, its role in pregnant women is not clearly defined. Several recent small studies have shown the effectiveness of LUS used in pregnant women [1, 10]. LUS can be performed by clinicians after a minimal training period and the ultrasound techniques used are similar to those used in obstetric units [11]. The advantages and disadvantages of LUS are described in Box 22.1.

Box 22.1 Advantages and Disadvantages of LUS

Advantages

- LUS provides real-time two-dimensional visualization of the lung tissues, including the pleura.
- Ultrasound (US) devices are portable and can be made quickly available at the bedside, thus reducing the risk involved with patient transportation.
- LUS involves no radiation exposure, compared to chest radiography or computed tomography (CT) that do.
- US devices are readily available in smaller hospitals compared to other modalities of imaging including CT.
- US is cheaper compared to other imaging modalities and requires only a single operator to perform the procedure, thus reducing the cost.

- LUS has 90–100% accuracy compared to CT for diagnosing certain acute lung pathologies.
- LUS can be repeated; allowing frequent follow-up with consistent reproducibility.

Disadvantages

- Air in the subcutaneous tissue significantly impedes the penetration of US into the tissues, limiting visualization and image interpretation.
- LUS cannot penetrate deeper lung tissues and therefore cannot be used in investigation or diagnosis of deep lung disorders.
- Excess tissue over the chest wall (e.g obesity, breast tissue) can limit visualization of the lung field.

22.4 Concepts and Techniques Used in Lung Ultrasound

22.4.1 How Lung Ultrasound Works

The commonly held belief since the inception of ultrasound imaging is that air is an enemy of ultrasound as it dissipates and reflects the ultrasound wave. The lung is an aerated organ surrounded by pleura, caged within the ribs and surrounded by soft tissue. The appearance of images on LUS depends upon a phenomenon called acoustic impedance (AI). AI is a measure of the resistance of the US wave as it passes through a tissue. Acoustic impedance depends upon the density of the tissue and the speed of the sound waves. As the density of the tissue increases, AI increases accordingly. Soft tissue structures and air-filled alveoli provide a substantial difference in AI to the penetrating ultrasound waves and thereby prevent the reconstruction of a real image of the organ while generating multiple artifacts. When the air-tissue interface is replaced with fluids and cellular materials, the AI between the two mediums narrows, and the US waves are transmitted faster back to the probe. Lung US takes advantage of these artifacts to provide the observers with diagnostic information. The pleural line is a hyperechoic line that appears deep between the ribs with repetitive movements pairing with respiration and is used as a vantage point in lung US. The principles of using these artifacts in diagnosing lung disorders are similar to those used in gynecologic ultrasonography in the classification of ovarian masses [11, 12].

22.4.2 Basic Principles of Lung Ultrasound

As per Lichtenstein, LUS in critical illness depends upon seven important principles: [13].

1. A simple instrument needed to perform LUS.
2. The thorax is the site where gas and fluid are separated by gravity or are pathologically mixed to produce artifacts.
3. The lung is the most voluminous organ and standardized points may be used to define areas of interest in it.
4. All diagnostic signs arise from the pleural line.
5. Artifacts are clinically relevant in LUS.
6. The lung is a living organ therefore the signs arising from the pleural lines are dynamic.
7. Almost all acute life-threatening lung disorders involve the pleura.

22.4.3 Type of Probe for Lung Ultrasound

The probes used in critical care include transducers of varying frequency which should be selected based on the required use. The three basic transducers are, namely, the phased array, the linear array, and the curvilinear probe [14]. Even though the micro-convex transducer is considered the probe of choice for identifying pneumothorax, using any of the three probes for LUS is appropriate. The linear array probe has a high frequency with a range of 5–13 MHz and hence provides better visualization of superficial structures such as the pleural line. It has poor penetration at depths greater than 6 cm, hence deeper structures

and artifacts may not be well visualized. The curvilinear (or convex probe) has a frequency of 1–8 MHz which enables deeper tissue penetration, allowing visualization to a depth of 30 cm. The disadvantages of curvilinear probes include poor visualization of superficial structures and the posterolateral alveolar pleural syndrome (PLAPS); i.e. difficulty in accessing this specific anatomical location in obese supine patients. The phased array probe has a frequency of 2–8 MHz but has a smaller footprint compared to the curvilinear probe, which allows it to visualize structures between the ribs [15] (Fig. 22.1).

22.4.4 Positioning for Lung Ultrasound

Lung US can be performed in the sitting, supine, or semi-recumbent position. However critically ill pregnant women and non-obstetric patients usually lie in the supine position. The probe is usually positioned longitudinally (rarely transverse) with the marker directed cranially. Thus, cranial structures are visualized on the left side of the screen, whereas caudal structures are seen on the right. Examination of the thorax using US involves the division of the thorax into multiple segments. The literature is replete with ways of dividing the thorax; the different methods described are based on the acuity of presentation, severity of illness, and patient condition. The most commonly used method involves dividing each lung into three zones with six segments. This bedside LUS in emergency (BLUE) protocol, has been validated and has also been shown to have excellent diagnostic accuracy. Some physicians recommend dividing the thorax into four segments involving the anterior and lateral chest when diagnosing pulmonary edema [14, 16–18]. In an acute setting involving critically ill patients, the anterior two segments of the chest can be studied alone to rule out interstitial syndrome due to cardiogenic pulmonary edema as the etiology of respiratory failure [9].

22.4.5 Methods to Study Lung Ultrasound

Lung US involves studying predefined areas to investigate for lung abnormalities. A complete LUS examination involves dividing the entire thorax into 12 regions. Each hemithorax is divided by the anterior and posterior axillary line into three zones, namely, anterior (zone 1), lateral (zone 2), and posterior zones (zone 3), and each segment is divided into upper and lower halves resulting in six areas for investigation. The posterior segment is best approached in a supine critically ill patient by crossing the arm across the chest and slight lateral positioning (see Fig. 22.2) [16].

The BLUE protocol is an alternative method used for diagnosing causes of acute respiratory

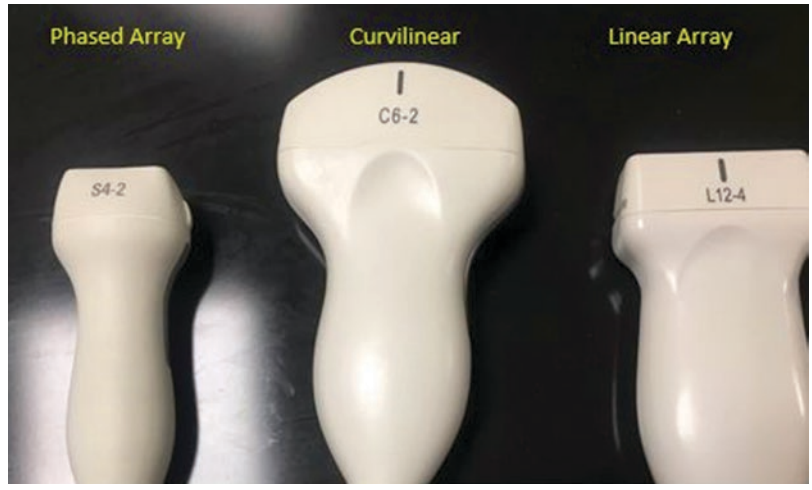


Fig. 22.1 Common ultrasound probes for pulmonary exam

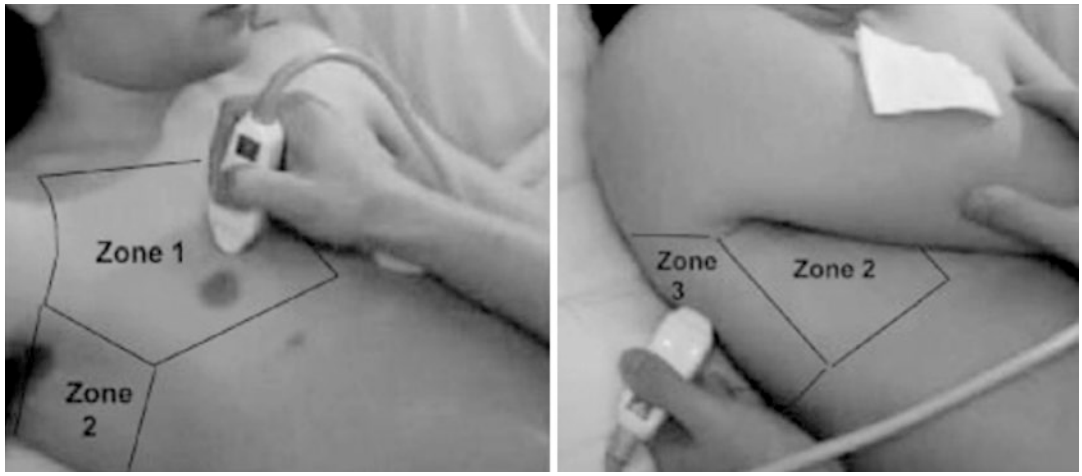


Fig. 22.2 Exam zones for lung ultrasound

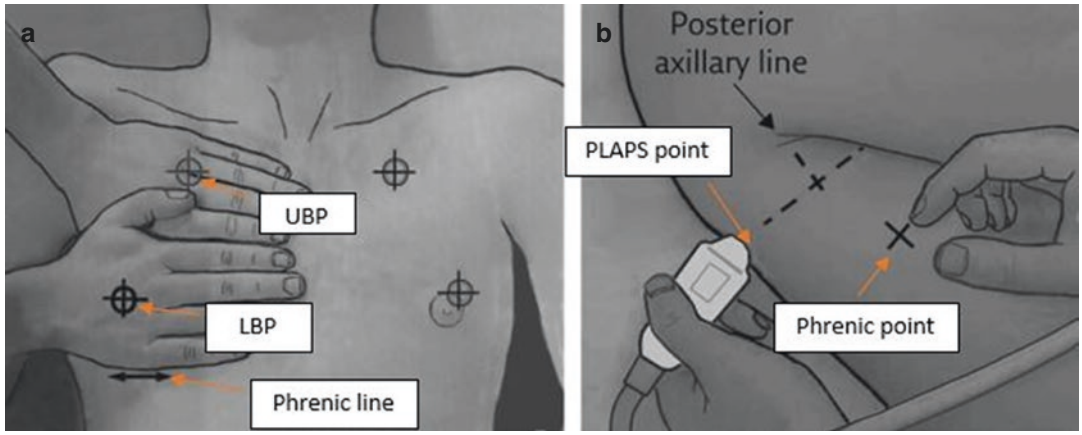


Fig. 22.3 The five reference points of the BLUE protocol

failure using LUS. In this protocol, this comparison provided the name for the protocol. The hands of the clinician are placed partially overlapping over the chest; the little finger of the upper hand should touch the lower border of the clavicle with the tips of the longer fingers touching the midline of the chest. The lower hand is placed over the upper hand with the thumbs of both hands overlapping. The upper blue point (UBP) is at the base of middle and ring finger of the upper hand, the lower blue point (LBP) corresponds to the middle of the lower hand, the phrenic line corresponds with the caudal edge of the lower hand, the phrenic point is identified at the junction where the phrenic line and the midaxillary line meet, and the PLAPS point is identified by an imaginary line drawn from the lower blue point to the posterior axillary line (Fig. 22.3) [19].

22.5 Selective List of Signs and Artifacts Used in Lung Ultrasonography

1. Bat sign (Fig. 22.4): In the longitudinal scan, two consecutive ribs are identified by hyperechoic lines which are separated approxi-

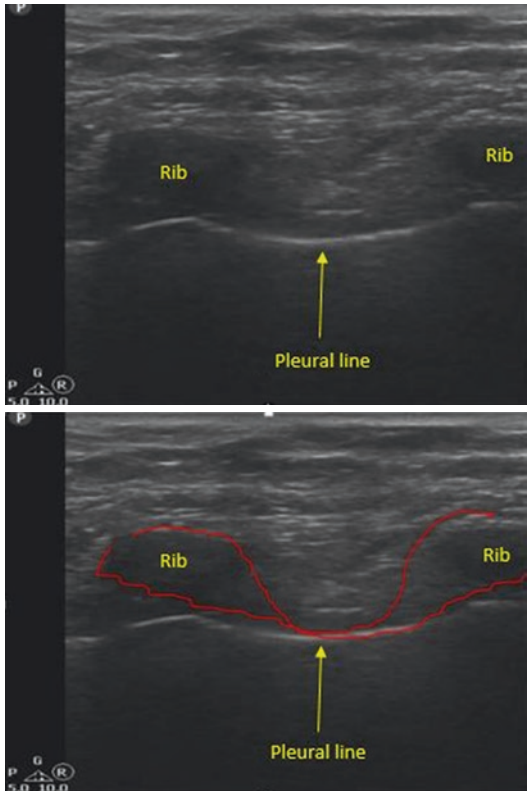


Fig. 22.4 The bat sign

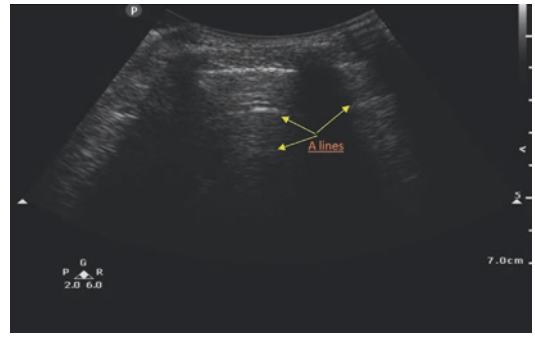


Fig. 22.5 A lines

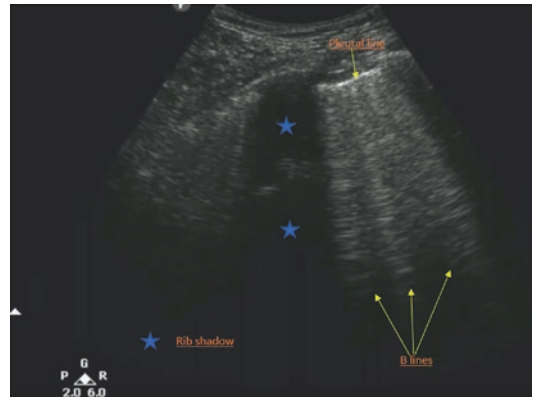


Fig. 22.6 B-lines

mately by 2 cm. A virtual line passing through the top of these ribs forms the rib line. Roughly half a centimeter below is another horizontal hyperechoic line called the pleural line which represents the lung surface. This pattern formed by the ribs along with the pleural surface is reminiscent of a bat (blue outline). This is the basic step used in LUS to identify the lung surface.

2. A-line (Fig. 22.5): A horizontal hyperechoic line artifact appears parallel to the pleural line. The artifact is formed when air blocks the ultrasound beam and returns to the central unit. A-lines are a normal artifact and can be repetitive with the distance between the pleural line and the A-line equaling that of the skin-pleural line distance.
3. B-line (Fig. 22.6): An abnormal fluid-air artifact seen in interstitial syndrome. B-lines are long, vertical, hyperechoic artifacts arising from the pleural line. They obliterate the A-lines and move during lung sliding. Three or more B-lines visible in the longitudinal view between the ribs are called lung rockets.
4. Seashore sign (Fig. 22.7): This is the equivalent of lung sliding visualized in the B-mode of lung ultrasonography. In the M-mode, when the transducer is applied over the lung window, the immobile extrapleural structures appear as parallel lines to the transducer surface. The subpleural structures produce a speckled appearance due to lung motion. The combination of parallel lines and speckled areas form the seashore sign.
5. Stratosphere sign (Fig. 22.8): This sign indicates absence of lung sliding when seen in the M-mode. It is characterized by the exclusive presence of horizontal lines (which replace the normal combination of horizontal lines and speckled areas seen in the seashore sign).

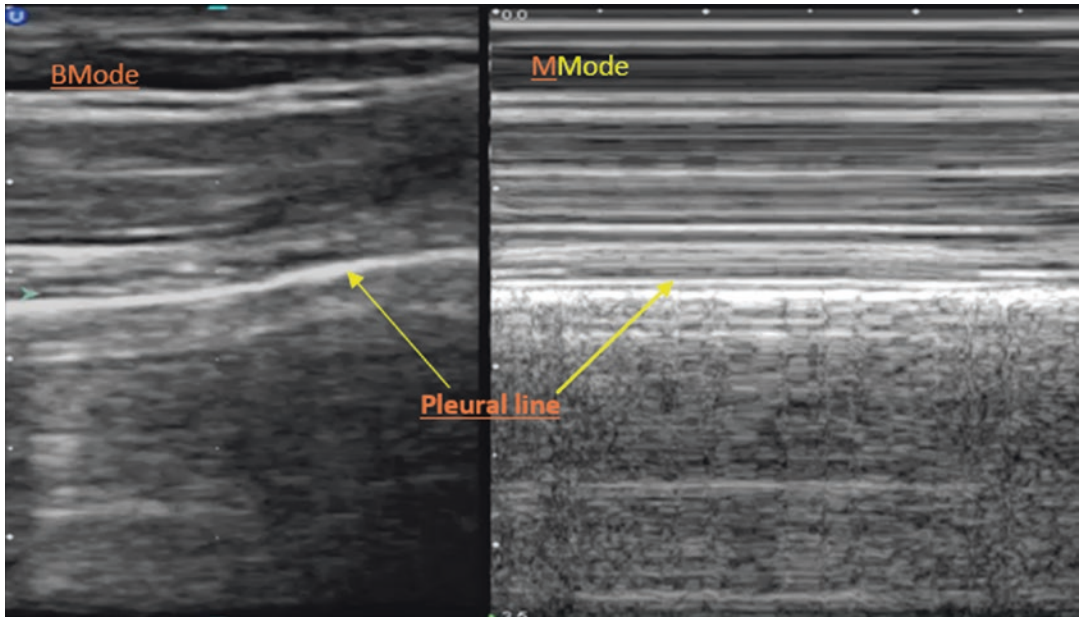


Fig. 22.7 Seashore sign in B mode and M mode

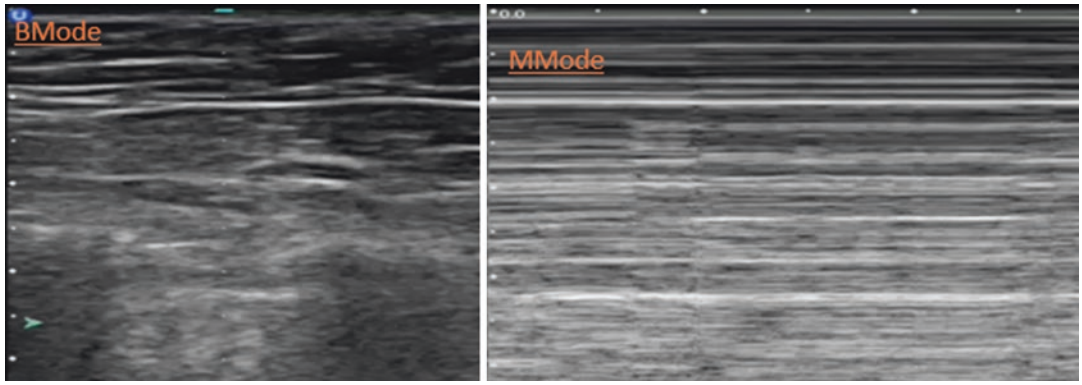


Fig. 22.8 Stratosphere sign

6. Lung point: A pattern used in detecting pneumothorax. Characterized by the absence of lung sliding or moving B-lines at a physical location where this pattern consistently transitions into an area of lung sliding. This point represents the physical limit of the pneumothorax.
7. Lung pulse: A normal sign characterized by 2D or M-mode visualization of pleural line vibrations transmitted from the cardiac pulse.
8. Quad sign: One of the static signs used to diagnose pleural effusion. The quad is bordered by the pleural line, the upper and lower rib shadows and the lung surface (four borders).
9. Sinusoid sign: A dynamic sign used to identify pleural effusion. A sinusoid pattern is observed in the M-mode as a result of variation in interpleural distances during the respiratory cycle.
10. Tissue-like sign: A pattern seen in acute trans-lobar consolidation. The lung appears as a tissue-like structure that is echoic and has trabeculations like the liver.
11. Shred sign (Fig. 22.9): A pattern seen in non trans-lobar consolidation. A shredded fractal line demarcates the consolidated lung from the aerated lung.

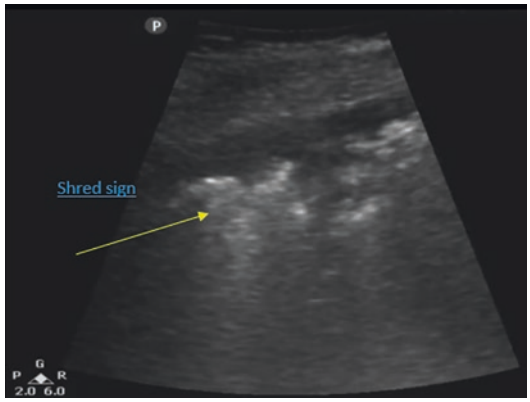


Fig. 22.9 Shred sign

Box 22.2 LUS findings to diagnose pneumothorax in pregnant patients

- Absence of lung sliding
- Absence of B-lines
- Absence of lung pulse
- Presence of lung point
- M-mode US—Absence of seashore sign and presence of stratosphere sign

22.6 Critical Respiratory Illness during Pregnancy

Pneumothorax during pregnancy is a very rare phenomenon and can be primary (spontaneous) or secondary due to underlying lung disease. Spontaneous pneumothorax can occur during any trimester of pregnancy and most likely arises from the rupture of an apical bleb due to the increased respiratory demand of the peripartum period. The accelerated pattern of breathing, repeated Valsalva maneuvers, intubation, and positive pressure ventilation may increase the risk of further pneumothoraxes in pregnancy. Some of the risk factors for spontaneous pneumothorax are cocaine use, asthma, hyperemesis gravidarum, previous episode of pneumothorax, and lung infection. The recurrence rate of pneumothorax is particularly high in pregnant patients with rates up to 44%. Signs and symptoms of pneumothorax in pregnant women are no different from the general population including pleuritic chest pain and dyspnea, while physical signs include tachycardia, tachypnea, ipsilateral diminished or absent breath sounds, and cyanosis. While pneumothorax causes respiratory distress in the mother, it can also compromise oxygen supply to the fetus [20, 21].

Chest radiography is the initial diagnostic test for pneumothorax. However the detection rate of pneumothorax by anterior view in chest X-rays is 31–37% in addition to exposure to potentially harmful radiation [22, 23]. Lung US has a sensitivity and specificity of 91% and 98%, respectively, in detecting pneumothorax compared to computed tomography of the chest, which is considered the gold standard test in diagnosing pneumothorax. LUS also has the advantage of no radiation exposure side effects compared to computed tomography and standard chest radiography [24]. Box 22.2 presents the LUS findings that should suggest a diagnosis of pneumothorax in pregnant women.

Management of pneumothorax in pregnant women is similar to the non-obstetric population with options including observation, single time aspiration, insertion of chest tube, and (rarely) video-assisted thoracostomy [25].

The alveolar-interstitial syndrome is an umbrella term that includes several heterogenous conditions characterized by diffuse involvement of the interstitium and the alveoli with impairment of the alveolar capillary exchange capacity. The term interstitial syndrome is frequently used in LUS and in the acute setting, denoting cardiogenic and non-cardiogenic pulmonary edema characterized by fluid accumulation in the interstitial spaces and/or alveoli of the lung. The alveolar syndromes include alveolar consolidation which may be caused by a variety of processes including pneumonia, pulmonary embolism, lung contusions, and atelectasis [26].

Pulmonary edema is a rare but potentially life-threatening condition when it occurs during preg-

nency. Its estimated incidence ranges from 0.08% to 1.3%. Pulmonary edema is a relatively common cause for respiratory failure in pregnant women [27, 28].

Pulmonary edema can occur during the antenatal, intrapartum, and postpartum periods but is most common antepartum and immediately postpartum. The mechanism of pulmonary edema development is similar for both pregnant women and non-obstetric patients. It occurs secondary to alteration in the balance of oncotic and hydrostatic pressures between the capillary and lung interstitium or due to an increase in capillary permeability. Interstitial edema is defined as fluid accumulation in the interstitial spaces, which can be clinically silent and precedes the development of alveolar edema [29]. Interstitial and alveolar edema develop when the pulmonary venous pressure rises above 25 mg and 30 mmHg, respectively [30].

The LUS findings used to diagnose pulmonary edema/interstitial syndrome are presented in Box 22.3. Interstitial syndrome is defined when more than two B-lines are seen between two ribs using an ultrasound. The presence of three or four B-lines is identified as septal rockets, which correlate with Kerley's lines (subpleural interlobular septa). Five or more B-lines forms a pattern called ground-glass rockets, as they correlate with ground-glass lesions [31].

Box 22.3 LUS findings to diagnose Pulmonary Edema (i.e. B-Lines) in pregnant patients:

Always Present
1. Comet-tail artifact
2. Arises from the pleural line
3. Moves in concert with lung sliding

Almost Always Present
4. Has well-defined features
5. Long and spreading without fading
6. Obliterates A-line

LUS has a sensitivity and specificity of 98% and 88%, respectively, compared to chest radiograph which has estimated sensitivity of 50–68% and specificity of 76–83% in detecting pulmonary edema in non-pregnant women [10]. Several studies have concluded that LUS detects lung fluids earlier than other radiological tests. A recent small prospective LUS study performed in women with severe preeclampsia reinforced that the presence of B-lines in asymptomatic pregnant women with known severe preeclampsia helps in identifying pulmonary edema prior to severe deterioration of arterial oxygenation. LUS findings may therefore be used to direct administration of intravenous fluids and to avoid excessive fluid administration in women with severe preeclampsia [32].

Pneumonia in pregnancy. Community-acquired pneumonia (CAP) is the most common fatal non-obstetric infectious complication requiring hospital admission [33]. The incidence of CAP is similar between pregnant women and non-obstetric patients with an incidence ranging 0.2–8.5% per 1000 deliveries [34]. Pregnant women with pneumonia are more prone to develop preterm labor and pulmonary edema and increase the risk of preterm birth, small for gestational age, and lower Apgar score. Aspiration pneumonia is more common in pregnant women due to lower esophageal sphincter tone and slower gastric emptying particularly during peripartum airway manipulation [35].

Thoracic CT scan is considered the gold standard in diagnosing pneumonia but this imaging is not likely to be used as the imaging modality of first choice due to concerns about radiation exposure in pregnant women and due to the risks involved in transportation of critically ill patients in general. The sensitivity and specificity of LUS in diagnosing pneumonia compared to chest X-ray is 94% and 98%, respectively, based on a prospective observational study conducted in Europe, while meta-analysis of several studies have shown a pooled sensitivity and pooled spec-

Box 22.4 LUS findings commonly found in pneumonia:

- Tissue-like sign: Echoic tissue-like pattern with regular trabeculations
- Shred sign: Irregular, shredded pleural line
- Air bronchogram: presence of hyperechoic opacities
- Abolished lung sliding

ificity ranging from 84–90% to 88–93%, respectively [36, 37].

Alveolar consolidation, including pneumonia, can be diagnosed placing the ultrasound probe in the posterolateral alveolar pleural syndrome (PLAPS) point, and detects 90% of the cases. This differs from other respiratory disorders such as pleural effusion, pneumothorax, and interstitial edema where extensive location of probe placement is needed for diagnosis. Box 22.4 presents the common LUS findings in pneumonia.

22.7 Common Protocols Used in Lung Ultrasonography

22.7.1 BLUE (Bedside Lung Ultrasound in Emergency) Protocol

The BLUE protocol was demonstrated was specifically designed for rapid diagnosis of acute respiratory failure in a clinically challenging situation. In the hands of a trained physician, the entire study can be completed in 3 min, whereas a novice may require longer. The BLUE protocol can be used in pregnant women in the same way it is used in the non-obstetric population. The protocol integrates vascular and lung ultrasound findings to diagnose pneumonia, pulmonary edema, pulmonary embolism, chronic obstructive pulmonary disease (COPD) exacerbation or asthma, and pneumothorax. These constitute the diagnoses in 97% of patients with acute respiratory symptoms. The diagnosis made with LUS is accurate in 90.5% of the cases [38].

The BLUE protocol (Fig. 22.10) has eight profiles including three sub profiles when scanning the anterior chest wall [9, 13, 31]:

- A-profile: Presence of lung sliding with repetitive A-lines, which indicates PAOP is less than 18 mm Hg [39].
- A-DVT profile: The presence of an A-profile along with a positive deep vein thrombosis scan identified using venous ultrasound. This profile is associated with PE and has a sensitivity and specificity of 81% and 99% respectively.
- A-V PLAPS profile: The presence of A-profile with no evidence of deep vein thrombosis but with identification of an ill-defined structural image in the alveolar, pleural, or combined space at the PLAPS point. The A-V PLAPS profile has a sensitivity of 42% and specificity of 96% for pneumonia.
- Nude profile: A-profile without DVT or PLAPS. The nude profile is associated with COPD or asthma with a sensitivity and specificity of 89% and 97%, respectively.
- A'-profile: A-profile with abolished lung sliding and exclusive A-line on the anterior area of supine patients. The A'-profile is suggestive of pneumothorax. When a lung point is observed with this profile it confirms pneumothorax with a sensitivity and specificity of 88% and 100%, respectively.
- B-profile: Combined lung sliding and lung rockets in the four anterior blue points. The B-profile has a sensitivity and specificity of 97% and 95%, respectively in detecting pulmonary edema.
- B'-profile: Absence of lung sliding and presence of anterior lung rockets. Indicates pneumonia with a low sensitivity of 11% but a high specificity of 100%.

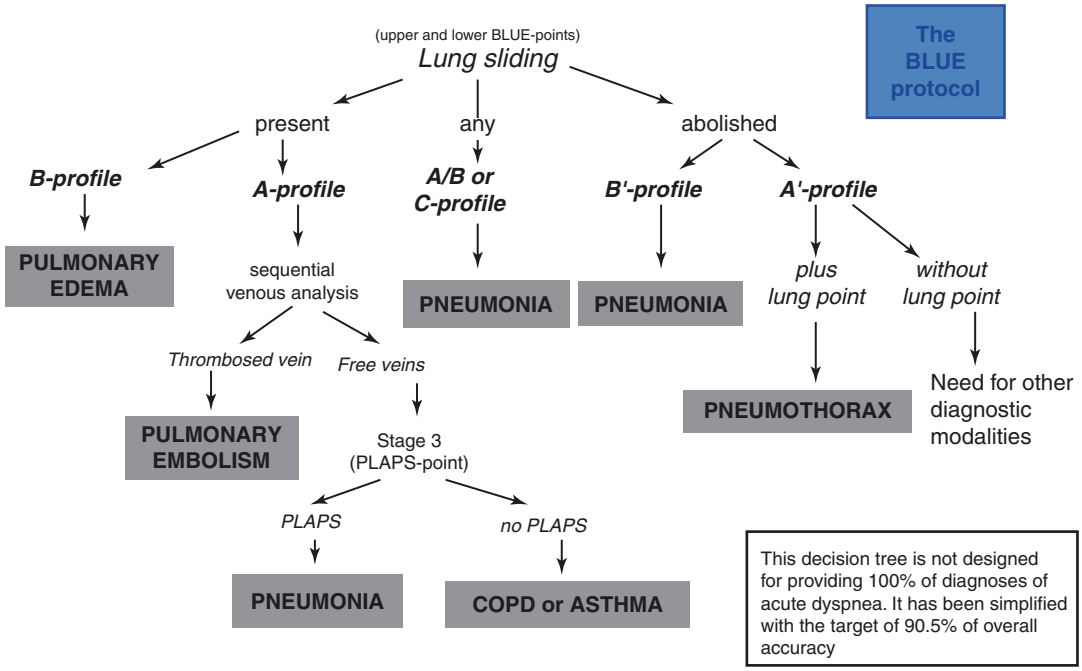


Fig. 22.10 BLUE protocol algorithm

- A/B-profile: Predominant B-profile in one lung and predominant A-profile in the other lung. Indicative of pneumonia.
- C-Profile: Presence or absence of lung sliding combined with anterior lung consolidative sign. The C-profile indicates pneumonia with a sensitivity and specificity of 21.5% and 99%, respectively.

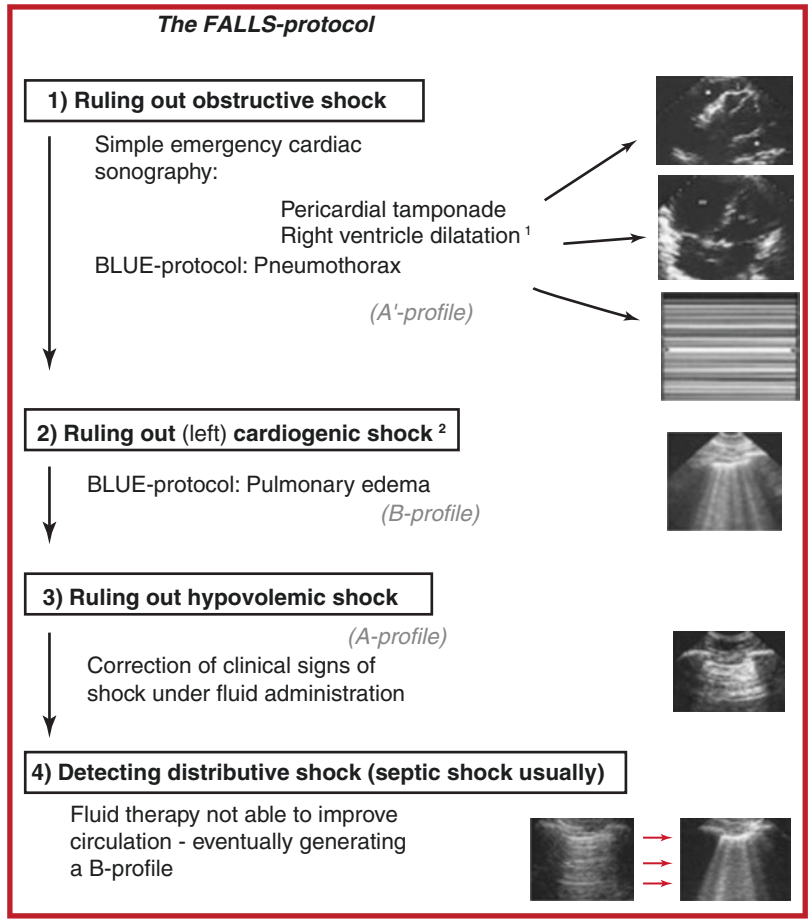
22.7.2 FALLS Protocol

This acronym for fluid administration limited by LUS (FALLS) is a tool used for identifying causes of circulatory failure using LUS (Fig. 22.11). It uses a sequential approach to rule out the main causes of shock based on the Weil-Shubin classification, namely, hypovolemic, cardiogenic, obstructive, and distributive shock. The FALLS protocol has not been studied specifically in pregnant women. The protocol begins with evaluation of obstructive shock by viewing the pericardial space for any effusion/tamponade followed by right ventricular volume to suggest pulmonary embolism and then search for pneumothorax. If obstructive shock is ruled out, a B-profile is sought as it could suggest cardiogenic shock (in the right setting). The absence of a B-profile makes cardiogenic shock unlikely. Following this, fluids are provided for possible hypovolemic or distributive shock with close ultrasound follow-up to seek for lung artifacts. Hypovolemic shock usually resolves prior to development of interstitial syndrome. A transition such as disappearance of A-lines and appearance of B-lines suggests that the patient has been adequately fluid resuscitated and possibly has distributive shock [40].

Summary. Lung ultrasound is now well established as a useful diagnostic and follow-up tool in the critical care setting. Recent studies suggest that there is no difference in the imaging obtained from pregnant women and the non-obstetric population, making LUS a useful bedside tool to assess and manage acute dyspneic gravid patients.

Fig. 22.11 FALLS protocol

Lichtenstein D: **Lung Ultrasound for the Diagnosis and Management of an Acute Circulatory Failure.** *In Lung Ultrasonography in the Critically Ill. heidelberg, Berlin, New York: Springer-Verlag; 2016:225-259.*



References

1. Arbeid E, Demi A, Brogi E, Gori E, Giusto T, Soldati G, et al. Lung ultrasound pattern is normal during the last gestational weeks: an observational pilot study. Gynecol Obstet Investig. 2016;82:398.
2. Garcia-Rio F, Pino JM, Gomez L, Alvareq-Sala R, Villasante C, Villamor J. Regulation of breathing and perception of dyspnea in healthy pregnant women. Chest. 1996;110:446–53.
3. Yeomans ER, Gilstrap LC, III. Physiologic changes in pregnancy and their impact on critical care. Crit Care Med. 2005;33(10):S256–8.
4. Milne JA. The respiratory response to pregnancy. Postgrad Med J. 1979;55:318–24.
5. Chesnutt AN. Physiology of normal pregnancy. Crit Care Clin. 2004;20(4):609–15.
6. Pollock W, Rose L, Dennis C-L. Pregnant and postpartum admissions to the intensive care unit: a systematic review. Intensive Care Med. 2010;36(9):1465–74.
7. Soubra SH, Guntupalli KK. Critical illness in pregnancy: an overview. Crit Care Med. 2005;33:S248–55.
8. Lowe SA. Diagnostic radiography in pregnancy: risks and reality. Aust N Z J Obstet Gynaecol. 2004;44(3):191–6.
9. Lichtenstein DA, Mezière GA. Relevance of lung ultrasound in the diagnosis of acute respiratory failure. Chest. 2008;134(1):117–25.
10. Cardinale L, Priola AM, Moretti F, Volpicelli G. Effectiveness of chest radiography, lung ultrasound and thoracic computed tomography in the diag-

nosis of congestive heart failure. World J Radiol. 2014;6(6):230–7.
11. Pachtman S, Koenig S, Meirowitz N. Detecting pulmonary edema in obstetric patients through point-of-care lung ultrasonography. Obstet Gynecol. 2017;129(3):525–9.
12. Volpicelli G. Lung Sonography. J Ultrasound Med. 2013;32:165–71.
13. Lichtenstein DA. Lung ultrasound in the critically ill. Ann Intensive Care. 2014;4(1):1.
14. Volpicelli G, Elbarbary M, Blaivas M, Lichtenstein DA, Mathis G, Kirkpatrick AW, Melniker L, Gargani L, Noble VE, Via G, et al. International Liaison Committee on Lung Ultrasound (ILC-LUS) for International Consensus Conference on Lung Ultrasound (ICC-LUS). International evidence-based recommendations for point-of-care lung ultrasound. Intensive Care Med. 2012;38:577–91.
15. Markowitz J. Chapter 4. Probe selection, machine controls, and equipment. In: Carmody KA, Moore CL, Feller-Kopman D, editors. Handbook of critical care and emergency ultrasound. New York, NY: McGraw-Hill; 2011.
16. Doerschug KC, Schmidt GA. Intensive care ultrasound: III. Lung and pleural ultrasound for the intensivist. Ann Am Thorac Soc. 2013;10(6):708–12.
17. Miller A. Practical approach to lung ultrasound. BJA Educ. 2016;16(2):39–45.
18. Gargani L, Volpicelli G. How I do it: lung ultrasound. Cardiovasc Ultrasound. 2014;12(1):25.
19. Lichtenstein D. Introduction to lung ultrasound. In: Whole body ultrasonography in the critically ill. Heidelberg, Berlin, New York: Springer-Verlag; 2010. p. 117–27.
20. Tanase Y, et al. A case of spontaneous pneumothorax during pregnancy and review of the literature. Kobe J Med Sci. 2007;53(5):251–5.
21. Garg R, Sanjay DV, Usman K, Rungta S, Prasad R. Spontaneous pneumothorax: an unusual complication of pregnancy—a case report and review of literature. Ann Thorac Med. 2008;3(3):104–5. https://doi.org/10.4103/1817-1737.41915.
22. Carr JJ, Reed JC, Choplin RH, Pope TL Jr, Case LD. Plain and computed radiography for detecting experimentally induced pneumothorax in cadavers: implications for detection in patients. Radiology. 1992;183(1):193–9.
23. Nagarsheth K, Kurek S. Ultrasound detection of pneumothorax compared with chest X-ray and computed tomography scan. Am Surg. 2011;77(4):480–4.
24. Alrajhi K, Woo MY, Vaillancourt C. Test characteristics of ultrasonography for the detection of pneumothorax: a systematic review and analysis. Chest. 2012;141:703–8.
25. Lal A, et al. Pneumothorax and pregnancy. Chest J. 2007;132(3):1044–8.
26. Volpicelli G, Elbarbary M, Blaivas M, et al. International evidence-based recommendations for point-of-care lung ultrasound. Intensive Care Med. 2012;38:577.
27. Sciscione AC, Ivester T, Largoza M, Manley J, Shlossman P, Colmorgen GHC. Acute pulmonary edema in pregnancy. Obstet Gynecol. 2003;101(3):511.
28. Gracia V-D, Paulino CM-R, Smith A. Pregnancy and severe chronic hypertension: maternal outcome. Hypertens Pregnancy. 2004;23(3):285–93.
29. Cunningham JH, Richardson RH, Smith JD. Interstitial pulmonary edema. Heart Lung. 1977;6(4):617–23.
30. Khan AN, Al-Jahdali H, AL-Ghanem S, Gouda A. Reading chest radiographs in the critically ill (part II): radiography of lung pathologies common in the ICU patient. Ann Thorac Med. 2009;4(3):149–57.
31. Lichtenstein D. Novel approaches to ultrasonography of the lung and pleural space: where are we now? Breathe. 2017;13(2):100–11.
32. Zieleskiewicz L, et al. Lung ultrasound predicts interstitial syndrome and hemodynamic profile in parturients with severe preeclampsia. Anesthesiology. 2014;120(4):906–14.
33. Brito V, Niederman MS. Pneumonia complicating pregnancy. Clin Chest Med. 2011;32(1):121–32.
34. Lim WS, Macfarlane JT, Colthorpe CL. Am J Respir Med. 2003;2:221.
35. Mighty HE. Acute respiratory failure in pregnancy. Clin Obstet Gynecol. 2010;53(2):360–8.
36. Alzahrani SA, Al-Salamah MA, Al-Madani WH, Elbarbary MA. Systematic review and meta-analysis for the use of ultrasound versus radiology in diagnosing of pneumonia. Crit Ultrasound J. 2017;9:6.
37. Xia Y, Ying Y, Wang S, Li W, Shen H. Effectiveness of lung ultrasonography for diagnosis of pneumonia in adults: a systematic review and meta-analysis. J Thorac Dis. 2016;8(10):2822–31.
38. Lichtenstein D. BLUE-protocol. In: Whole body ultrasonography in the critically ill. Heidelberg, Berlin, New York: Springer-Verlag; 2010. p. 189–202.
39. Lichtenstein D, Mezière G, Lagoueyte JF, Biderman P, Goldstein I, Gepner A. A-lines and B-lines: lung ultrasound as a bedside tool for predicting pulmonary artery occlusion pressure in the critically ill. Chest. 2009;136:1014–20.
40. Lichtenstein D. FALLS-protocol: lung ultrasound in hemodynamic assessment of shock. Heart Lung Vessel. 2013;5(3):142–7.

Management of Ventilation

23

Julien Viau-Lapointe and Stephen Earl Lapinsky

Bullet Points

- Respiratory failure affects approximately 1 in 500 pregnancies.
- Pregnancy-specific conditions causing respiratory failure include preeclampsia and amniotic fluid embolism.
- Respiratory failure may also be caused by conditions aggravated by the pregnant state (e.g., gastric aspiration, venous thromboembolism, cardiac valvular lesions).
- Conditions unrelated to pregnancy (e.g., asthma, bacterial pneumonia) can also lead to respiratory failure during pregnancy, as seen in the general population.
- The main adaptations of management to the presence of pregnancy are adjustment to the altered maternal respiratory physiology, expert care during the high-risk intervention of endotracheal intubation, and the need to balance maternal benefit with fetal risk with regard to fetus radiological investigations and drug therapy.
- Noninvasive ventilation may be useful in conditions with a short-term requirement for ventilator support.
- Limited data exist regarding prolonged invasive mechanical ventilatory management in pregnancy.
- Hypoxemia is likely harmful to the fetus, but the precise targets are unknown.
- Hypocapnia should be avoided, and the pregnant woman (and fetus) may tolerate some degree of hypercapnia.
- Delivery of the fetus may be considered, provided benefit (or at least no harm) is anticipated for the mother as well as the fetus.

J. Viau-Lapointe
Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, ON, Canada

Hôpital Maisonneuve-Rosemont, University of Montreal, Montreal, QC, Canada
e-mail: Julien.vl@gmail.com

S. E. Lapinsky (✉)
Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, ON, Canada

Mount Sinai Hospital, Toronto, ON, Canada
e-mail: Stephen.lapinsky@utoronto.ca

23.1 Introduction

Respiratory failure occurs in approximately 1 in 500 pregnancies [1], more commonly in the postpartum period than during the pregnancy.

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_23

Pregnancy increases the risk or severity of several conditions, including asthma, aspiration, thromboembolism, and viral pneumonitis. Furthermore, several pregnancy-specific conditions may precipitate respiratory failure, such as preeclampsia, amniotic fluid embolism, and peripartum cardiomyopathy.

Management of respiratory failure during pregnancy is influenced by the altered maternal respiratory physiology (see Chap. 20) and the high-risk intervention of endotracheal intubation (see Chap. 21). The presence of a fetus can affect investigations and management in these patients. Limited data exist regarding prolonged mechanical ventilation management in pregnancy, particularly regarding oxygenation and carbon dioxide targets. Delivery of the fetus may be considered in an attempt to improve maternal respiratory function, but this should usually be reserved for cases where benefit to the fetus is also anticipated.

23.2 Causes of Acute Maternal Respiratory Failure

Respiratory failure during pregnancy and the peripartum period may result from pregnancy-specific conditions, pulmonary or cardiac conditions which are aggravated or precipitated by the pregnant state, or conditions unrelated to pregnancy (Table 23.1).

23.2.1 Cardiogenic Pulmonary Edema

Pulmonary edema may occur during pregnancy as a result of preeclampsia, cardiac disease, or other conditions, both specific and nonspecific to pregnancy.

Table 23.1 Causes of respiratory failure in pregnancy

Unrelated to pregnancy	Aggravated by pregnancy	Unique to pregnancy
Bacterial pneumonia Restrictive lung disease Obstructive lung disease Cystic fibrosis	Pulmonary edema due to preexisting cardiac disease ARDS Aspiration pneumonitis Viral pneumonia Pulmonary embolism	Preeclampsia Amniotic fluid embolism Pulmonary edema due to peripartum cardiomyopathy

Preeclampsia is complicated by pulmonary edema in about 2.9% of patients with this condition [2]. The hemodynamic findings in preeclampsia include increased afterload, normal or low left ventricular preload, and a normal or low cardiac output. Impaired systolic and diastolic function may also occur [3]. Pulmonary edema associated with preeclampsia usually presents in the immediate postpartum period due to increased central volume. This is usually related to peripartum fluid administration and the return of blood from the contracting uterus. Low colloid oncotic pressure and abnormal vascular permeability likely also contribute. Mirror syndrome is a rare cause of respiratory failure, associated with fetal hydrops [4]. The pathophysiology is unclear, but the mother develops edema and pulmonary edema "mirroring" the fetal syndrome, and this can mimic pulmonary edema secondary to preeclampsia.

Women with preexisting heart disease are at risk of cardiac decompensation during and after pregnancy as the blood volume and cardiac output requirements increase. Women with cyanotic heart disease, mitral and aortic valve stenotic lesions, or systolic dysfunction are most at risk [5]. Pulmonary edema may occur during pregnancy or in the postpartum period, related to shifts in intravascular volume associated with delivery. For example, during pregnancy, the elevation in cardiac output and heart rate increases the gradient across a stenotic mitral valve [6]. The reduced systemic vascular resistance (SVR) occurring in pregnancy actually mitigates the adverse effects of mitral and aortic regurgitation. However, the low SVR may worsen the effects of Eisenmenger's syndrome and uncorrected tetralogy of Fallot. These pregnancy-related changes in SVR and cardiac output may increase shunt fraction, producing hypoxemia and precipitating pulmonary edema. Pulmonary edema may also occur in the presence of a cardiac condition specific to pregnancy such as peripartum cardiomyopathy, a disorder occurring in 1 of 1000–4000 pregnancies [7]. The pregnant woman may present with acute left ventricular failure with resultant congestive heart failure. This condition is

also associated with an increased risk of pulmonary and systemic thromboembolism [8].

23.2.2 Acute Respiratory Distress Syndrome (ARDS)

ARDS is a diffuse lung inflammatory process leading to capillary leak and surfactant loss [9]. It manifests clinically with hypoxemia and bilateral lung opacities on chest imaging. Pregnant patients appear to be predisposed to ARDS compared to nonpregnant patients due to their increased circulating blood volume, decreased serum albumin level, and an upregulation of components of the acute inflammatory response [10, 11]. ARDS is a clinical syndrome caused by various etiologies. These etiologies may be unrelated to pregnancy such as sepsis, overrepresented in pregnancy such as aspiration pneumonia, or unique to pregnancy such as amniotic fluid embolism. ARDS is relatively rare during pregnancy (59.6 per 100,000 live births in 2012), but its incidence may rise in specific situations such as the recent H1N1 influenza epidemic [12]. In contrast, maternal mortality related to ARDS is decreasing with improvements in management and earlier diagnosis of less severe cases [12]. Neonatal outcomes in maternal ARDS are not well studied, but observational evidence suggests high rates of fetal death, prematurity, and perinatal asphyxia [13].

Pneumonia is the most common cause of ARDS during pregnancy, including chemical pneumonitis related to aspiration events [12]. Factors predisposing to aspiration during pregnancy include increased intra-abdominal pressure, decreased tone of the lower esophageal sphincter, and the use of the supine position for delivery [14]. Most cases of aspiration occur in the delivery suite. As noted above, pregnant women are also susceptible to respiratory complications of viral pneumonitis especially from influenza and varicella viruses [15].

Transfusion-related acute lung injury (TRALI) occurs as a complication of blood component therapy in pregnant and nonpregnant patients [16]. This manifests as sudden dyspnea during or within 6 h of transfusion of plasma-containing blood products. The clinical picture is similar to ARDS from other causes, and the differential diagnosis includes transfusion-associated circulatory fluid overload (TACO).

Amniotic fluid embolism is an uncommon but devastating condition occurring in about 7.7 per 100,000 pregnancies, with a mortality as high as 86% and accounting for 14% of all maternal deaths [17, 18]. This condition is usually associated with uterine manipulation or labor and delivery. It is characterized by sudden cardiovascular collapse with respiratory failure. The pathophysiology involves traumatic opening of uterine vessels with amniotic fluid contents precipitating acute pulmonary hypertension and biventricular dysfunction. Survivors of the initial event may develop disseminated intravascular coagulation and ARDS.

Other conditions associated with ARDS during pregnancy are preeclampsia, sepsis especially due to pyelonephritis or puerperal infections, and trophoblastic embolism.

23.2.3 Other Conditions

Pulmonary infections: Changes that occur in the immune system during pregnancy to allow tolerance to paternally derived fetal antigens increase maternal susceptibility to certain infections [15]. The major effect is a down regulation of cell-mediated immunity, with an intact or upregulated humoral immune response [19] (See also Chap. 15).

The incidence of community-acquired pneumonia is no higher in the pregnant population than in the general population, but this condition is an important cause of maternofetal morbidity and mortality [20]. An increased incidence of complications of pneumonia, including respiratory failure, occurs in pregnancy. Furthermore, pneumonia may adversely affect the pregnancy, precipitating preterm labor, small for gestational age, and intrauterine and neonatal death [20, 21]. The microbiological spectrum is similar to nonpregnant patients. Delayed diagnosis may occur, because of reluctance by physicians or the patient to obtain a chest radiograph due to inappropriate concern of radiation exposure. Treatment uses a

similar antibacterial approach to that in the nonpregnant patient, but some drugs such as tetracyclines and quinolones should be avoided if possible [21].

Influenza pneumonitis may cause significant morbidity in pregnancy; during influenza epidemics, the maternal mortality rate is higher than that of the general population [22]. During the 2009 influenza A (H1N1) pandemic, pregnant women had a seven times higher risk of ICU admission than nonpregnant women of similar age, and mortality in this group ranged from 8% to 11% [23]. Varicella pneumonia may also be associated with increased morbidity and mortality during pregnancy, even though not all studies have confirmed this increased risk [24]. Although the fungal infection coccidioidomycosis is uncommon, it is more likely to disseminate in pregnant women, producing severe disease with respiratory failure [25].

Asthma: Asthma affects up to 10% of the general population and is therefore a common disorder in pregnancy [26]. The effect of pregnancy on asthma is variable, but approximately one-third of asthmatics will deteriorate during their pregnancy [27]. Labor and delivery may increase the risk for asthmatic patients, related in part to the drugs commonly administered. Oxytocin used for labor induction and for postpartum hemorrhage carries little risk, but 15-methyl prostaglandin F2-alpha, methylergonovine, and ergonovine may cause bronchospasm. Many narcotics (other than fentanyl) release histamine, which can worsen bronchospasm. Status asthmaticus in pregnancy is a rare, life-threatening condition, and management is similar to nonpregnant patients [28]. Chronic obstructive pulmonary disease (COPD) remains relatively uncommon in pregnant women despite increasing maternal age. Management is similar to the nonpregnant patient.

Pulmonary thromboembolic disease: Thromboembolism occurs during pregnancy with an incidence about 5 times as great as in matched nongravid controls. It is a leading cause of maternal mortality, accounting for about 10% of pregnancy-related deaths in the United States [29, 30]. The incidence of thromboembolism peaks in the postpartum period, particularly after cesarean section. The source may be identified by duplex ultrasonography, particularly if there are deep venous thrombosis symptoms. Diagnosis is performed using ventilation-perfusion (V/Q) scanning or computed tomography (CT) pulmonary angiography, both of which can be safely performed in pregnancy [31]. During pregnancy, V/Q scanning usually produces high-quality scans, due to these patients' lack of comorbidity and younger age, while CT angiography exposes the mother's breast tissue to a significant dose of radiation with concerns about an increased risk of breast cancer [32]. Both tests are associated with a low fetal radiation exposure.

Restrictive lung disease: Most interstitial lung diseases (ILD) occur in populations older than woman in their childbearing years and are therefore relatively uncommon during pregnancy. Conditions which do occur in this age group include lymphangioleiomyomatosis and systemic lupus erythematosus, both of which may worsen as a result of pregnancy [33, 34]. The adverse physiological effect of these conditions is hypoxemia. The pulmonary diffusion defect is aggravated by the increased cardiac output in pregnancy which shortens alveolar capillary transit time. This situation is obviously worsened by the increased oxygen requirement during pregnancy.

Women with chest wall abnormalities producing a restrictive disease (e.g., kyphoscoliosis or neuromuscular weakness) have a different physiological problem – the potential inability to meet the increased ventilation requirements of pregnancy. Oxygenation is less of a concern, but these patients are at risk of developing hypercapnic respiratory failure [35].

Cystic fibrosis: Median survival for cystic fibrosis (CF) has increased, and pregnancy is increasingly common in this patient group [36]. Due to the significant pulmonary effects of this condition, respiratory failure is a concern. Poor prognostic factors include an FEV1 less than 60% predicted and pulmonary hypertension. Although the risk of mechanical ventilation and mortality is increased in women with CF, the overall risk is low [36].

23.3 Ventilatory Targets (Table 23.2)

23.3.1 Oxygen

Little data exist to identify the optimal oxygen and carbon dioxide goals for ventilatory support during pregnancy. Although it has been suggested that maternal oxygenation should be maintained at an arterial PaO_2 greater than 70 mmHg (or saturation > 95%) [13], there are no studies to support this threshold. It is important to recognize that maternal oxygen saturation is only one of the factors affecting fetal oxygenation – uterine blood flow and placental perfusion impact oxygen delivery and may be affected by catecholamines, the presence of alkalosis, or reduced venous return produced by elevated intrathoracic pressure [37]. Studies have attempted to address the issue of maternal oxygenation in a variety of ways. A mathematical model using animal data suggested that decreasing maternal arterial oxygen saturation from 96% to 85% would decrease fetal umbilical vein saturation from about 70–55% [38]. A short-term clinical study using inhalation of 10% oxygen to generate controlled maternal hypoxemia (saturation < 85%) demonstrated no adverse effects on fetal monitoring [39]. While optimizing maternal oxygenation should always be the target, harm from mild maternal hypoxemia has not been clearly established, and emerging data from nonpregnant populations suggests that hyperoxia could be harmful [40, 41]. Hypoxemia caused by shunt (intrapulmonary or intracardiac) or by marked ventilation-perfusion mismatch is less responsive to increased FiO_2. Strategies aimed at improving mixed venous oxygen saturation (i.e., improving cardiac output) may be especially beneficial in this situation.

Table 23.2 Mechanical ventilation during pregnancy: comparison with the nonpregnant patient

Parameter	Nonpregnant patient	Pregnant patient
Tidal volume	6 mL/kg IBW	6 mL/kg IBW
Plateau pressure limit	<30 cmH_2O	Accept higher (e.g., 35 cmH_2O or based on transpulmonary pressure estimation)
Oxygen saturation goal	Usually >88–92% Avoid hyperoxia	Usually >94%—Unclear if this is necessary Avoid hyperoxia
Arterial carbon dioxide ($PaCO_2$) limit	Permissive hypercapnia (sometimes as high as 100 mmHg)	Avoid hypocapnia and alkalosis. Pregnancy normal = 28–32 mmHg Limited data on hypercapnia, but moderate levels (e.g., 50 mmHg) may be safe
Patient positioning	Semi-upright (45 degree)	Left lateral decubitus for hemodynamics Head elevation important to avoid reflux
Prone positioning	Good data of benefit in ARDS	Technically difficult, (since COVID): "Likely also beneficial"

IBW ideal body weight (based on height), *PEEP* positive end-expiratory pressure, *FiO2*, fraction of inspired oxygen

23.3.2 Carbon Dioxide ($PaCO_2$)

$PaCO_2$ levels in mid to late pregnancy are reduced to about 28–32 mmHg, due to the increased respiratory drive generated by progesterone. The question arises as to whether this should be the ventilation target and whether permissive hypercapnia is harmful. Excessive hypocapnia and alkalosis may cause fetal harm by reducing placental perfusion [42]. Permissive hypercapnia has become an accepted approach during pressure-limited ventilation in the nonpregnant patient, but the effects of hypercapnia on the fetus have not been adequately studied. The theoretical concerns include reducing the gradient for excretion of fetal CO_2 and the development of fetal respiratory acidosis. Although this fetal acidosis may affect oxygenation by right-shifting the oxyhemoglobin dissociation curve, it likely does not have the same ominous implications for the fetus as lactic acidosis secondary to hypoxia. A small observational clinical study in women undergoing cesarean section compared mildly reduced CO_2 levels (mean 23 mmHg) with mild hypercapnia (mean 39.3 mmHg) [43]. Women

with low CO_2 levels delivered babies with a lower Apgar score and delayed neonatal breathing. In another study, CO_2 levels during delivery were altered by local versus general anesthesia, with or without a CO_2 absorber [44]. Hypercapnic women (mean CO_2 57.6 mmHg) delivered babies with statistically higher Apgar scores compared with two other groups with CO_2 levels of 26.4 and 30.1 mmHg. Case reports and series describing status asthmaticus during pregnancy have described severe maternal hypercapnia with $PaCO_2$ levels greater than 100 mmHg for more than 24 h, with good maternal and neonatal outcomes [28]. These studies suggest that transient hypercapnia is likely to be tolerated by the fetus and that avoidance of marked hypocapnia is wise.

23.4 Ventilation Management

23.4.1 Noninvasive Ventilation

Noninvasive ventilation (NIV) is increasingly used in nonpregnant patients for short-term ventilatory support to avoid potential complications associated with endotracheal intubation and sedation. The use of NIV in pregnancy may be hampered by concerns regarding the risk of aspiration due to the decreased gastroesophageal sphincter tone, increased intragastric pressure, and decreased gastric emptying occurring in pregnancy [14]. However, this modality is clearly beneficial in some situations and has a role in obstetric respiratory complications which reverse rapidly [45]. When determining whether initiating NIV is appropriate for a pregnant woman, one should always consider the risk versus the potential benefit of avoiding invasive ventilation. High-flow nasal cannula may be preferred when the risk of aspiration is particularly high, as this method does not require pressurized sealing of the airway.

Most studies in pregnant patients report NIV for chronic respiratory failure in the context of neuromuscular disease [46]. Few data are available on initiation of NIV in the acute setting. It has been used in hypoxemic respiratory failure due to pulmonary edema, ARDS, and pneumonia. When NIV was successful, most cases required less than 12 h of ventilation [45]. Among a cohort of 186 pregnant women requiring mechanical ventilation for H1N1, 83 (45%) of them initially received NIV, and invasive ventilation was ultimately avoided in 38 (46% of the NIV group) [47]. NIV failure was associated with more severe respiratory failure, septic shock, neurological symptoms, and a higher mortality. NIV is usually administered using a face mask, but the use of the helmet interface has also been described [48].

For critically ill pregnant patients, NIV should only be used if the patient is alert and protecting her airway with good spontaneous respirations and when the disease process potentially requiring mechanical ventilation is expected to be relatively brief.

23.4.2 Invasive Mechanical Ventilation

Pregnant women were predominantly excluded or not reported as a subgroup in the major mechanical ventilation trials. Data and recommendations are therefore based on observational studies, physiological concepts, and expert opinions (Table 23.2). Physiological changes of the respiratory system increase with pregnancy duration and therefore are mostly relevant for mechanical ventilation during the third trimester. In terms of respiratory mechanics of positive pressure ventilation, the main physiological effect of pregnancy is a reduced chest wall compliance generated by the enlarging uterus.

No data exist to guide the choice of ventilator mode in pregnancy. A case control study comparing ventilation of pregnant versus nonpregnant patients in Australia during the 2009 influenza pandemic showed no difference in mode and ventilator settings used [49]. Small case series suggest a potential benefit from the use of airway pressure release ventilation (APRV) in pregnant women with lung injury, as this mode provides non-injurious ventilation but still optimizes lung volumes [50, 51]. This remains an area to be further studied both in pregnant and nonpregnant patients.

Low tidal volume ventilation (5–6 mL/kg of ideal body weight) is considered optimal management for patients with [52, 53] and without ARDS [54]. Lung volumes are stable throughout pregnancy, although tidal volume increases [55]. Ideal body weight based on height can still be used in pregnant women. In patients with severe lung disease, established benefits of low tidal volume ventilation must be weighed against the potential risk of permissive hypercapnia (see Ventilatory targets).

Increased abdominal content with gravidity will lead to a decreased functional residual capacity (FRC) which renders pregnant women susceptible to atelectasis and alveolar de-recruitment [55]. Recruitment maneuvers and higher PEEP levels applied at the beginning of mechanical ventilation could prevent alveolar de-recruitment and may be beneficial [56]. Careful hemodynamic monitoring must be provided to detect secondary decreases in cardiac output, as this may be associated with hypotension that is potentially deleterious to the fetus.

Due to the reduced chest wall compliance, airway pressures in pregnant women will be higher for a given tidal volume. The increase in airway pressures expected during pregnancy is unknown and likely depends on the added abdominal volume. Plateau (end-inspiratory occlusion) pressure is often monitored as a surrogate for assessing lung distension. Avoidance of alveolar overdistention is part of the management of low tidal volume ventilation in ARDS [52, 53]. Plateau pressure is affected by lung volume, total positive end-expiratory pressure (PEEP), and the lung and chest wall compliance. The increase in airway pressures caused by decreasing chest wall compliance is not harmful, as it does not contribute to the transpulmonary pressure applied to the alveolus and does not create lung strain [57, 58]. Unfortunately, routine monitoring of airway pressures does not allow differentiation between the contributions of the lung and the chest wall to overall compliance. One method of separating the two components in order to monitor transpulmonary pressure alone is the use of esophageal pressure balloon catheters [58]. Esophageal pressure is used as a surrogate for pleural pressure in order to determine the chest wall contribution to the airway pressures and calculate the transpulmonary pressure (Fig. 23.1). This method can also be used to set PEEP in ARDS [59]. It may therefore have a role in guiding mechanical ventilation in pregnant women, although its exact significance is still a matter of controversy. Transpulmonary peak end-expiratory pressure should be set at greater than zero cmH_2O, and peak inspiratory pressures should be minimized, but no data exist to identify a safe upper-limit transpulmonary peak and plateau or delta transpulmonary pressure.

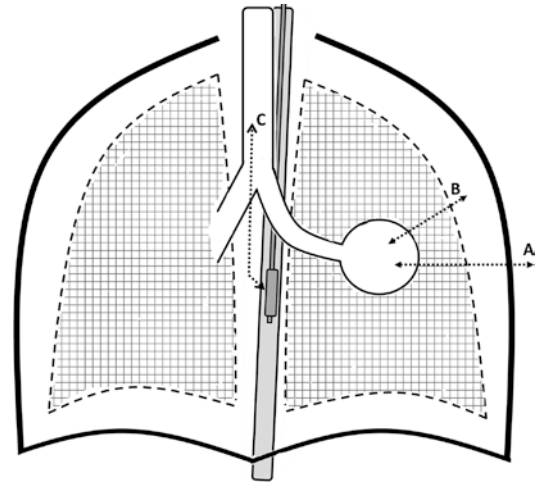


Fig. 23.1 Explanation of pulmonary pressures. Alveolar pressure (A) represents the difference between the pressure in the alveolus and atmosphere. Transpulmonary pressure (B) is the pressure distending the alveolus measured by the difference between the alveolar and pleural pressures. Transpulmonary pressure can be estimated by the difference between the airway pressure and the esophageal balloon pressure (C)

For pregnant patients with refractory hypoxemia, case reports and small series have described the use of neuromuscular blockers (NMB), recruitment maneuvers, high-frequency oscillation ventilation (HFOV), inhaled nitric oxide (iNO), and prone positioning [60–63].

NMB are often used to decrease patient-ventilator asynchrony in patients with refractory hypoxemia in the setting of ARDS. Such use was considered controversial after meta-analyses of observational data demonstrated increased mortality among ARDS patients treated with NMBs. Later meta-analyses [64] and a randomized trial

demonstrated a significant mortality benefit in patients with early ARDS (with a P/F ratio < 150) of a 48 h infusion of specific NMBs [65]. The RCT excluded pregnant patients from the trial due to safety concerns regarding the use of NMBs during pregnancy. Although sporadic doses of NMBs seem to be safe during pregnancy, a 48 h infusion may carry some risks [66] (see below: Imaging and Drug therapy).

Prone positioning has been proven beneficial on mortality in ARDS patients with a P/F ratio < 150 in a landmark study [67]. Pregnant women were excluded from this study as well; it remains unknown whether they would similarly benefit. While the prone position may be considered to produce pressure effects on the uterus and maternal blood vessels, a prospective study showed that prone position provides complete relief of uterine compression of the large maternal vessels [68]. A small number of published case reports and conference abstracts have described successful use of prone positioning in pregnancy [60, 69].

HFOV and iNO have both been reported as rescue therapies during pregnancy [70, 71]. These two strategies are less commonly used for the management of severe ARDS due to negative results of recent trials [72–74]. HFO may still be beneficial as a rescue intervention for severe ARDS, although the role in pregnant patients is unknown [75].

During the 2009 H1N1 influenza pandemic, a significant number of pregnant women were managed with veno-venous extracorporeal life support (VV-ECLS) for ARDS with reasonably good outcome [76]. Evidence is therefore increasing for efficacy of this technique, and patients have even recovered and gone on to deliver healthy babies after ECLS [77] (see also Chap. 14 regarding the use of ECMO during pregnancy and the postpartum period).

23.5 Other Aspects of Management

23.5.1 Role of Delivery

It is possible that urgent delivery of the pregnant patient with respiratory failure may be beneficial for the mother's respiratory status and for the fetus [78]. However, this benefit to the mother has not been demonstrated in all studies [79–81]. We retrospectively analyzed the respiratory effects of delivery in ten women ventilated with respiratory failure [81]. Only six patients demonstrated improvement in oxygenation (50% decrease in oxygenation index) or compliance (50% increase) [81]. A recent case series of pregnant women with respiratory failure documented the maternal effects of delivery in 71 women requiring mechanical ventilation who underwent cesarean section within 48 h of intubation. Patients with an obstetric cause for ARDS (e.g., preeclampsia) demonstrated an improvement in oxygenation and shorter duration of ventilation, findings which were not observed in women with non-obstetric causes for ARDS [82]. Potential indications for delivery in acute respiratory failure are therefore limited to fetal distress, obstetrical disease requiring delivery such as severe preeclampsia, and severe lung disease where risks to the fetus are prohibitive. If the fetus is at potential risk due to severe maternal hypoxemia and is at a gestational age with an expectation of reasonable pulmonary function, there may be a benefit to the fetus in delivery. This decision will require input from a multidisciplinary team including critical care, maternal-fetal medicine, and neonatology.

The mode of delivery should be determined by the obstetrician, based on usual obstetrical principles. Oxygen consumption may theoretically be increased by labor and vaginal delivery, which potentially could be avoided by operative delivery. Cesarean section also allows more rapid delivery, but the increased physiological stress might be associated with higher mortality [83]. In the situation of a ventilated woman with a pregnancy at a viable gestational age, the ICU should be prepared for urgent delivery and neonatal resuscitation. All necessary equipment and drugs should be immediately available, as well as contact details for obstetric and neonatal support.

23.5.2 Imaging

Thoracic imaging is not uncommonly needed during pregnancy and is essential to the management of the ventilated patient. Modalities often

required are chest radiography and chest computed tomography (CT). Fetal teratogenicity risks are thought to be greatest during the first trimester and related to the total dose administered (usually requiring >50 mGy) [84]. Carcinogenesis (childhood cancer) arises due to random DNA mutations which can occur at any radiation dose with no lower safe threshold. However, the risk at low fetal exposure is minimal, increasing to roughly a doubling of the risk of fatal childhood cancer at a fetal dose of 50 mGy [84]. When in doubt, benefits and risks of imaging during pregnancy should be discussed with radiology, as safer imaging modalities may be indicated.

Fetal radiation exposure of a single chest radiology during pregnancy is minimal (Table 23.3) and can be decreased by using abdominal shielding and a collimated X-ray beam. The amount of radiation to the fetus using abdominal shielding is 0.01 mGy [84]. For patients undergoing mechanical ventilation, routine chest radiography is not necessary [85], but it is appropriate not to refrain from ordering clinically indicated chest radiographs. Chest CT involves a higher fetal radiation up to 0.66 mGy [84], but is still considered safe in pregnancy with or without contrast [31, 86].

Point-of-care cardiac and lung ultrasound is an emerging imaging modality in the ICU and is recommended for the assessment of respiratory failure [87]. Ultrasound is generally a safe modality for fetuses, but ultrasound thermal effects can be harmful, and the uterus should not be imaged by inexperienced personnel [88] (see Chap. 22 for more details on the topic of lung ultrasound).

Table 23.3 Estimated fetal and maternal radiation exposure to chest imaging modalities (Adapted from [31])

	Estimated fetal dose (mGy)	Effective maternal dose to whole body (mSv)	Estimated maternal dose to breasts (mGy)
Chest radiography	0.002	0.1	–
CT	0.32–0.74	1–2.5	10–60
V/Q scan	0.03–0.66	4–18	0.98–1.07

23.5.3 Drug Therapy

Optimal ventilation often requires analgesic, sedative, and neuromuscular-blocking (NMB) medications. The safety of continuous analgesia and sedation in pregnant patients and their fetuses is unknown (see Chap. 38 for Medication use during pregnancy). If sedation, analgesia, or NMBs are used, the obstetrical team and neonatal team should be informed of the potential risk of neonatal respiratory depression and withdrawal after delivery.

Opioids are provided to patients undergoing mechanical ventilation to treat pain associated with intubation and other painful conditions. No malformations have been described with the short-term use of morphine or fentanyl [89].

Benzodiazepines are used in the ICU as both anxiolytic and amnestic medications.

Some studies have found a link between their use in the first trimester and major congenital malformations, but controversy exists about this association [90, 91]. When administered during the third trimester or close to delivery, benzodiazepines can cause a neonatal withdrawal syndrome or the floppy infant syndrome [92].

No human clinical data suggests teratogenicity with the use of propofol [89]. Case reports describe its use during mechanical ventilation with no significant harm other than hypotension with an associated decrease in uteroplacental perfusion. A single report of propofol infusion in two pregnant women undergoing prolonged neurosurgical procedures describes development of an acidosis not typical of a propofol infusion syndrome [93].

Dexmedetomidine, a relatively new sedative alpha-2-agonist agent, has been used during cesarean delivery both intravenously and intrathecally. Its use as an infusion in the ICU for ventilated pregnant women has been described in one case report [94]. Dexmedetomidine crosses the placenta [95] and its impact on the newborn is unknown. The drug can also induce uterine contractions [89].

The optimal analgesic and sedative regimen during pregnancy is not known, but it may be wise to avoid benzodiazepine during the first trimester and dexmedetomidine at any point until

further evidence of its safety. In 2017, the Food and Drug Administration of the United States submitted a warning stating that repeated or lengthy use of general anesthetic or sedative drugs in pregnant women during their third trimester may affect the development of children's brains [96]. The statement is controversial as it was based largely on animal studies; human data is sparse and inconclusive. Nevertheless, the current standard of care in the ICU is to minimize sedation, and this practice is even more relevant in the pregnant patient. Further studies on the long-term cognitive and developmental impact on human offspring are much needed.

NMBs are used in the ICU for intubation and for prevention of ventilator asynchrony and ARDS. Depolarizing NMBs such as succinylcholine are not appropriate for indications other than intubation due to their short duration of action. Non-depolarizing NMBs cross the placenta in variable amounts. The fetal-maternal drug concentration ratio of atracurium, vecuronium, rocuronium, and pancuronium varies between 0.07 and 0.26 [66]. The significant physiological changes occurring in pregnancy and the peripartum period alter the pharmacokinetics and dynamics of most neuromuscular-blocking agents [89, 97]. There are no human data for cisatracurium except for occasional case reports [98].

Most data on NMB during pregnancy has been obtained during cesarean delivery or other surgical interventions during the second and third trimesters [66]. Little is known about the effects of a NMB infusion or exposure during the first trimester. One report described prolonged administration for 10 days leading to fetal paralysis and resultant neonatal arthrogryposis [99]. On the other hand, one case report described good outcomes after a 10 h pancuronium infusion during the third trimester [100]. Thus, use of multiple doses or prolonged infusion of NMBs should be avoided or used with caution and for the shortest time possible.

Other unique considerations for the use of NMBs during pregnancy include exacerbation of prolonged neuromuscular blockade with hypermagnesemia induced for prevention of seizures in preeclampsia [101]. In mothers with pseudocholinesterase deficiency, both they and the affected infants can develop prolonged neuromuscular blockade [89].

23.6 Outcome after Mechanical Ventilation during Pregnancy

Maternal and neonatal outcomes after mechanical ventilation are poorly studied. They depend on multiple factors including the presence of maternal comorbidities, indications for mechanical ventilation (i.e., case mix), duration of ventilation, and number and severity of failing organs.

One study that used administrative data found a maternal mortality of 9% for pregnant women mechanically ventilated for ARDS [12]. Mortality increased with increased duration of mechanical ventilation from 6.9% for less than 96 h to 14.0% when greater than 96 h. Functional and psychological maternal outcomes after mechanical ventilation during pregnancy are entirely unknown.

Neonatal outcomes are poorly studied as well. Neonatal mortality after maternal respiratory failure and mechanical ventilation in pregnancy ranges from 0% to 24.4% in different studies [47, 79, 82, 102]. Other potentially important neonatal outcomes such as admission to a neonatal ICU and complications are rarely described. Only one study has provided some data on long-term neonatal outcome after maternal ventilation in the ICU [82]. This retrospective review of 71 women with gestation greater than 25 weeks ventilated due to with respiratory failure demonstrated a hospital maternal mortality of 5.6%. Neonatal survival to hospital discharge was 100%, although 20% of babies required mechanical ventilation and 20% demonstrated neurological impairment at 6 months [82].

References

1. Pollock W, Rose L, Dennis CL. Pregnant and postpartum admissions to the intensive care unit: a systematic review. Intensive Care Med. 2010;36:1465–74.

2. Sibai BM, Mabie BC, Harvey CJ, et al. Pulmonary edema in severe preeclampsia-eclampsia: analysis of thirty-seven consecutive cases. Am J Obstet Gynecol. 1987;156:1174–9.
3. Benedetti TJ, Kates R, Williams V. Hemodynamic observation of severe preeclampsia complicated by pulmonary edema. Am J Obstet Gynecol. 1985;152:33–4.
4. Braun T, Brauer M, Fuchs I, et al. Mirror syndrome: a systematic review of fetal associated conditions, maternal presentation and perinatal outcome. Fetal Diagn Ther. 2010;27:191–203.
5. Siu SC, Sermer M, Colman JM, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. Circulation. 2001;104:515–21.
6. Siu SC, Colman JM. Heart disease and pregnancy. Heart. 2001;85:710–5.
7. Arany Z, Elkayam U. Peripartum cardiomyopathy. Circulation. 2016;133:1397–409.
8. Pearson GD, Veille JC, Rahimtoola S, et al. Peripartum cardiomyopathy: National Heart, Lung, and Blood Institute and Office of Rare Diseases (National Institutes of Health) workshop recommendations and review. JAMA. 2000;283:1183–8.
9. Definition Task Force ARDS, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307:2526–33.
10. Bandi VD, Munnur U, Matthay MA. Acute lung injury and acute respiratory distress syndrome in pregnancy. Crit Care Clin. 2004;20:577–607.
11. Lapinsky SE. Pregnancy joins the hit list. Crit Care Med. 2012;40:1679–80.
12. Rush B, Martinka P, Kilb B, et al. Acute respiratory distress syndrome in pregnant women. Obstet Gynecol. 2017;129:530–5.
13. Cole DE, Taylor TL, McCullough DM, et al. Acute respiratory distress syndrome in pregnancy. Crit Care Med. 2005;33:S269–78.
14. Rowe TF. Acute gastric aspiration: prevention and treatment. Semin Perinatol. 1997;21(4):313–9.
15. Kourtis AP, Read JS, Jamieson DJ. Pregnancy and infection. N Engl J Med. 2014;370:2211–8.
16. Cantwell R, Clutton-Brock T, Cooper G, et al. The eighth report on confidential enquiries into maternal deaths in the United Kingdom. BJOG. 2011;118(S1):1–203.
17. Abenhaim HA, Azoulay L, Kramer MS, et al. Incidence and risk factors of amniotic fluid embolisms: a population-based study on 3 million births in the United States. Am J Obstet Gynecol. 2008;199:49e1–8.
18. Clark SL, Hankins GD, Dudley DA, et al. Amniotic fluid embolism: analysis of the national registry. Am J Obstet Gynecol. 1995;172:1158–69.
19. Priddy KD. Immunologic adaptations during pregnancy. JOGNN. 1997;26:388–94.
20. Rodrigues J, Neiderman MS. Pneumonia complicating pregnancy. Am J Obstet Gynecol. 1992;13:678–92.
21. Lim WS, Macfarlane JT, Colthorpe CL. Pneumonia and pregnancy. Thorax. 2001;56:398–405.
22. Mosby LG, Rasmussen SA, Jamieson DJ. 2009 pandemic influenza A (H1N1) in pregnancy: a systematic review of the literature. Am J Obstet Gynecol. 2011;205:10–8.
23. Lapinsky SE. Critical illness as a result of influenza a/H1N1 infection in pregnancy. BMJ. 2010;340:c1235.
24. Zhang HJ, Patenaude V, Abenhaim HA. Maternal outcomes in pregnancies affected by varicella zoster virus infections: population-based study on 7.7 million pregnancy admissions. J Obstet Gynaecol Res. 2015;4:62–8.
25. Bercovitch RS, Catanzaro A, Schwartz BS, et al. Coccidioidomycosis during pregnancy: a review and recommendations for management. Clin Infect Dis. 2011;53:363–8.
26. Kwon HL, Triche EW, Belanger K, Bracken MB. The epidemiology of asthma during pregnancy: prevalence, diagnosis, and symptoms. Immunol Allergy Clin N Am. 2006;26:29–62.
27. Stenius-Aarniala B, Piirilä P, Teramo K. Asthma and pregnancy: a prospective study of 198 pregnancies. Thorax. 1988;43:12–8.
28. Elsayegh D, Shapiro JM. Management of the obstetric patient with status asthmaticus. J Intensive Care Med. 2008;23:396–402.
29. Miller MA, Chaloub M, Bourjeily G. Peripartum pulmonary embolism. Clin Chest Med. 2011;32:147–64.
30. Clark SL, Belfort MA, Dildy GA, et al. Maternal death in the 21st century: causes, prevention, and relationship to cesarean delivery. Am J Obstet Gynecol. 2008;199:36e1–5.
31. Leung AN, Bull TM, Jaeschke R, et al. An official American Thoracic Society/Society of Thoracic Radiology clinical practice guideline: evaluation of suspected pulmonary embolism in pregnancy. Am J Respir Crit Care Med. 2011;184:1200–8.
32. Pahade JK, Litmanovich D, Pedrosa I, et al. Quality initiatives: imaging pregnant patients with suspected pulmonary embolism: what the radiologist needs to know. Radiographics. 2009;29:639–54.
33. Freymond N, Cottin V, Cordier JF. Infiltrative lung diseases in pregnancy. Clin Chest Med. 2011;32(1):133–46.
34. Boggess KA, Easterling TR, Raghu G. Management and outcome of pregnant women with interstitial and restrictive lung disease. Am J Obstet Gynecol. 1995;173:1007–14.
35. Lapinsky SE, Tram C, Mehta S, et al. Restrictive lung disease in pregnancy. Chest. 2014;145:394–8.
36. Patel EM, Swamy GK, Heine RP, et al. Medical and obstetric complications among pregnant women with cystic fibrosis. Am J Obstet Gynecol. 2015;212:98e1–9.
37. Aoyama K, Seaward PG, Lapinsky SE. Fetal outcome in the critically ill pregnant woman. Crit Care. 2014;18:307.

38. Meschia G. Fetal oxygenation and maternal ventilation. Clin Chest Med. 2011;32:15–9.
39. Polvi HJ, Pirhonen JP, Erkkola RU. The hemodynamic effects of maternal hypo- and hyperoxygenation in healthy term pregnancies. Obstet Gynecol. 1995;86:795–9.
40. Stub D, Smith K, Bernard S, et al. Air versus oxygen in ST-segment-elevation myocardial infarction. Circulation. 2015;131:2143–50.
41. Girardis M, Busani S, Damiani E, et al. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: the oxygen-ICU randomized clinical trial. JAMA. 2016;316:1583–9.
42. Buss DD, Bisgard GE, Rawlings CA, Rankin JH. Uteroplacental blood flow during alkalosis in the sheep. Am J Phys. 1975;228:1497–500.
43. Peng AT, Blancato LS, Motoyama EK. Effect of maternal hypocapnia v. eucapnia on the foetus during caesarean section. Br J Anaesth. 1972;44:1173–8.
44. Ivankovic AD, Elam JO, Huffman J. Effect of maternal hypercarbia on the newborn infant. Am J Obstet Gynecol. 1970;107:939–46.
45. Al-Ansari MA, Hameed AA, Al-Jawder SE, et al. Use of noninvasive positive pressure ventilation in pregnancy: case series. Ann Thorac Med. 2007;2:23–5.
46. Allred CC, Matías Esquinas A, Caronia J, et al. Successful use of noninvasive ventilation in pregnancy. Eur Respir Rev. 2014;23:142–4.
47. Zhang PJ, Li XL, Cao B, et al. Clinical features and risk factors for severe and critical pregnant women with 2009 pandemic H1N1 influenza infection in China. BMC Infect Dis. 2012;12:29.
48. Frassanito L, Draisci G, Pinto R, et al. Successful application of helmet non-invasive ventilation in a parturient with acute respiratory distress syndrome. Minerva Anestesiol. 2011;77:1121–3.
49. Pollock WE, Bellomo R, Webb S, et al. Provision of mechanical ventilation to pregnant/postpartum women with H1N1 influenza: a case-control study. Aust Crit Care. 2013;26:83.
50. Hirani A, Marik PE, Plante LA. Airway pressure-release ventilation in pregnant patients with acute respiratory distress syndrome: a novel strategy. Respir Care. 2009;54:1405–8.
51. Folk JJ, Landsberg DM, Robinson KA, Spector LA. Airway pressure release ventilation and respiratory failure during pregnancy. A report of three cases. J Reprod Med. 2015;60(1–2):65–70.
52. Acute Respiratory Distress Syndrome NetworkBrower RG, Matthay MA, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342:1301–8.
53. Fan E, Del Sorbo L, Goligher EC, et al. An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. Am J Respir Crit Care Med. 2017;195(9):1253–63.
54. Serpa Neto A, Cardoso SO, Manetta JA, et al. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: a meta-analysis. JAMA. 2012;308(16):1651–9.
55. LoMauro A, Aliverti A. Respiratory physiology of pregnancy: physiology masterclass. Breathe. 2015;11:297–301.
56. Talab HF, Zabani IA, Abdelrahman HS, et al. Intraoperative ventilatory strategies for prevention of pulmonary atelectasis in obese patients undergoing laparoscopic bariatric surgery. Anesth Analg. 2009;109:1511–6.
57. Ranieri VM, Brienza N, Santostasi S, et al. Impairment of lung and chest wall mechanics in patients with acute respiratory distress syndrome: role of abdominal distension. Am J Respir Crit Care Med. 1997;156:1082–91.
58. Akoumianaki E, Maggiore SM, Valenza F, et al. The application of esophageal pressure measurement in patients with respiratory failure. Am J Respir Crit Care Med. 2014;189:520–31.
59. Talmor D, Sarge T, Malhotra A, et al. Mechanical ventilation guided by esophageal pressure in acute lung injury. N Engl J Med. 2008;359:2095–104.
60. Samanta S, Samanta S, Wig J, Baronia AK. How safe is the prone position in acute respiratory distress syndrome at late pregnancy? Am J Emerg Med. 2014;32:687e1–3.
61. Robinson JN, Banerjee R, Landzberg MJ, Thiet MP. Inhaled nitric oxide therapy in pregnancy complicated by pulmonary hypertension. Am J Obstet Gynecol. 1999;180:1045–6.
62. Netteburg D, Bsat F, Healy A, et al. The use of high-frequency oscillatory ventilation in a patient with H1N1 pneumonia. J Matern Fetal Neonatal Med. 2011;24:264–6.
63. Reina R, Montefiore P, Lambert F, et al. Critically ill pregnant/postpartum patients with acute respiratory failure due to H1N1 2009 influenza infection: characteristics and outcome [abstract]. Am J Respir Crit Care Med. 2010;181:A6116.
64. Alhazzani W, Alshahrani M, Jaeschke R, et al. Neuromuscular blocking agents in acute respiratory distress syndrome: a systematic review and meta-analysis of randomized controlled trials. Crit Care. 2013;17(2):R43.
65. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med. 2010;363:1107–16.
66. Guay J, Grenier Y, Varin F. Clinical pharmacokinetics of neuromuscular relaxants in pregnancy. Clin Pharmacokinet. 1998;34:483.

67. Guérin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013;368:2159–68.
68. Nakai Y, Mine M, Nishio J, et al. Effects of maternal prone position on the umbilical arterial flow. Acta Obstet Gynecol Scand. 1998;77:967–9.
69. Kenn S, Weber-Carstens S, Weizsaecker K, Bercker S. Prone positioning for ARDS following blunt chest trauma in late pregnancy. Int J Obstet Anesth. 2009;18:268–71.
70. Brown CM. Severe influenza a virus (H1N1) infection in pregnancy. Obstet Gynecol. 2010;115:412–4.
71. Ellington SR, Hartman LK, Acosta M, et al. Pandemic 2009 influenza a (H1N1) in 71 critically ill pregnant women in California. Am J Obstet Gynecol. 2011;204:S21–30.
72. Young D, Lamb SE, Shah S, et al. High-frequency oscillation for acute respiratory distress syndrome. N Engl J Med. 2013;368:806–13.
73. Ferguson ND, Cook DJ, Guyatt GH, et al. High-frequency oscillation in early acute respiratory distress syndrome. N Engl J Med. 2013;368:795–805.
74. Karam O, Gebistorf F, Wetterslev J, Afshari A. The effect of inhaled nitric oxide in acute respiratory distress syndrome in children and adults: a Cochrane systematic review with trial sequential analysis. Anaesthesia. 2017;72:106–17.
75. Meade MO, Young D, Hanna S, et al. Severity of hypoxemia and effect of high frequency oscillatory ventilation in ARDS. Am J Respir Crit Care Med. 2017;196:727. Epub ahead of print
76. Nair P, Davies AR, Beca J, et al. Extracorporeal membrane oxygenation for severe ARDS in pregnant and postpartum women during the 2009 H1N1 pandemic. Intensive Care Med. 2011;37:648–54.
77. Saad AF, Rahman M, Maybauer DM, et al. Extracorporeal membrane oxygenation in pregnant and postpartum women with H1N1-related acute respiratory distress syndrome: a systematic review and meta-analysis. Obstet Gynecol. 2016;127:241–7.
78. Daily WH, Katz AR, Tonnesen A, et al. Beneficial effect of delivery in a patient with adult respiratory distress syndrome. Anesthesiology. 1990;72:383–6.
79. Tomlinson MW, Caruthers TJ, Whitty JE, et al. Does delivery improve maternal condition in the respiratory-compromised gravida? Obstet Gynecol. 1998;91:108–11.
80. Mabie WC, Barton JR, Sibai BM. Adult respiratory distress syndrome in pregnancy. Am J Obstet Gynecol. 1992;167:950–7.
81. Lapinsky SE, Rojas-Suarez JA, Crozier TM, et al. Mechanical ventilation in critically-ill pregnant women: a case series. Int J Obstet Anesth. 2015;24:323–8.
82. Hung CY, Hu HC, Chiu LC, et al. Maternal and neonatal outcomes of respiratory failure during pregnancy. J Formos Med Assoc. 117:2017, 413. [Epub ahead of print]
83. Jenkins TM, Troiano NH, Graves CR, et al. Mechanical ventilation in an obstetric population: characteristics and delivery rates. Am J Obstet Gynecol. 2003;188:549–52.
84. American College of Obstetricians and Gynecologists' Committee on Obstetric Practice. Committee opinion no. 656: guidelines for diagnostic imaging during pregnancy and lactation. Obstet Gynecol. 2016;127:e75–80.
85. Ganapathy A, Adhikari NK, Spiegelman J, Scales DC. Routine chest x-rays in intensive care units: a systematic review and meta-analysis. Crit Care. 2012;16:R68.
86. Tirada N, Dreizin D, Khati NJ, et al. Imaging pregnant and lactating patients. Radiographics. 2015;35:1751–65.
87. Frankel HL, Kirkpatrick AW, Elbarbary M, et al. Guidelines for the appropriate use of bedside general and cardiac ultrasonography in the evaluation of critically ill patients-part I: general ultrasonography. Crit Care Med. 2015;43:2479–502.
88. Bly S, Van den Hof MC. Obstetric ultrasound biological effects and safety. J Obstet Gynaecol Can. 2005;27:572–80.
89. Briggs GG, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th ed. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins Health; 2015.
90. Wikner BN, Stiller CO, Bergman U, et al. Use of benzodiazepines and benzodiazepine receptor agonists during pregnancy: neonatal outcome and congenital malformations. Pharmacoepidemiol Drug Saf. 2007;16:1203–10.
91. Enato E, Moretti M, Koren G. The fetal safety of benzodiazepines: an updated meta-analysis. J Obstet Gynaecol Can. 2011;33:46–8.
92. McElhatton PR. The effects of benzodiazepine use during pregnancy and lactation. Reprod Toxicol. 1994;8:461–75.
93. Hilton G, Andrzejowski JC. Prolonged propofol infusions in pregnant neurosurgical patients. J Neurosurg Anesthesiol. 2007;19:67–8.
94. Duan M, Lee J, Bittner EA. Dexmedetomidine for sedation in the parturient with respiratory failure requiring noninvasive ventilation. Respir Care. 2012;57:1967–9.
95. Yu M, Han C, Jiang X, et al. Effect and placental transfer of dexmedetomidine during caesarean section under general anaesthesia. Basic Clin Pharmacol Toxicol. 2015;117:204–8.
96. Federal Drug Agency (2016) FDA Drug Safety Communication: FDA review results in new warnings about using general anesthetics and sedation drugs in young children and pregnant women. https://www.fda.gov/drugs/drugsafety/ucm532356.htm. Accessed June 12, 2017.
97. Ward SJ, Rocke DA. Neuromuscular blocking drugs in pregnancy and the puerperium. Int J Obstet Anesth. 1998;7:251–60.

98. Gavand Y, Krausz-Grignard M, Barrucand B, et al. Anaesthesia for caesarean section in a pregnant woman with cor triatriatum. Ann Fr Anesth Reanim. 2011;30:688–91.
99. Jago RH. Arthrogryposis following treatment of maternal tetanus with muscle relaxants. Arch Dis Child. 1970;45:277–9.
100. Eisenberg VH, Eidelman LA, Arbel R, Ezra Y. Legionnaire's disease during pregnancy: a case presentation and review of the literature. Eur J Obstet Gynecol Reprod Biol. 1997;72:15–8.
101. Yoshida A, Itoh Y, Nagaya K, et al. Prolonged relaxant effects of vecuronium in patients with deliberate hypermagnesemia: time for caution in cesarean section. J Anesth. 2006;20:33–5.
102. Rojas-Suarez J, Dueaas C, Paternina A, et al. Clinical characteristics and outcomes of obstetric patients requiring mechanical ventilation in Colombia. Chest. 2012;142(4):S787.

Part VI

The Neuromuscular System

Brain Function Monitoring of Critically Ill Pregnant Patients

24

Evgeni Brotfain, Alexander Zlotnik, and Moti Klein

Bullet Points

- The human brain undergoes unique anatomical changes during pregnancy.
- The cerebral blood flow increases up to 22% during the pregnancy.
- Recent studies demonstrated neuroprotective effects of estrogen and progesterone, especially in traumatic brain injury setup.
- Two categories of pregnant patients may require neuromonitoring in ICU: those with typical obstetric disorders and those with common neurological injuries.
- The clinical examination is a cornerstone component of neuromonitoring in the ICU.
- The main aim of invasive ICP monitoring is to keep the ICP lower than 20 mmHg.
- O3 regional oximetry is a new noninvasive method for assessing cerebral tissue oxygenation in the ICU.
- MRI brain has the advantage over CT of not requiring ionizing radiation.
- Ultrasound is an accurate, noninvasive tool for assessment of pupil size and optic nerve diameter.
- Repeated EEG assessment has to be done for differential diagnosis of epilepsy or exclusion of nonconvulsive status in pregnant patients.

24.1 Physiologic Changes in Brain Function during Pregnancy

The central nervous system (CNS) undergoes significant changes during pregnancy [1]. Using volumetric magnetic resonance imaging (MRI), Oatridgea et al. [2] showed that the brain decreases in size during pregnancy while no significant change occurs in the size of the ventricles. The pituitary gland increases in size during pregnancy [3], and the volume of the epidural space decreases [2, 3]. The decrease in epidural space was until recently thought to be caused by engorgement of the epidural venous plexus secondary to aortocaval compression by the large gravid uterus [2, 3]. However, a more recent report has shown that the epidural space volume decreases as early as the eighth to 12th week of pregnancy [4, 5]. A small gravid uterus is not

E. Brotfain (✉) · A. Zlotnik · M. Klein
Department of Anesthesiology and Critical Care, Soroka Medical Center, Ben-Gurion University of the Negev, Beer-Sheva, Israel
e-mail: evgenibr@clalit.org.il; alexander.zlotnik.71@gmail.com

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_24

expected to cause mechanical obstruction, suggesting that other factors may be responsible for this phenomenon. Among these have been proposed the compensated respiratory alkalosis of pregnancy, the decrease in plasma and cerebrospinal fluid protein levels during pregnancy, and the influence of circulating pregnancy hormones [4, 5]. Of note, intracranial pressure (ICP) remains within the physiologic range throughout pregnancy [5].

24.1.1 Cerebral Blood Flow (CBF)

The brain undergoes a dramatic increase in blood flow during pregnancy, culminating in a 22% increase in cerebral blood flow (CBF) in the third trimester of pregnancy compared to the nonpregnant state [5]. Nevo et al. [6] demonstrated a decrease in cerebrovascular resistance (CVR) during pregnancy which was inversely proportional to the increase in the CBF. The decrease in CVR and the resultant increase in CBF may be due to intracerebral vasodilation induced by estrogen [6, 7]. In normotensive adults, CBF approximates 50 mL/100 g/min, provided that cerebral perfusion pressure remains between 60 and 160 mmHg [8]. Above and below these limits, CBF becomes linearly dependent on perfusion pressure. Cerebral autoregulation appears to remain intact during normal pregnancy (based on assessments made using the transient hyperemic response test and trans-cranial Doppler) [9]. Of note, the subarachnoid pial arteries, which are important contributors to the CVR [10, 11], undergo very little structural and functional change during pregnancy [5].

24.2 The Neuroprotective Role of Estrogen and Progesterone

Research during the past three decades has provided increasing evidence that estrogen and progesterone are neuroactive hormones and that they exert significant neuroprotective effects [12]. Epidemiological studies have found sex differences in the incidence of a wide range of unrelated neurological and psychiatric disorders, and it has been suggested that among other factors, estrogen and progesterone may contribute to these differences [13]. Studies on laboratory animals receiving estrogen after traumatic brain injury (TBI) demonstrated a reduction in brain edema, less disruption of the blood-brain barrier, and an improvement in neuronal survival [14–16]. Studies in humans demonstrate that females have lower mortality rates and better functional outcomes after TBI compared to males, suggesting a possible neuroprotective role of estrogen [17, 18]. Furthermore animal models also show a strong correlation between the degree of reduction in brain edema and plasma progesterone concentrations after severe head injury [19]. These promising laboratory data have already led to a series of randomized clinical trials to assess the effect of progesterone administration in patients suffering from TBI [17–19].

24.3 Brain Function Monitoring in the Intensive Care Unit (ICU)

Adverse cerebral outcomes are a well-recognized complication of a variety of surgical procedures [20]. Despite this, monitoring of cerebral function is not as frequently applied as cardiovascular hemodynamic monitoring and probably remains underutilized.

Clinical examination remains the foundation of neuromonitoring in the ICU [20]. This statement remains true for pregnant women being treated in the ICU. First and foremost is patient level of awareness. However, this assessment must take into account the effect of sedative drugs which can markedly influence neurological responses. The Clinical Practice Guidelines for Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit recommend daily clinical assessment of visual and motor responses to verbal orders and noxious stimuli [21]. Depth of coma can be evaluated using the Glasgow Coma Scale (GCS) [22].

Numerous noninvasive and invasive techniques are available for monitoring cerebral func-

tion. Noninvasive techniques for monitoring the brain include multichannel continuous electroencephalography (EEG); bispectral index (BIS) monitors; O3® regional oximetry; devices for monitoring somatosensory evoked potentials (SSEPs); and serial use of imaging techniques such as trans-cranial Doppler TCD, computerized tomography (CT), magnetic resonance imaging (MRI), and cerebral angiography [20]. The invasive neuromonitoring techniques most commonly used are intracranial pressure (ICP) and jugular venous bulb oxygen saturation (SjO2) monitoring systems.

Invasive monitoring techniques are often unavailable in medical centers that do not provide neurosurgical services. Imaging therefore remains the mainstay of brain monitoring in many ICUs. Regardless, CT is the imaging modality of choice in the initial evaluation of traumatic brain injury or when acute hemorrhage is suspected. It may assist in determining the presence of a mass requiring surgical intervention and in identifying early signs of intracranial hypertension. MRI has excellent spatial resolution. This is particularly useful for patients with traumatic brain injury because it enables identification of pathologic abnormalities that remain undetected or poorly characterized by CT (e.g., traumatic axonal injury, fat embolism to the brain). MRI has the additional advantage of not requiring ionizing radiation [23, 24]. However, while both CT and MRI provide important structural information, neither provides data regarding the severity of functional injury. Both CT and MRI may be used during pregnancy if indicated (see below).

Intracranial pressure is the neurological parameter most frequently monitored invasively in the ICU. It is usually recorded via a ventriculostomy drain or an intraventricular catheter. ICP monitoring is especially useful in patients suffering from severe acute cerebral syndromes (e.g., subarachnoid hemorrhage) and in patients with traumatic brain injury with a GCS score of less than 8 and/or abnormal brain CT findings (e.g., hematoma, contusion, swelling, herniation, or compression of the basal cisterns) [25]. The main aim of ICP monitoring is to forestall a rise of ICP to values greater than 20 mmHg. Such an increase, combined with loss of autoregulation (often seen in cases of subarachnoid hemorrhage or traumatic brain injury), can result in a critical reduction in cerebral perfusion pressure and blood flow, leading to secondary cerebral ischemia [25]. Cerebral perfusion is a function of the mean arterial pressure minus the ICP, thus the importance of maintaining a low ICP value.

Cerebral blood flow can also be accurately measured by cerebral CT, direct angiography, or positron emission tomography (PET). However, these procedures are not only expensive and time consuming but also entail risk; they require that the patient be transported to the imaging suite, the use of contrast agents, and exposure to radiation. Of note, CBF can also be determined indirectly by trans-cranial Doppler (TCD). TCD measures the velocity of blood flow in the cerebral arteries using only an ultrasound probe [26]. This tool may therefore be preferred during pregnancy, providing it yields the required information.

Several methods are available for measuring brain oxygenation. Among these the most commonly used are direct jugular venous bulb oxygen saturation (SjO_2) and brain tissue oxygen ($PbtO_2$) monitoring systems and noninvasive techniques for monitoring cerebral metabolic oxygen saturation [22, 25, 26]. SjO_2 is measured via a catheter placed in the jugular bulb which allows sampling of blood almost exclusively drained from the intracranial circulation [25, 26]. Low cerebral blood flow and the presence of ischemia are both factors that increase oxygen extraction and consequently decrease the SjO_2. Normal SjO_2 values range between 50% and 75% [25, 26]. SjO_2 values that are either too low or too high are associated with a poor outcome [27, 28]. Direct $PbtO_2$ monitoring systems (e.g., the Integra Licox Oxygen Monitoring System) are commonly used in the ICU for assessing cerebral oxygenation. Such systems are incorporated within standard ICP/CPP probe monitors inserted through a burr hole into an area of brain tissue that appears normal on CT (usually the frontal lobe on the side of maximum injury) [29]. The probe can also be used to continuously measure the level of metabolites indicating brain injury (e.g., lactate, pyruvate, and glutamate) and

estimate the pyruvate-to-lactate ratio and to measure the level of intraparenchymal brain glucose [29]. O3® regional oximetry is another method for assessing cerebral tissue oxygenation [30]. This noninvasive technology uses near-infrared spectroscopy (NIRS) to obtain continuous assessment of tissue oxygenation [30].

SSEPs constitute evoked EEG responses to an electrical stimulus typically applied to the median or tibial nerve. The main variable used for prognosis is the cortical response [31–33]. Multichannel continuous scalp SSEP monitoring can fill an important role in the ICU particularly when the nature of the injury or the need for heavy sedation limits the usefulness of the clinical examination for providing information about the acutely injured brain [34]. Importantly, SSEPs are less affected by pharmacological agents or hypothermia than is the EEG. Thus, SSEPs can be measured during long periods of sedation and even hypothermia [31–34]. The use of SSEPs during pregnancy requires no special considerations.

24.4 Brain Function Monitoring in Critically Ill Pregnant Patients

Two categories of pregnant ICU patients may require neuromonitoring: those with typical obstetric disorders (e.g., eclampsia, preeclampsia, intracranial hemorrhage, benign intracranial hypertension) and those with neurological injuries that may also occur in the general population (e.g., severe TBI). The latter often also requires prolonged sedation in the ICU which complicates neuromonitoring [35, 36].

Most pregnant women (50–80%) are admitted to the ICU due to obstetric problems, particularly hemorrhagic or hypertensive disorders [35–37]. Among those admitted with neurological compromise, most require intensive brain function monitoring [38].

Clinical neurological examination remains the mainstay of neuromonitoring during the ICU stay of any pregnant patient. This includes periodic estimation of GCS and pupil size and daily evaluation of focal neurologic deficits [35–39].

Measurement of pupil size by ultrasound is more accurate than visual assessment and is especially advantageous when visual assessment is impossible (e.g., in patients with severe periorbital edema) [35–39]. Furthermore, noninvasive sonographic measurements of optic nerve sheath diameter correlate well with ICP values measured using invasive techniques [40]. An optic nerve diameter greater than 6 mm is strongly associated with an elevated ICP [40].

Radiographic studies indicated for maternal evaluation, including CT of the head, should not be deferred or delayed due to concerns regarding fetal exposure to radiation (see Guidelines for the Management of a Pregnant Trauma Patient [41]). The decision to use any imaging modality should be driven by maternal wellbeing first and foremost. If specific imaging is required to determine optimal maternal management, the wellbeing of the unborn child should not prevent its use, although all possible measures should be taken to protect the fetus during imaging. Both the mother and family should be informed of the risk.

CT has been associated with increased fetal exposure to radiation. The degree of exposure varies depending on the maternal body part being scanned, the gestational age of the fetus, the number and thickness of scanning slices, and the type of imaging equipment. Despite the theoretical potential risk of radiation exposure, studies have shown that the dose of radiation absorbed by the fetus during CT of the head of the mother is negligible [42]. Exposure to radiation after the tenth week of pregnancy tends to produce growth restriction or CNS effects rather than teratogenic changes [39, 40, 43–45].

With regard to MRI, no known adverse have been reported in human fetuses to date [23, 24, 39]. However, the gadolinium-based contrast agents used during MRI may cross the placenta [23, 24, 39]. Animal investigations have demonstrated potential toxic fetal effects, including growth retardation and congenital anomalies following exposure to gadolinium, but the doses studied were 2–7 times higher than those routinely used in human MRI studies [39].

24.5 Brain Monitoring in Specific Pathologic States during Pregnancy (Table 24.1)

24.5.1 Preeclampsia/Eclampsia

Preeclampsia is associated with endothelial dysfunction and increased permeability across the vascular wall, which could possibly contribute to cerebral edema in severe cases [2, 46]. Moreover, it has been proposed that the endothelial dysfunction in preeclampsia may also lead to an increase in maternal CBF, although this remains uncertain [6, 46]. Some studies have documented that preeclampsia is associated with increased cerebral perfusion pressure and that eclampsia is associated with loss of autoregulation of CBF and consequently with cerebral hyperperfusion [6, 46]. Thrombocytopenia is also not infrequent in preeclampsia. Increased cerebral perfusion pressure, hyperperfusion, and thrombocytopenia may all contribute to the increased risk of intracaranial hemorrhage in patients with preeclampsia or eclampsia [11]. The diagnosis of eclampsia is based on the findings of encephalopathy or seizures in late pregnancy or in the postpartum period, combined with typical findings on imaging [11]. Pregnant women presenting with encephalopathy or seizures should undergo brain CT or MRI in order to exclude edema, hemorrhage, or other brain lesions. Women with preeclampsia who are sedated and suffer recurrent seizures or delayed awakening may also require EEG assessment to rule out epilepsy or nonconvulsive status [22, 26].

24.5.2 Intracranial Hemorrhage

The incidence of intracranial hemorrhage during pregnancy ranges from 3.8 to 18.1 per 100,000 deliveries [47, 48]. There are two major causes of intracranial hemorrhage in pregnancy: cerebrovascular disease and arterial-venous malformations [47]. The diagnosis of intracranial or subarachnoid hemorrhage can be verified by CT and lumbar puncture (in that order) [48, 49]. In cases of arterial-venous malformation, cerebral angiography may be required [48, 49].

The Clinical Practice Guidelines for Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit state that daily neurologic assessment and continuous ICP monitoring are the cornerstones of neuromonitoring for pregnant women with intracranial hemorrhage [21]. Insertion of an intraventricular catheter can facilitate both ICP monitoring and intraventricular blood drainage [48, 49]. Daily trans-cranial Doppler studies can assist in ruling out progression of vasospasm [49, 50].

24.5.3 Intracranial Tumors

Intracranial tumors often present with symptoms of increased ICP. Unfortunately, the symptoms of increased ICP (i.e., headache, nausea, vomiting) are similar to those of early normal pregnancy as well as to those of eclampsia and preeclampsia. This similarity may delay diagnosis, potentially affecting maternal care. Neuroimaging should therefore be considered to differentiate between these conditions should questions arise regarding the severity of these symptoms in a pregnant woman. Imaging should not be postponed due to concerns regarding fetal exposure to radiation lest maternal (and thereby fetal) condition deteriorate due to unnecessary deferral of treatment. MRI is the imaging of choice in the first trimester as it involves no exposure to ionizing radiation [51, 52].

The incidence of diagnosis of intracranial tumors during pregnancy has been suggested to be higher than the observed equivalent nonpregnant populations [51]. However, there are no statistics to support this clinical observation. The intracranial tumors most commonly diagnosed in pregnant women are pituitary tumors, meningiomas, gliomas, and metastases from breast cancer [51, 52].

24.5.4 Other Cerebral Disorders in Pregnancy

Benign or idiopathic intracranial hypertension is a rare disorder of unknown etiology most often seen in obese women of reproductive age. Pregnancy and exogenous estrogens may both

Table 24.1 Brain monitoring in specific pathologic states during pregnancy

Device	Preeclampsia/eclampsia	Intracranial hemorrhage	Intracranial tumors	Idiopathic intracranial hypertension	Traumatic brain injury
Multichannel continuous electroencephalography (EEG)/SSEP monitors	Rare, if patient is sedated and nonconvulsive status must be ruled out	Same	Same	No; (daily neurological and ophthalmological assessment preferred)	Yes Especially if patient is heavily sedated and nonconvulsive status must be ruled out
Invasive ICP monitoring (including PbtO2, brain glucose, pyruvate, glutamate, etc.)	No	Frequent use, Some ICP devices also allow continuous CSF drainage	Rare Severe brain edema, Hydrocephalus, secondary intracranial bleeding	No	Yes Please see traumatic Brain Foundation guidelines
Noninvasive brain O3 regional oximetry	Possible, but insufficient human data	Yes Frequent use	Possible, in case of secondary complications (severe brain edema, hydrocephalus, intracranial bleeding)	No	Yes There is not much data comparing between invasive and noninvasive brain oxygen monitoring
Trans-cranial Doppler (TCD)	Yes Frequent	Yes Frequent	Yes Frequent	Optional	Yes Frequent
Bispectral index (BIS) monitor	Yes Frequent use, especially for patients that are heavily sedated and/or paralyzed	Yes Frequent use, especially for patients that are heavily sedated and/or paralyzed	Yes Frequent use, especially for patients that are heavily sedated and/or paralyzed	No Useless	Yes Frequent use, especially for patients that are heavily sedated and/or paralyzed
CT brain	Yes Frequent use For differential diagnosis with other pathological states	Yes Frequent use For differential diagnosis with other pathological states and for follow-up	Yes Frequent use For differential diagnosis with other pathological states and for follow-up	Optional	Yes Frequent use For differential diagnosis with other pathological states and for follow-up
MRI brain	Only if CT is unavailable	Rare	Yes Might be better alternative than CT, especially in small subtentorial tumors and secondary complications	No	Rare Possibly with concomitant spine injury
Angiography	No	Yes, especially when aneurysm rupture is suspected	Rare	No	Rare Provides optimal respolution in most cases of traumatic injury of intra- and extracranial arteries

promote or aggravate idiopathic intracranial hypertension [52]. The signs and symptoms of idiopathic intracranial hypertension and the prognosis of visual outcome following this condition are similar in pregnant and nonpregnant women [53]. The cornerstone of diagnosis and monitoring in idiopathic intracranial hypertension is daily neurological and ophthalmological assessment [52, 53]. If the condition continues to progress, repeated lumbar punctures or continuous spinal fluid drainage for 48 h may improve vision.

24.6 Summary

In summary, neuromonitoring of pregnant women in the ICU should follow convention. Time is of the essence in many neurological conditions. Hence deferral of maternal treatment may ultimately affect maternal, and thereby also fetal, outcome. The presence of the fetus should therefore not deter the clinician from using the required diagnostic modalities or performing the treatment procedures indicated. This holds true regardless of whether the cause of maternal ICU admission is a typical obstetric disorder or a neurological injury incidental to pregnancy.

References

1. Dewhurst's Textbook of Obstetrics & Gynaecology, Chapter 1, Eighth Edition. Keith Edmonds, D. editor. First published: 5 January 2012. https://doi.org/10.1002/9781119979449.
2. Oatridgea A, Holdcroftb A, Saeeda N, Hajnala JV, Puria BK, Fusic L, et al. Changes in brain size during and after pregnancy: study in healthy women and women with preeclampsia. Am J Neuroradiol. 2002;23:19–26.
3. Elster AD, Saunders TG, Vines FS, Chen MY. Size and shape of the pituitary gland during pregnancy and postpartum: measurement with MR imaging. Radiology. 1991;181:531–5.
4. Bromage PR. Continuous lumbar epidural analgesia for obstetrics. Can Med Assoc J. 1961;85:1136.
5. Cipolla MJ. The adaptation of the cerebral circulation to pregnancy: mechanisms and consequences. J Cereb Blood Flow Metab. 2013;1:1–7.
6. Nevo O, Soustiel JF, Thaler I. Maternal cerebral blood flow during normal pregnancy: a cross-sectional study. Am J Obstet Gynecol. 2010;203(33):465–78.
7. Roof RL, Hall ED. Estrogen-related gender difference in survival rate and cortical blood flow after impact-acceleration head injury in rats. J Neurotrauma. 2000;17:1155–69.
8. Agnoli A, Fieschi C, Bozzao L, Battistini N, Prencipe M. Autoregulation of cerebral blood flow: studies during drug-induced hypertension in normal subjects and in patients with cerebral vascular diseases. Circulation. 1968;38:800–12.
9. Sherman RW, Bowie RA, Henfrey MME, Mahajan RP, Bogod D. Cerebral haemodynamics in pregnancy and pre-eclampsia as assessed by transcranial Doppler ultrasonography. Br J Anaesth. 2002;89:687–92.
10. Heistad DD, Marcus ML, Abboud FM. Role of large arteries in regulation of cerebral blood flow in dogs. J Clin Invest. 1978;62:761–8.
11. Bateman BT, Schumacher HC, Bushnell CD, Pile-Spellman J, Simpson LL, Sacco RL, et al. Intracerebral hemorrhage in pregnancy. Frequency, risk factors and outcome. Neurology. 2006;67:424–9.
12. Digre KB, Varner MW, Corbett JJ. Pseudotumor cerebri and pregnancy. Neurology. 1984;34:721–9.
13. Allitt BJ, Johnstone VP, Richards K, Yan EB, Rajan R. Progesterone exacerbates short-term effects of traumatic brain injury on supragranular responses in sensory cortex and over-excites Infragranular responses in the long term. J Neurotrauma. 2016;33:375–89.
14. Arevalo MA, Santos-Galindo M, Bellini MJ, Azcoitia I, Garcia-Segura LM. Actions of estrogens on glial cells: implications for neuroprotection. Biochim Biophys Acta. 2010;1800:1106–12.
15. Brann DW, Dhandapani K, Wakade C, Mahesh VB, Khan MM. Neurotrophic and neuroprotective actions of estrogen: basic mechanisms and clinical implications. Steroids. 2007;72:381–405.
16. Bruce-Keller AJ, Keeling JL, Keller JN, Huang FF, Camondola S, Mattson MP. Antiinflammatory effects of estrogen on microglial activation. Endocrinology. 2000;141:3646–56.
17. Bunting H, Still R, Williams DR, Gravenor M, Austin MW. Evaluation of plasma glutamate levels in normal tension glaucoma. Ophthalmic Res. 2010;43:197–200.
18. Chen J, Lei T, Ritz MF, Mendelowitsch A. Effect of 17 beta-estradiol on the brain damage and metabolic changes in rats. J Tongji Med Univ. 2001;21:62–4. 74
19. Cimarosti H, O'Shea RD, Jones NM, Horn AP, Simao F, Zamin LL a. The effects of estradiol on estrogen receptor and glutamate transporter expression in organotypic hippocampal cultures exposed to oxygen--glucose deprivation. Neurochem Res. 2006;31:483–90.
20. Grocott HP, Davie S. S, C. Fedorow C. monitoring of brain function in anesthesia and intensive care. Curr Opin Anesthesiol. 2010;23:759–64.
21. Barr J, Fraser JL, Puntillo K, Ely EW, Gelinas C, Dasta JF, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013;41:264–306.

22. Stocchetti N, Le Roux P, Vespa P, Oddo M, Citerio G, Andrews PJ, et al. Clinical review: Neuromonitoring—an update. Crit Care. 2013;17:201–13.
23. Maas AI, Hukkelhoven CW, Marshall LF, Steyerberg EW. Prediction of outcome in traumatic brain injury with computed tomographic characteristics: a comparison between the computed tomographic classification and combinations of computed tomographic predictors. Neurosurgery. 2005;57:1173–82.
24. Wijman CA, Mlynash M, Caulfield AF, Hsia AW, Eyngorn I, Bammer R, et al. Prognostic value of brain diffusion-weighted imaging after cardiac arrest. Ann Neurol. 2009;65:394–402.
25. Vidgeon SD, Strong AJ. Multimodal cerebral monitoring in traumatic brain injury. JICS. 2012;2:126–33.
26. Ristic A, Sutter R, Steiner LA. Current neuromonitoring techniques in critical care. J Neuroanaesthesiol Crit Care. 2015;2:97–103.
27. Gupta AK, Hutchinson PJ, Rawi A, Gupta S, Swart M, Kirkpatrick PJ, et al. Measuring brain tissue oxygenation compared with jugular venous oxygen saturation for monitoring cerebral oxygenation after traumatic brain injury. Anesth Analg. 1999;88:549–53.
28. Alten J, Mariscalco MM. Critical appraisal of Perez et al. jugular venous oxygen saturation or arteriovenous difference of lactate content and outcome in children with severe traumatic brain injury. Pediatr Crit Care Med. 2005;6:480–2.
29. Huschak G, Hoell T, Hohaus C. Clinical evaluation of a new multiparameter neuromonitoring device: measurement of brain tissue oxygen, brain temperature, and intracranial pressure. J Neurosurg Anesthesiol. 2009;21:155–60.
30. Kok WF, van Harten AE, Koene BMJA, Mariani MA, Koerts J, Tucha O, et al. A pilot study of cerebral tissue oxygenation and postoperative cognitive dysfunction among patients undergoing coronary artery bypass grafting randomized to surgery with or without cardiopulmonary bypass. Anaesthesia. 2014;69:613–22.
31. Oddo M, Rossetti AO. Predicting neurological outcome after cardiac arrest. Curr Opin Crit Care. 2011;17:254–9.
32. Hakimi K, Kinney G, Kraft G, Micklesen P, Robinson L. Reliability in interpretation of median somatosensory evoked potentials in the setting of coma: factors and implications. Neurocrit Care. 2009;11:353–61.
33. Zandbergen EG, Koelman JH, de Haan RJ, Hijdra A. SSEPs and prognosis in postanoxic coma: only short or also long latency responses. Neurology. 2006;67:583–6.
34. Gan TJ, Glass PS, Windsor A. Bispectral index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. BIS utility study group. Anesthesiology. 1997;87:808–15.
35. Soubra SH, Guntupalli KK. Critical illness in pregnancy: an overview. Crit Care Med. 2005;33:248–55.
36. Karnad DR, Guntupalli KK. Critical illness and pregnancy: review of a global problem. Crit Care Clin. 2004;20:555–76.
37. Orsinia J, Butalaa A, Diaza L, Muzyloa E, Mainardia C, Kastell P. Clinical profile of obstetric patients admitted to the medical-surgical intensive care unit (MSICU) of an Inner-City hospital in New York. J Clin Med Res. 2012;4:314–7.
38. Trikha A, Singh PM. The critically ill obstetric patient—recent concepts. Indian J Anaesth. 2010;54:421–7.
39. Puri A, Khadem P, Ahmed S, Yadav P, Al-Dulaimy K. Imaging of trauma in a pregnant patient. Semin Ultrasound CT MR. 2012;33:37–45.
40. Geeraerts T, Merceron S, Benhamou D, Vigue´ B, Duranteau J. Non-invasive assessment of intracranial pressure using ocular sonography in neurocritical care patients. Intensive Care Med. 2008;34:2062–7.
41. Jain V, Chari R, Maslovitz S, Farine D. Guidelines for the management of a pregnant trauma patient. J Obstet Gynaecol Can. 2015;37:553–71.
42. Ratnapalan S, Bona N, Koren G, Motherisk Team. Ionizing radiation during pregnancy. Can Fam Physician. 2003;49:873–4.
43. Vaizey CJ, Jacobson MJ, Cross FW. Trauma in pregnancy. Br J Surg. 1994;81:1406–15.
44. Brent RL. The effect of embryonic and fetal exposure to x-ray, microwaves, and ultrasound: counseling the pregnant and nonpregnant patient about these risks. Semin Oncol. 1989;16:347–68.
45. Mossman KL, Hill LT. Radiation risks in pregnancy. Obstet Gynecol. 1982;60:237–42.
46. Roberts JM, Taylor RN, Goldfien A. Clinical and biochemical evidence of endothelial cell dysfunction in the pregnancy syndrome preeclampsia. Am J Hypertens. 1991;4:700–8.
47. Tate J, Bushnell C. Pregnancy and stroke risk in women. Women's Health (Lond Engl). 2011;7:363–74.
48. Takahashi JC, Iihara K, Ishii A, Watanabe E, Ikeda T, Miyamoto S. Pregnancy-associated intracranial Hemorrhage: results of a survey of neurosurgical institutes across. Japan J Stroke Cerebrovasc Dis. 2014;23:65–71.
49. Dias MS, Sekhar LN. Intracranial hemorrhage from aneurysms and arteriovenous malformations during pregnancy and puerperium. Neurosurgery. 1990;27:855–65.
50. Ursell MR, Marras CL, Farb R, Rowed DW, Black SE, Perry JR. Recurrent intracranial hemorrhage due to postpartum cerebral angiopathy implications for management. Stroke. 1998;29:1995–8.
51. Lynch JC, Gouvea F, Emmerich JC, Kokinovrachos G, Pereira C, Welling L, et al. Management strategy for brain tumor diagnosed during pregnancy. Br J Neurosurg. 2011;25:225–30.
52. Greenberg H, Deck M, Vikram B. Metastasis to the base of the skull: clinical findings in 43 patients. Neurology. 1981;31:530–7.
53. Baron RH, Kupersmith MJ. Idiopathic intracranial hypertension in pregnancy. J Neurol. 2002;249:1078–81.

Maternal Stroke

25

Eliza Cushman Miller and Lisa Leffert

Bullet Points

- Stroke is a rare complication of pregnancy, but a leading cause of maternal morbidity and mortality, particularly in high-risk populations such as women with preeclampsia.
- The term "stroke" refers to a heterogeneous group of acute cerebrovascular disorders, including arterial ischemic stroke, venous infarction due to cerebral venous thrombosis, and nontraumatic intracerebral and subarachnoid hemorrhage, which vary considerably in their pathophysiology and management.
- The majority of pregnancy-related strokes occur postpartum, often after hospital discharge.
- Any new onset neurological deficit in a pregnant or postpartum woman should trigger activation of a rapid response stroke protocol, which typically includes immediate evaluation by a neurologist, either in person or via telemedicine, and emergent brain imaging within 20–30 min.
- The management of pregnancy-related stroke requires an interdisciplinary approach including neurologists, intensivists, and obstetricians.
- Fibrinolytic therapy with alteplase for acute ischemic stroke may be given in pregnancy after careful interdisciplinary consideration of the relative risks and benefits, and mechanical thrombectomy should be offered to selected patients with large artery occlusions.
- Intracerebral or subarachnoid hemorrhage in pregnant and postpartum patients requires specialized management, either in a neurocritical care unit or in a general critical care unit with close involvement of neurology and neurosurgery consultants.
- Delivery method after stroke should be decided on a case-by-case basis, based on obstetric considerations. Prior stroke does not necessarily preclude vaginal delivery.

E. C. Miller
Department of Neurology, Division of Stroke and Cerebrovascular Disease, Columbia University College of Physicians and Surgeons, New York, NY, USA

L. Leffert (✉)
Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, MA, USA
e-mail: LLEFFERT@mgh.harvard.edu

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_25

- Obstetricians should discuss warning signs for stroke with high-risk patients prior to hospital discharge. The BE-FAST mnemonic (Balance, Eyes, Face, Arm, Speech, Time to call the emergency medical service) can help to recognize stroke symptoms.

25.1 Introduction

Although pregnancy-related stroke is rare, occurring in about 34 per 100,000 deliveries [1], it remains a leading cause of maternal mortality [2]. Certain subpopulations, such as women with preeclampsia, are at considerably higher risk [3, 4]. This chapter provides an overview of pregnancy-related stroke, including epidemiology, stroke symptoms, acute stroke management, and long-term complications.

25.2 Definitions, Epidemiology, and Risk Factors

The term "stroke" encompasses a heterogeneous group of disorders with a wide range of presentations, causes, and treatments. Stroke falls into two broad categories: ischemic stroke, caused by interruption of blood supply to a specific area of the brain or spinal cord, and hemorrhagic stroke, with nontraumatic bleeding into the subarachnoid space, ventricles, or brain parenchyma [5]. Both ischemic and hemorrhagic strokes exhibit a wide range of pathophysiological mechanisms. (Tables 25.1 and 25.2).

Table 25.1 Ischemic stroke mechanisms and risk factors

Mechanism	Risk factors
Cardioembolism	Atrial fibrillation (may be paroxysmal/occult) Patent foramen ovale ("paradoxical" embolism) Amniotic fluid embolism Endocarditis Rheumatic heart disease Congenital heart disease Valvular heart disease Congestive heart failure Cardiomyopathy (including postpartum cardiomyopathy) Cardiac tumors (myxoma, fibroelastoma) Cardiac procedures/surgery
Large artery atherosclerosis (aortic arch, extracranial carotid arteries, intracranial large arteries); may cause artery-to-artery embolus or symptomatic stenosis/thrombosis	Hyperlipidemia Peripheral arterial disease Diabetes
Small vessel disease	Hypertension Hyperlipidemia Diabetes Small vessel arteriopathy
Cryptogenic	Young age Lack of other risk factors
Cervical artery dissection (carotid or vertebral)	Fibromuscular dysplasia Marfan syndrome Connective tissue disorders (Ehlers-Danlos type IV) Trauma (chiropractic adjustment, motor vehicle accident)
Arteritis/vasculitis	Rheumatological/autoimmune disorders Infections (herpesviruses, syphilis, HIV)

Table 25.1 (continued)

Mechanism	Risk factors
Vasospasm (reversible cerebral vasoconstriction syndrome)	Drug use (cocaine, methamphetamines, marijuana, synthetic cannabinoids) Serotonergic or sympathomimetic medications (antidepressants, antiemetics, antipsychotics, vasopressors, stimulants) Postpartum state Migraine Female sex
Venous infarction (cerebral venous sinus thrombosis)	Sickle cell disease Primary hypercoagulable states Connective tissue disorders Postpartum Oral contraceptive use Hormone replacement therapy Malignancy
Moyamoya syndrome/disease	Sickle cell disease Down syndrome Neurofibromatosis type I Idiopathic moyamoya disease (regional variants)
Genetic disorders causing stroke	CADASIL CARASIL Susac syndrome MELAS Fabry disease Sickle cell disease RCVL (cerebroretinal vasculopathy syndrome)

HIV human immunodeficiency virus; *CADASIL* cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, *CARASIL* cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy, *MELAS* mitochondrial encephalopathy with lactic acidosis and stroke-like episodes, *RCVL* retinal vasculopathy with cerebral leukodystrophy

25.2.1 Epidemiology

The incidence of pregnancy-related stroke appears to be rising [6, 7]. Although the effect of pregnancy on stroke risk is most prominently seen in younger women who are less likely to have other stroke risk factors [8–10], older pregnant women are at higher absolute risk of stroke than their younger counterparts [10, 11]. Stroke is a component of many of the leading causes of maternal mortality including cardiovascular disease and preeclampsia [12]. While many young women recover well from pregnancy-associated strokes, mortality may be as high as 13% in some high-risk groups [13]. The majority of pregnancy-associated strokes occur postpartum, often after a woman has been discharged home after delivery [11]. Stroke risk is highest in the first 2 weeks postpartum, but the increased risk extends out to 12 weeks postpartum [14].

25.2.2 Risk Factors

While traditional vascular risk factors such as older age, hypertension, hyperlipidemia, diabetes, heart disease (including atrial fibrillation), and smoking may be present in women with pregnancy-related stroke, many unique pregnancy-related mechanisms such as preeclampsia-related vasculopathy, amniotic fluid embolism, or peripartum cardiomyopathy may occur [15, 16].

Hypertensive disorders of pregnancy: Up to 40–70% of maternal preeclampsia-related deaths are due to stroke, the majority of which are hemorrhagic [12, 17]. Women with hypertensive disorders of pregnancy are at five- to six-fold risk of pregnancy-associated stroke compared with pregnant women without these disorders [7, 18]. Preeclampsia is strongly associated with the vasculopathy known as "reversible cerebral vasoconstriction syndrome" (RCVS), often with

Table 25.2 Hemorrhagic stroke mechanisms and risk factors

Mechanism	Risk factor
Intracerebral (intraparenchymal) hemorrhage	Hypertension Coagulopathy Antithrombotic medications Cerebral amyloid angiopathy (elderly) Preeclampsia/eclampsia Arteriovenous malformation Dural arteriovenous fistula Cavernous malformation Brain tumors or metastases Brain abscess Moyamoya disease or syndrome
Aneurysmal subarachnoid hemorrhage (aSAH)	Female sex Japanese ancestry Smoking Heavy alcohol use Cocaine use First-degree relative with aSAH Autosomal dominant polycystic kidney disease Type IV Ehlers-Danlos syndrome Endocarditis (mycotic aneurysms)
Non-aneurysmal subarachnoid hemorrhage	Reversible cerebral vasoconstriction syndrome Septic emboli Cortical vein thrombosis Perimesencephalic venous bleeding
Spontaneous intraventricular hemorrhage	Hypertension Coagulopathy
Cerebral venous sinus thrombosis with hemorrhage	Sickle cell disease Primary hypercoagulable states Postpartum Oral contraceptive use Hormone replacement therapy Malignancy
Hemorrhagic conversion of arterial ischemic stroke	Uncontrolled hypertension Antithrombotic medication use Embolic infarct

accompanying posterior reversible encephalopathy syndrome (PRES), which can result in both hemorrhagic and ischemic stroke [19–21]. (See below *Reversible cerebral vasoconstriction syndrome and posterior reversible encephalopathy syndrome*.) Having traditional vascular risk factors further increases stroke risk in women with preeclampsia, as do some infections [13, 19].

Hematological disorders: Women with hematological disorders are at higher risk for both thrombotic and hemorrhagic stroke during pregnancy and the postpartum period [22–24]. Sickle cell disease is a risk factor for preeclampsia [25] and for stroke [7]. Women with known antiphospholipid syndrome are often placed on therapeutic anticoagulation during pregnancy to decrease stroke risk, although this approach is controversial [26, 27]. Women with rheumatological disorders such as lupus and connective tissue diseases may also be at increased risk for stroke during pregnancy [28]. Any woman with a stroke during pregnancy without a clearly identifiable cause warrants evaluation for underlying prothrombotic disorders, coagulopathies, or rheumatological disorders.

Heart disease, including congenital heart disease, cardiomyopathy, and valvular disease: Women with congenital and acquired heart disease are at higher lifetime risk for thromboembolic events, including stroke. The causes of this

association are complex; heart disease is usually associated with ischemic stroke, hypertension and underlying vascular lesions are associated with more hemorrhagic strokes, and ischemic heart disease is often accompanied by hypertension. Regardless of cause, such women require a multidisciplinary approach to their obstetric care [29]. Chronic anticoagulation for mechanical heart valves should be continued during pregnancy and postpartum [30, 31]. Although warfarin provides significantly better protection against maternal stroke than low molecular weight heparin or unfractionated heparin, there is a risk of embryological complications if warfarin is given before 12 weeks gestational age. At warfarin doses of less than 5 mg/day, the fetal risks of warfarin and low molecular weight heparin appear to be similar [32]. Evidence does not support the benefit of anticoagulation for stroke prevention in most patients with congestive heart failure [33], although the trials have not included pregnant women. Patent foramen ovale, a condition present in 25% of the population, is associated with cryptogenic stroke particularly when combined with an underlying hypercoagulable state (including pregnancy) [34, 35]. The management of pregnant women with heart disease is discussed further in Chap. 10.

Migraine: A history of migraines has been associated with a 15-fold increased odds of pregnancy-related stroke, increasing the risk of both ischemic stroke and intracerebral hemorrhage [36]. Proposed mechanisms include the association of migraine with vascular risk factors such as obesity, smoking, and hyperlipidemia [36], the increased prevalence of patent foramen ovale among migraineurs [37], and pro-inflammatory responses in migraine contributing to endothelial dysfunction [38]. A pregnant woman should be questioned about history of migraine, particularly with high-risk features (e.g., history of aura or neurological symptoms such as numbness, hemiplegia, or aphasia) to help to establish her risk profile. Migraines typically improve during pregnancy and often recur postpartum due to hormonal shifts [39]. Therefore when headache occurs during pregnancy or in the early postpartum period, the characteristics and context of the headache need to be clearly established. For example, preeclampsia-associated headache may be mistaken for migraines. Sudden onset of severe "thunderclap" headache, headache that worsens in the supine position, or any headache associated with a new neurologic deficit, including visual symptoms, should be urgently evaluated by a neurologist.

Vascular malformations and cerebral aneurysms: Evidence conflicts as to whether the risk of cerebral aneurysm and arteriovenous malformation (AVM) rupture is higher during pregnancy and the puerperium [26, 40–46]. When ruptures do occur during pregnancy, they tend to be in the second and third trimesters [47, 48]. Caution should be exercised in recommending intervention on asymptomatic, unruptured AVMs, as the risks of intervention may outweigh the risks of bleeding [49]. Similarly, risk of aneurysm rupture depends on multiple factors such as size, rate of aneurysm growth, and morphology; decisions should be made on a case-by-case basis in consultation with a vascular neurologist and/or neurosurgeon [50]. Decisions about delivery method for patients with unruptured cerebral aneurysms and AVMs should include interdisciplinary consultation between neurology experts, obstetric providers, and anesthesiologists. In many instances, these women can deliver vaginally, unless otherwise indicated by maternal status or obstetric considerations, without increase in risk of rupture [51]. Neuraxial labor analgesia and anesthesia have been successfully used for vaginal and cesarean deliveries in pregnant women with unresected, partially or fully resected AVMs, or cerebral aneurysms [52, 53].

25.3 Anatomy, Signs, and Symptoms of Stroke

Symptoms of stroke depend on the lesion location, making warning signs challenging for patients and physicians to recognize. Nevertheless, certain common patterns emerge: "anterior circulation" stroke syndromes result from occlusion of the internal carotid artery or its branches and typically affect language, attention,

and motor and/or sensory function. "Posterior circulation" strokes result from occlusion of arteries originating in the vertebrobasilar system and affect vision, balance, sensation, and cranial nerve functions.

Hemorrhagic strokes may also present with focal symptoms and/or signs of global cerebral dysfunction, such as severe headache, nausea/vomiting, blurred vision, confusion, and decreased level of consciousness. Cerebral venous sinus thrombosis (CVST) may present insidiously with gradually worsening headache over several days, progressing to signs or symptoms of increased intracranial pressure (ICP) such as blurred or double vision, stiff neck, nausea and vomiting, and papilledema.

Many women may initially ignore stroke symptoms, particularly in the first days or weeks postpartum when the stress of caring for a newborn can be overwhelming. Obstetricians should discuss warning signs for stroke with patients prior to hospital discharge. The BE-FAST mnemonic (Balance, Eyes, Face, Arm, Speech, Time to call the emergency medical service) can help to recognize stroke symptoms [54]. Women at high risk (e.g., those with preeclampsia) should be monitored for high blood pressure and new neurological symptoms in the early weeks postpartum.

25.4 Management of Acute Stroke

A detailed guide to management of ischemic and hemorrhagic stroke is beyond the scope of this chapter, but some guiding principles apply.

25.4.1 Acute Ischemic Stroke

The management of acute ischemic stroke begins with prompt recognition of symptoms, often the weak point in the "stroke chain of survival." Any sudden onset neurological deficit should trigger activation of a rapid response stroke protocol, often termed a "Code Stroke," including immediate evaluation by a neurologist (either in person or through telemedicine). Emergent computed tomography (CT) or magnetic resonance imaging (MRI) should be obtained, ideally within 20 min of arrival to the hospital or symptom discovery (if the stroke occurs in-house) [55]. After 25 weeks' gestation, the risks to the fetus of radiation from CT are negligible; before this, the slight risks can be discussed with the patient and her family and are generally outweighed by the maternal benefit of rapid diagnosis and treatment. Iodinated contrast may be given in pregnancy, although it confers a theoretical risk of neonatal hypothyroidism; however, again, this risk must be weighed against the risk of catastrophic maternal stroke. MRI without gadolinium contrast is generally considered safe in pregnancy [56], but is more time-consuming and may lead to delays in diagnosis and treatment.

The American Heart Association (AHA) and the American Stroke Association (ASA) recommend consideration of alteplase or thrombectomy in pregnancy or postpartum *when perceived benefits outweigh the risks of bleeding* [55]. In the absence of hemorrhage, fibrinolytic therapy with recombinant tissue plasminogen activase (alteplase) should be considered in all patients (regardless of pregnancy), if the onset of symptoms was within 4.5 h [57–59]. The recommended dose is 0.9 mg/kg up to a maximum of 90 mg, with 10% of the dose given as a bolus over 1 min and the remainder as an infusion over 60 min. There is no evidence of teratogenicity of alteplase at stroke treatment doses in animal studies [59]. Administration of fibrinolytic therapy should not be delayed by waiting for routine laboratory results (other than serum glucose level), electrocardiogram, or additional imaging beyond the initial study to rule out intracerebral hemorrhage, unless there is high suspicion for a coagulopathy or acute cardiac process such as aortic dissection. Women being treated with antiplatelet therapies may be given alteplase, but therapeutic anticoagulation is an absolute contraindication. After treatment with alteplase is initiated, cerebrovascular imaging (usually CT angiography) should be obtained if a large vessel occlusion is suspected. If a large vessel occlusion is identified via CT angiography, women with

acute stroke should be considered for mechanical thrombectomy [60–64]. Decisions regarding fibrinolytic therapy and thrombectomy in pregnant or newly postpartum patients should always be made in consultation with a neurologist, in collaboration with the obstetrician, and if feasible, with the patient, herself. Telemedicine protocols may be used to consult emergently with a neurologist if there is none available on-site [55].

Complications of alteplase include headache, angioedema, and bleeding complications, including systemic bleeding, hemorrhagic conversion of cerebral infarction, or potentially placental hemorrhage. Any neurological deterioration during administration of alteplase should prompt cessation of the infusion and immediate head CT without contrast to assess for bleeding. If intracranial hemorrhage is found, coagulation studies and fibrinogen levels should be obtained, and alteplase should be reversed with cryoprecipitate (10 units over 10–30 min). Additional treatment options include tranexamic acid 1000 mg infused over 10 min or ε-aminocaproic acid (Amicar) 4–5 g over 1 h [55]. Tranexamic acid has been safely administered in pregnancy [65], though Amicar is considered a Pregnancy Category C drug and should only be given if the benefits outweigh the risks.

Recent major surgery (e.g., cesarean delivery) within the prior 14 days is typically a warning category for fibrinolytic therapy use; in some cases, the benefit of alteplase may outweigh the bleeding risk, and the decision to administer it should be made in consultation with the obstetrician. Similarly, recent dural puncture is not an absolute contraindication to fibrinolytics and should be considered on a case-by-case basis [55, 59]. Women with acute pregnancy-related ischemic stroke who received reperfusion therapy either with alteplase or mechanical thrombectomy have been shown to have similarly favorable maternal functional outcomes when compared with nonpregnant women who underwent such treatment [15, 66–78]. Fetal outcome data is sparse, with some early fetal losses that may be related to the underlying disease process itself. Choice of delivery method after ischemic stroke should be based on obstetric indications [79].

25.4.2 Intracerebral Hemorrhage (ICH)

Up to half of pregnancy-related strokes are hemorrhagic, many of which occur postpartum [16, 80]. While these women typically have better outcomes when compared with nonpregnant women with hemorrhagic stroke [16], the mortality rate remains around 10%. ICH accounted for 70% of maternal mortality in women with hypertensive disorders of pregnancy in one study [12]. Early life-threatening complications of ICH include expansion of the hematoma, hydrocephalus, increased intracranial pressure (ICP), and brain herniation. Strategies for preventing rebleeding include blood pressure management [81, 82], reversal of anticoagulant medications, and source control. The clinical significance of additional hemorrhage exceeds the risk of thrombosis even given the prothrombotic state of pregnancy, justifying reversal. After the initial CT identifying the bleed, repeat CT should be obtained within 6 h (or sooner, if neurological exam deteriorates) to assess for hematoma expansion. CT or conventional angiography should be performed to identify vascular lesions amenable to endovascular or neurosurgical intervention [83].

Hydrocephalus due to obstruction of the cerebral ventricular drainage system can develop rapidly. Management of severe hydrocephalus may require placement of an external ventricular drain to relieve increased ICP. Signs of high ICP include severe headache, hyperreflexia, nausea, vomiting, blurred or double vision, and decreased level of consciousness. Management of increased ICP includes elevation of the head of the bed, judicious use of analgesic and anxiolytic medications such as propofol to minimize pain and agitation, hyperosmolar therapy (e.g., with mannitol (1 g/kg), and maintenance of normothermia (including the use of cooling devices when warranted). Mannitol may be given during pregnancy without deleterious fetal effects [84, 85]. Hypertonic saline (30 mL bolus of 23.4% NaCl) is used in life-threatening situations with impending brain herniation, but published data on fetal outcomes are not available. Corticosteroids are not recommended for treatment of cytotoxic

edema and may worsen outcomes in patients with cerebral edema due to ischemic stroke [86] or PRES [87], a common cause of ICH in patients with eclampsia (see *Posterior reversible encephalopathy syndrome*). Central venous catheters should be placed in the subclavian or femoral veins, if feasible, rather than in the internal jugular vein, and the head should be kept midline to help prevent cerebral venous congestion.

Seizures should be aggressively controlled in women with ICH. Electroencephalography should be performed for at least 24 h in any woman who is comatose following a hemorrhagic stroke, as more than half of seizures may be subclinical [88]. Brief use of hyperventilation (goal pCO2 25–35 mmHg) may be employed as a temporizing measure pending emergent surgery, but should not be continued for more than 30 min due to risk of cerebral and placental ischemia from vasoconstriction [89]. Some women may require emergent decompressive craniectomy and clot evacuation.

25.4.3 Subarachnoid Hemorrhage

Subarachnoid hemorrhage (SAH), or bleeding into the space between the brain parenchyma and the arachnoid matter, may occur due to aneurysmal rupture or other mechanisms (see Table 25.2). SAH has been reported in rare cases as a complication associated with dural puncture in obstetric patients [90]. Classically, SAH is heralded by a sudden onset "thunderclap" headache often described by the patient as the "worst headache of my life." The initial management of SAH is similar to that of ICH: blood pressure management, reversal of anticoagulant medications, and source control. Prompt CT angiography or conventional angiography should be performed to assess for a "culprit" aneurysm which may be either clipped or coiled; both procedures have been successfully performed in pregnant women [47]. SAH may be complicated by hydrocephalus, cerebral edema, increased ICP, and delayed cerebral ischemia due to vasospasm [91]. Nimodipine, which is commonly given for neuroprotection as part of post-SAH protocols, is safe during pregnancy [92]. SAH should be managed in a subspecialized neurocritical care unit, if possible.

25.4.4 Cerebral Venous Sinus Thrombosis

Cerebral venous sinus thrombosis (CVST) occurs when a clot arises in the dural sinuses, into which the large cerebral veins drain. As the clot propagates, venous congestion, cerebral edema, increased ICP, infarction, and hemorrhage may develop. Because this condition develops slowly, patients may only present for medical attention when headache pain becomes intolerable or catastrophic bleeding occurs.

Pregnancy or the postpartum state is a common cause of CVST in women, likely due to the associated hypercoagulability, venous stasis, and endothelial damage [93, 94]. There are also rare reports of inadvertent dural puncture during epidural placement that are associated with CVST [95, 96]. Cesarean delivery, preeclampsia, and infections all increase the risk of puerperal CVST [97].

The recommended treatment for CVST is therapeutic anticoagulation. In the case of CVST with concomitant ICH, anticoagulation can still be given, with limited evidence suggesting no associated increased bleeding risk in pregnant and postpartum women [93, 94].

25.4.5 Reversible Cerebral Vasoconstriction Syndrome and Posterior Reversible Encephalopathy Syndrome

RCVS (also known as postpartum angiopathy or Call-Fleming syndrome in the postpartum setting [98]) is a disorder of transient dysregulation of cerebrovascular tone, with poorly understood pathogenesis, but often seen in the setting of sympathetic overactivity [99]. Among the nonpregnant population, it is often associated with use of vasoactive substances, including sympathomimetic medications, recreational drugs including cannabis, and serotonergic medica-

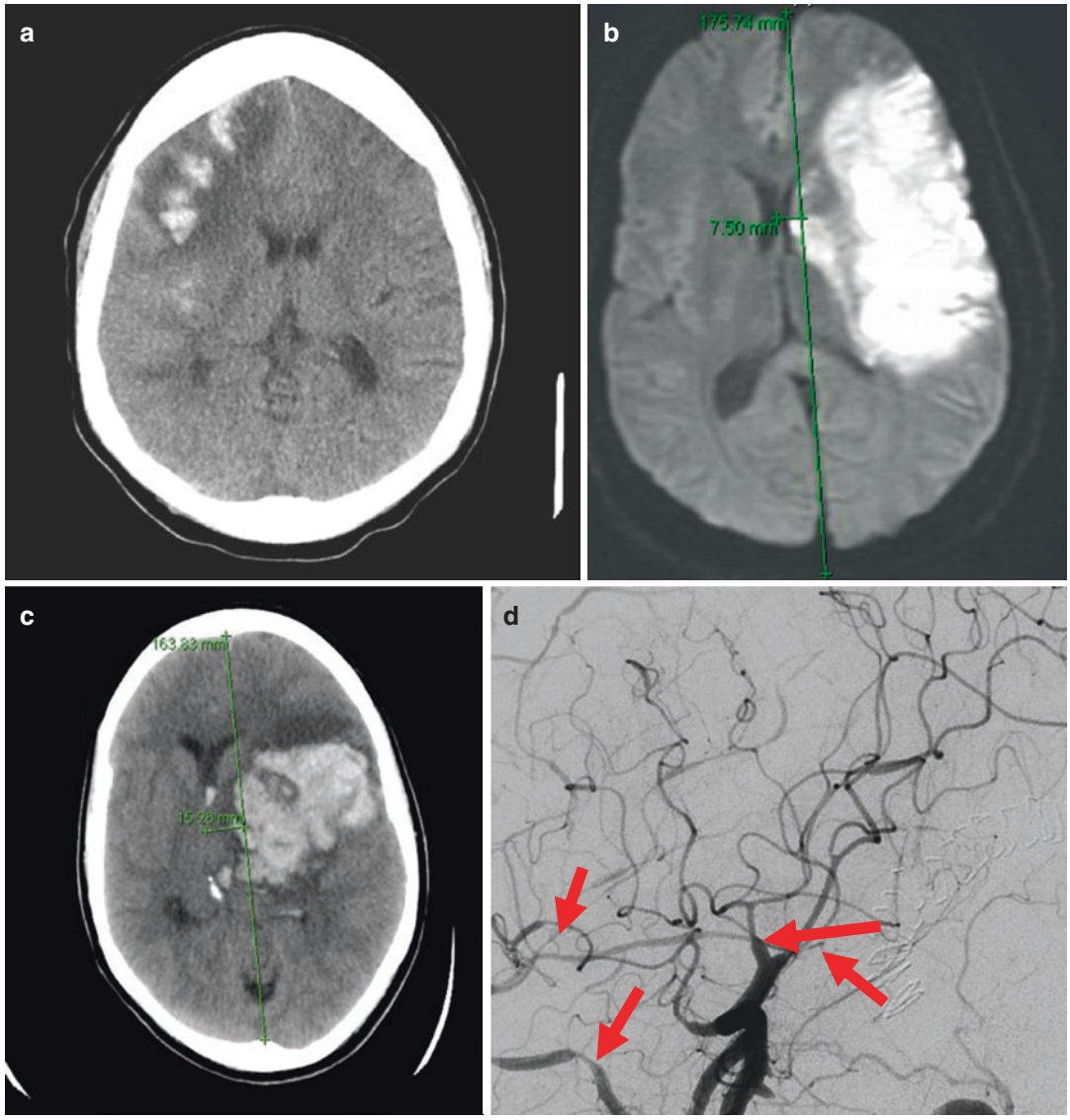


Fig. 25.1 Pregnancy-related stroke. (**a**) Diffusion-weighted magnetic resonance image of left middle cerebral artery acute embolic infarct in a 33-year-old woman, 4 weeks postpartum. Note midline shift due to swelling. (**b**) Computed tomography without contrast enhancement, showing right frontal infarction with hemorrhagic conversion in a young woman with sickle cell disease and preeclampsia, postpartum day 1. (**c**) Computed tomography without contrast enhancement, showing intracerebral hemorrhage on postpartum day 4, after uncomplicated pregnancy. (**d**) Cerebral angiogram demonstrating diffuse vasospasm (red arrows) in the patient from (**c**), due to reversible cerebral vasoconstriction syndrome (postpartum angiopathy). Vasospasm subsequently resolved, but the patient remained neurologically devastated

tions, including antidepressants [99, 100]. Symptoms are thought to be caused by transient vasoconstriction and/or vasodilation of cerebral arteries and typically include recurrent "thunderclap" or sudden onset headaches (reaching peak intensity within 1 min). RCVS ranges in severity from mild to fulminant [101] and can result in ischemic or hemorrhagic strokes, or both (Fig. 25.1) [100–106]. This disorder, which shares features with preeclampsia and with the

Table 25.3 Medications to avoid in reversible cerebral vasoconstriction syndrome (RCVS)

Selective serotonin reuptake inhibitors
Norepinephrine
Phenylephrine
Triptans
Monoamine oxidase inhibitors
Ergot derivatives (bromocriptine, methergine)
Nasal decongestants (phenylephrine or ephedrine based)
Calcineurin inhibitors

posterior reversible encephalopathy syndrome (PRES), has emerged as a prominent cause of pregnancy-related stroke [20, 21, 107–114]. There is no established treatment for pregnancy-related RCVS. Reported therapies include intravenous magnesium, calcium channel blockers such as verapamil or nimodipine, or in refractory cases, interventional therapies such as intraarterial calcium channel blockers or balloon angioplasty [105, 115–121]. Steroids are generally ineffective and may be harmful [122]. Use of sympathomimetic and serotonergic medications should be avoided. (Table 25.3). Transcranial Doppler can be used to monitor for developing vasospasm and may be repeated at regular intervals in the inpatient or outpatient setting during the highest-risk period [123, 124].

Posterior reversible encephalopathy syndrome (PRES), sometimes referred to as reversible posterior leukoencephalopathy syndrome or hypertensive encephalopathy, is a syndrome of subcortical and cortical cerebral edema, often predominantly affecting the parietal and occipital lobes and thus highly associated with visual symptoms. While PRES is not limited to obstetric patients, it is frequently seen in association with RCVS or preeclampsia, often in the postpartum period. Up to 97% of patients with eclampsia [125] and, in one series, up to 20% of patients with preeclampsia and neurological symptoms [126] showed signs of PRES on MRI. Despite its moniker, PRES is not always reversible and not always posterior and can result in devastating complications including status epilepticus, ischemic stroke, intracerebral hemorrhage, and malignant cerebral edema requiring decompressive craniectomy [127, 128]. Preeclampsia-associated PRES should be treated with aggressive blood pressure control, intravenous magnesium, seizure control, and immediate delivery (if occurring antepartum). Mannitol has not been shown to be superior to magnesium in treatment of eclampsia-associated PRES. [84] Steroids may precipitate PRES and should not be used to treat PRES-associated cerebral edema [87].

25.4.6 Blood Pressure Management after Acute Stroke

Acute brain injury (including stroke) results in disruption of cerebral autoregulation, making blood pressure (BP) management of critical importance. BP goals after acute stroke depend on the subtype and mechanism of the stroke. After ischemic stroke, a strategy of "permissive hypertension" is often adopted with the goal of maximizing collateral vessel perfusion to the ischemic penumbra, but this approach is not clearly advantageous [129]. In women with preeclampsia, blood pressure may be controlled after acute ischemic stroke, but patients should be monitored for worsening of neurological deficits, and hypotension should be avoided. Preferred antihypertensive agents include nicardipine and labetalol, both of which are safe during pregnancy and lactation. Some ischemic stroke patients, particularly those with large arterial occlusions, may develop a "pressure-dependent exam": a worsening of neurological function at lower blood pressures with subsequent recovery at higher pressures. This can be tested clinically at the bedside by testing neurological function before and after placing the patient in the Trendelenburg position. Any pressure-dependent stroke patient should be managed in a neurocritical care unit, if possible. If none is available, she should be monitored in an intensive care unit with hourly neurological checks, invasive blood pressure monitoring, and in selected cases, use of pressors to maintain blood pressure goals. After rtPA, BP should be kept under 180/105 mmHg to reduce the risk of hemorrhagic conversion [129]. BP goals are generally lower after ICH and SAH, with the goal of avoiding hematoma expansion or catastrophic

Table 25.4 AHA/ASA recommendations for early poststroke care[a]

Recommendation	Description
Admission to a stroke unit	Patients should be admitted to a specialized stroke unit that incorporates rehabilitation, if possible
Dysphagia screening	Patients should be screened for dysphagia before eating, drinking, or receiving oral medications, to identify patients at higher risk for aspiration events
Aspiration pneumonia precautions	May include instrumental evaluation (i.e., fiberoptic endoscopic evaluation of swallowing, videofluoroscopy, fiberoptic endoscopic evaluation) by a speech-language pathologist; antiseptic mouth care such as chlorhexidine swabs or rinses; early enteral feeding when patient unable to meet nutritional needs due to dysphagia
Oxygen	Supplemental oxygen is recommended to sustain oxygen saturation > 94%, in hypoxic patients only
Urinary catheters	Avoidance of indwelling catheter
Deep vein thrombosis	Intermittent pneumatic compression devices recommended for prophylaxis in all immobile stroke patients; elastic compression stockings not recommended; benefits of routine use of subcutaneous heparin for prophylaxis are uncertain
Mobilization	Physical and occupational therapy evaluation and treatment
Comorbidity management	Prompt treatment of urinary tract infection, congestive heart failure, or acute kidney injury; avoidance of hyperthermia and hyperglycemia
Nutritional supplementation	Identification of malnourished or at-risk patients for supplementation
Depression screening and treatment	Structured screening is recommended although the optimal method and timing is not known; patients with depression should be treated unless contraindications exist

[a]Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. January 2018:STR.0000000000000158. doi:https://doi.org/10.1161/STR.0000000000000158

rebleeding [81, 82, 130]. Women with PRES/RCVS may need lower goals (SBP < 140), but the efficacy of this approach is unknown. BP management after stroke must be balanced with the need for placental perfusion prior to delivery.

25.4.6.1 Early Poststroke Risks and Care

Common poststroke complications include urinary tract infections, aspiration pneumonia, thromboembolic events, pressure ulcers, delirium, and depression. As many are preventable by vigilant protocolized nursing care, the AHA/ASA recommends that all stroke patients be admitted to a specialized stroke unit for early poststroke care [129] (Table 25.4).

25.4.7 Delivery after Antepartum Stroke

Delivery risks in patients with stroke during pregnancy depend on the mechanism, timing, and severity of the stroke. In patients with ICH or SAH related to vascular lesions (e.g., AVM), vaginal delivery appears to be safe so long as the culprit lesion has been treated and the patient does not have signs or symptoms of obstructive hydrocephalus or increased ICP or have obstetric indications for cesarean delivery [52, 131] Peripartum planning by a treating team of obstetricians, neurologists/neurosurgeons, obstetric anesthesiologists, and intensivists should include assessment of whether it is safe and feasible for the woman to push during the second stage of labor and, if not, whether she is a candidate for a low-valsalva and forceps or vacuum assisted delivery with a neuraxial anesthetic. The same is true for women delivering soon after ischemic stroke [132] Cesarean delivery is not necessarily routinely recommended unless the maternal condition precludes a vaginal delivery or there are obstetric indications for a cesarean delivery [133].

The peripartum anesthetic management of these pregnant women follows the same principles as for patients with other intracranial lesions, including multidisciplinary care. Concerns about increased ICP, obstructed ventricles, or other features that might precipitate neurologic deterioration in the setting of general anesthesia or dural

puncture are crucial to decision-making. These women are often appropriate candidates for neuraxial analgesia or anesthesia if not otherwise contraindicated by anticoagulation or antiplatelet agents [134], depressed level of consciousness, or other neurologic concerns [135].

If general anesthesia is warranted, the same basic principles apply for any patient with intracranial lesion, pregnant or not. If there is concern for increased ICP, then consider adding an adjunct (e.g., remifentanil 0.5–1.0 μ/kg) to blunt the response to laryngoscopy. Patients with significant poststroke motor weakness (e.g., hemiparesis) may have altered response to muscle relaxants: a depolarizing relaxant may cause hyperkalemia, and a prolonged block may accompany non-depolarizing muscle relaxant use [136]. In these cases, high-dose remifentanil (e.g., 4 μ/kg) can be substituted for succinylcholine and be paired with an induction agent for rapid sequence induction [137]. The successful use of intracranial pressure-moderating techniques such as mild hyperventilation (keeping maternal paCO2 at approximately 25–30 mmHg) [138] and judicious use of furosemide and mannitol have also been described in pregnant patients with increased ICP [139, 140].

Patients who have suffered strokes may exhibit "recrudescence" of prior neurologic deficits in the setting of hypotension, surgery or anesthetic agents, or other metabolic stressors [141–143]. It is imperative to document a baseline neurological exam in patients with a history of stroke and activate a new "code stroke" should acute neurological changes occur during or after delivery.

25.5 Long-Term Effects of Pregnancy-Associated Stroke

Women who suffer pregnancy-related strokes and their families will have many questions about their prognosis and their future health. Involving a multidisciplinary team of providers to answer these questions can allay the anxiety that naturally follows such an unexpected event.

25.5.1 Recovering from Stroke

Although young patients have better functional outcomes after stroke compared to older patients [144], they often suffer severely diminished quality of life and ability to function after a stroke [145, 146]. Many patients suffer debilitating poststroke fatigue [147], which may affect a young woman's ability to work and care for her family. As depression is a common symptom after stroke [148] and childbirth, these women should be screened for depression at follow-up visits. Some evidence suggests that selective serotonin reuptake inhibitors, which are generally considered safe for breastfeeding, may aid in poststroke motor recovery [149]; however, serotonergic drugs should be avoided in patients with a history of RCVS. Cognitive behavior therapy is also effective for poststroke depression [150]. Modafinil may help severe poststroke fatigue [151]; however, the safety of this drug while pregnant or breastfeeding is unknown. A sleep study can help to diagnose occult obstructive sleep apnea, a common poststroke complication which can cause fatigue and nocturnal hypertension [152]. Support groups for young stroke survivors and their family members may help to mitigate feelings of isolation and depression. Social engagement and return to work, if possible, should be encouraged, as both appear to improve quality-of-life outcomes after stroke [153].

25.5.2 Long-Term Prognosis

There is little evidence to inform the risk of recurrent stroke in future pregnancies. One study found an almost ten-fold relative risk of recurrent stroke during the postpartum period compared to the nonpregnant state and an absolute recurrence rate of stroke during pregnancy or puerperium to be 1.8% at 5 years [154]. The pooled incidence of recurrent CVST in future pregnancies is approximately 8/1000 pregnancies (95% CI 3–22), according to an updated systematic review, and women with previous CVST may benefit from LMWH thromboprophylaxis [155, 156]. The

AHA/ASA does not recommend against future pregnancies in patients with prior stroke and recommends antiplatelet or anticoagulation as indicated based on defined low- or high-risk conditions, respectively [26, 79].

Any woman with a pregnancy-related stroke should be referred to a neurologist who subspecialized in stroke and cerebrovascular disease for follow-up after the acute rehabilitation phase is completed. Women with hypertensive disorders of pregnancy are at higher risk of cardiovascular and cerebrovascular disease later in life [157–167]. Modifiable risk factors such as obesity, hypertension, physical inactivity, tobacco use, poor diet, or substance abuse disorder are all potentially amenable to interventions during this period. Partnering with women to address these risk factors during the recovery period may reap substantial long-term benefits.

Acknowledgments We thank Dr. Joshua Z. Willey (Department of Neurology, Division of Stroke and Cerebrovascular Disease, Columbia University Medical Center) for his assistance in critically reviewing this chapter and Heloise Dubois (Massachusetts General Hospital) for her invaluable help on this project.

References

1. James AH, Bushnell CD, Jamison MG, Myers ER. Incidence and risk factors for stroke in pregnancy and the puerperium. Obstet Gynecol. 2005;106(3):509–16. https://doi.org/10.1097/01.AOG.0000172428.78411.b0.
2. CDC (ed.) *Pregnancy Mortality Surveillance System*. Centers for Disease Control and Prevention: Reproductive Health; 2016. http://www.cdc.gov/reproductivehealth/maternalinfanthealth/pmss.html. Published January 24, 2016. Accessed January 24, 2016.
3. Martin JN, Thigpen BD, Moore RC, Rose CH, Cushman J, May W. Stroke and severe preeclampsia and eclampsia: a paradigm shift focusing on systolic blood pressure. Obstet Gynecol. 2005;105(2):246–54. https://doi.org/10.1097/01.AOG.0000151116.84113.56.
4. Tang C-H, Wu C-S, Lee T-H, et al. Preeclampsia-eclampsia and the risk of stroke among peripartum in Taiwan. Stroke. 2009;40(4):1162–8. https://doi.org/10.1161/STROKEAHA.108.540880.
5. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44(7):2064–89. https://doi.org/10.1161/STR.0b013e318296aeca.
6. Kuklina EV, Tong X, Bansil P, George MG, Callaghan WM. Trends in pregnancy hospitalizations that included a stroke in the United States from 1994 to 2007: reasons for concern? Stroke. 2011;42(9):2564–70. https://doi.org/10.1161/STROKEAHA.110.610592.
7. Leffert LR, Clancy CR, Bateman BT, Bryant AS, Kuklina EV. Hypertensive disorders and pregnancy-related stroke: frequency, trends, risk factors, and outcomes. Obstet Gynecol. 2015;125(1):124–31. https://doi.org/10.1097/AOG.0000000000000590.
8. Kissela BM, Khoury JC, Alwell K, et al. Age at stroke: temporal trends in stroke incidence in a large, biracial population. Neurology. 2012;79(17):1781–7. https://doi.org/10.1212/WNL.0b013e318270401d.
9. Ban L, Sprigg N, Abdul Sultan A, et al. Incidence of first stroke in pregnant and nonpregnant women of childbearing age: A population-based cohort study from England. J Am Heart Assoc. 2017;6(4) https://doi.org/10.1161/JAHA.116.004601.
10. Miller EC, Gatollari HJ, Too G, et al. Risk of pregnancy-associated stroke across age groups in New York state. JAMA Neurol. 2016;73(12):1461–7. https://doi.org/10.1001/jamaneurol.2016.3774.
11. Hovsepian DA, Sriram N, Kamel H, Fink ME, Navi BB. Acute cerebrovascular disease occurring after hospital discharge for labor and delivery. Stroke. 2014;45(7):1947–50. https://doi.org/10.1161/STROKEAHA.114.005129.
12. Hasegawa J, Ikeda T, Sekizawa A, et al. Maternal death due to stroke associated with pregnancy-induced hypertension. Circ J. 2015;79(8):1835–40. https://doi.org/10.1253/circj.CJ-15-0297.
13. Miller EC, Gatollari HJ, Too G, et al. Risk factors for pregnancy-associated stroke in women with Preeclampsia. Stroke. 2017;48(7):1752–9. https://doi.org/10.1161/STROKEAHA.117.017374.
14. Kamel H, Navi BB, Sriram N, Hovsepian DA, Devereux RB, Elkind MSV. Risk of a thrombotic event after the 6-week postpartum period. N Engl J Med. 2014;370(14):1307–15. https://doi.org/10.1056/NEJMoa1311485.
15. Leffert LR, Clancy CR, Bateman BT, et al. Treatment patterns and short-term outcomes in ischemic stroke in pregnancy or postpartum period. Am J Obstet Gynecol. 2016;214(6):723.e1–723.e11. https://doi.org/10.1016/j.ajog.2015.12.016.
16. Leffert LR, Clancy CR, Bateman BT, et al. Patient characteristics and outcomes after Hemorrhagic stroke in pregnancy. Circ Cardiovasc Qual Outcomes. 2015;8(6 suppl 3):S170–8. https://doi.org/10.1161/CIRCOUTCOMES.115.002242.
17. MacKay AP, Berg CJ, Atrash HK. Pregnancy-related mortality from preeclampsia and eclampsia. Obstet Gynecol. 2001;97(4):533–8. http://www.ncbi.nlm.nih.gov/pubmed/11275024

18. Ros HS, Lichtenstein P, Bellocco R, Petersson G, Cnattingius S. Pulmonary embolism and stroke in relation to pregnancy: how can high-risk women be identified? Am J Obstet Gynecol. 2002;186(2):198–203.
19. Miller EC, Yaghi S, Boehme AK, Willey JZ, Elkind MSV, Marshall RS. Mechanisms and outcomes of stroke during pregnancy and the postpartum period: A cross-sectional study. Neurol Clin Pract. 2016;6(1):29–39. https://doi.org/10.1212/CPJ.0000000000000214.
20. Feske SK, Singhal AB. Cerebrovascular disorders complicating pregnancy. Continuum (Minneap Minn). 2014;20(1). Neurology of Pregnancy:80–99. https://doi.org/10.1212/01.CON.0000443838.95260.4b.
21. Razmara A, Bakhadirov K, Batra A, Feske SK. Cerebrovascular complications of pregnancy and the postpartum period. Curr Cardiol Rep. 2014;16(10):532. https://doi.org/10.1007/s11886-014-0532-1.
22. Coriu L, Ungureanu R, Talmaci R, et al. Hereditary thrombophilia and thrombotic events in pregnancy: single-center experience. J Med Life. 2014;7(4):567–71.
23. Chighizola CB, Andreoli L, de Jesus GR, et al. The association between antiphospholipid antibodies and pregnancy morbidity, stroke, myocardial infarction, and deep vein thrombosis: a critical review of the literature. Lupus. 2015;24(9):980–4. https://doi.org/10.1177/0961203315572714.
24. Khan M, Wasay M, Menon B, et al. Pregnancy and puerperium-related strokes in Asian women. J Stroke Cerebrovasc Dis. 2013;22(8):1393–8. https://doi.org/10.1016/j.jstrokecerebrovasdis.2013.04.024.
25. Howard J, Oteng-Ntim E. The obstetric management of sickle cell disease. *Best Practice & Research Clinical Obstetrics & ….* 2012. doi:https://doi.org/10.1016/j.bpobgyn.2011.10.001.
26. Ben-Ami S, Oron G, Ben-Haroush A, Blickstein D, Hod M, Bar J. Primary atherothrombotic occlusive vascular events in premenopausal women with history of adverse pregnancy outcome. Thromb Res. 2010;125(2):124–7. https://doi.org/10.1016/j.thromres.2009.05.017.
27. Legault KJ, Ugarte A, Crowther MA, Ruiz-Irastorza G. Prevention of recurrent thrombosis in Antiphospholipid syndrome: different from the general population? Curr Rheumatol Rep. 2016;18(5):26. https://doi.org/10.1007/s11926-016-0573-0.
28. Arkema EV, Palmsten K, Sjowall C, Svenungsson E, Salmon JE, Simard JF. What to expect when expecting with systemic lupus Erythematosus (SLE): a population-based study of maternal and Fetal outcomes in SLE and pre-SLE. Arthritis Care Res (Hoboken). 2016;68(7):988–94. https://doi.org/10.1002/acr.22791.
29. Canobbio MM, Warnes CA, Aboulhosn J, et al. Management of Pregnancy in patients with complex congenital heart disease: a scientific statement for healthcare professionals from the American Heart Association. Circulation. 2017;135(8):e50–87. https://doi.org/10.1161/CIR.0000000000000458.
30. Chan WS, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. Arch Intern Med. 2000;160(2):191–6.
31. Iturbe-Alessio I, Fonseca MC, Mutchinik O, Santos MA, Zajarias A, Salazar E. Risks of anticoagulant therapy in pregnant women with artificial heart valves. N Engl J Med. 1986;315(22):1390–3. https://doi.org/10.1056/NEJM198611273152205.
32. Steinberg ZL, Dominguez-Islas CP, Otto CM, Stout KK, Krieger EV. Maternal and fetal outcomes of anticoagulation in pregnant women with mechanical heart valves. J Am Coll Cardiol. 2017;69(22):2681–91. https://doi.org/10.1016/j.jacc.2017.03.605.
33. Homma S, Thompson JLP, Pullicino PM, et al. Warfarin and aspirin in patients with heart failure and sinus rhythm. N Engl J Med. 2012;366(20):1859–69. https://doi.org/10.1056/NEJMoa1202299.
34. Chen L, Deng W, Palacios I, et al. Patent foramen ovale (PFO), stroke and pregnancy. J Investig Med. 2016;64(5):992–1000. https://doi.org/10.1136/jim-2016-000103.
35. Miller BR, Strbian D, Sundararajan S. Stroke in the young: patent foramen ovale and pregnancy. Stroke. 2015;46(8):e181–3. https://doi.org/10.1161/STROKEAHA.115.009632.
36. Bushnell CD, Jamison M, James AH. Migraines during pregnancy linked to stroke and vascular diseases: US population based case-control study. BMJ. 2009;338:b664.
37. Ailani J. Migraine and patent foramen Ovale. Curr Neurol Neurosci Rep. 2014;14(2):426. https://doi.org/10.1007/s11910-013-0426-4.
38. Antonova M, Wienecke T, Olesen J, Ashina M. Prostaglandins in migraine. Curr Opin Neurol. 2013;26(3):269–75. https://doi.org/10.1097/WCO.0b013e328360864b.
39. Negro A, Delaruelle Z, Ivanova TA, et al. Headache and pregnancy: a systematic review. J Headache Pain. 2017;18(1):106. https://doi.org/10.1186/s10194-017-0816-0.
40. Bateman BT, Schumacher HC, Bushnell CD, et al. Intracerebral hemorrhage in pregnancy: frequency, risk factors, and outcome. Neurology. 2006;67(3):424–9. https://doi.org/10.1212/01.wnl.0000228277.84760.a2.
41. Kittner SJ, Stern BJ, Feeser BR, et al. Pregnancy and the risk of stroke. N Engl J Med. 1996;335(11):768–74. https://doi.org/10.1056/NEJM199609123351102.
42. Porras JL, Yang W, Philadelphia E, et al. Hemorrhage risk of brain arteriovenous malformations during pregnancy and puerperium in a North American cohort. Stroke. 2017;48(6):1507–13. https://doi.org/10.1161/STROKEAHA.117.016828.
43. Schneider SA, Wilkinson L, Bhatia KP, et al. Abnormal explicit but normal implicit sequence

learning in premanifest and early Huntington's disease. Mov Disord. 2010;25(10):1343–9. https://doi.org/10.1002/mds.22692.
44. Horton JC, Chambers WA, Lyons SL, Adams RD, Kjellberg RN. Pregnancy and the risk of hemorrhage from cerebral arteriovenous malformations. Neurosurgery. 1990;27(6):867–71–discussion871–2.
45. Liu X-J, Wang S, Zhao Y-L, et al. Risk of cerebral arteriovenous malformation rupture during pregnancy and puerperium. Neurology. 2014;82(20):1798–803. https://doi.org/10.1212/WNL.0000000000000436.
46. Gross BA, Du R. Hemorrhage from arteriovenous malformations during pregnancy. Neurosurgery. 2012; https://doi.org/10.1227/NEU.0b013e318256c34b.
47. Kataoka H, Miyoshi T, Neki R, Yoshimatsu J, Ishibashi-Ueda H, Iihara K. Subarachnoid hemorrhage from intracranial aneurysms during pregnancy and the puerperium. Neurol Med Chir (Tokyo). 2013;53(8):549–54.
48. Robba C, Bacigaluppi S, Bragazzi NL, et al. Aneurysmal subarachnoid hemorrhage in pregnancy-case series, review, and pooled data analysis. World Neurosurg. 2016;88:383–98. https://doi.org/10.1016/j.wneu.2015.12.027.
49. Mohr JP, Parides MK, Stapf C, et al. Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial. Lancet. 2014;383(9917):614–21. https://doi.org/10.1016/S0140-6736(13)62302-8.
50. Backes D, Rinkel GJE, Laban KG, Algra A, Vergouwen MDI. Patient- and aneurysm-specific risk factors for intracranial aneurysm growth: a systematic review and meta-analysis. Stroke. 2016;47(4):951–7. https://doi.org/10.1161/STROKEAHA.115.012162.
51. Kim YW, Neal D, Hoh BL. Cerebral aneurysms in pregnancy and delivery: pregnancy and delivery do not increase the risk of aneurysm rupture. Neurosurgery. 2013;72(2):143–9–discussion150. https://doi.org/10.1227/NEU.0b013e3182796af9.
52. Viscomi CM, Wilson J, Bernstein I. Anesthetic management of a parturient with an incompletely resected cerebral arteriovenous malformation. Reg Anesth. 1997;22(2):192–7.
53. Sharma SK, Herrera ER, Sidawi JE, Leveno KJ. The pregnant patient with an intracranial arteriovenous malformation. Cesarean or vaginal delivery using regional or general anesthesia? Reg Anesth. 1995;20(5):455–8.
54. Aroor S, Singh R, Goldstein LB. BE-FAST (balance, eyes, face, arm, speech, time): reducing the proportion of strokes missed using the FAST mnemonic. Stroke. 2017;48(2):479–81. https://doi.org/10.1161/STROKEAHA.116.015169.
55. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2018; https://doi.org/10.1161/STR.0000000000000158.
56. Bove RM, Klein JP. Neuroradiology in women of childbearing age. Continuum (Minneap Minn). 2014;20(1). Neurology of Pregnancy:23–41. https://doi.org/10.1212/01.CON.0000443835.10508.2b.
57. Friedman HS, Koroshetz WJ, Qureshi N. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1996;334:1405.
58. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with Alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008;359(13):1317–29. https://doi.org/10.1056/NEJMoa0804656.
59. Demaerschalk BM, Kleindorfer DO, Adeoye OM, et al. Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2016;47(2):581–641. https://doi.org/10.1161/STR.0000000000000086.
60. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med. 2015;372(24):2285–95. https://doi.org/10.1056/NEJMoa1415061.
61. Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med. 2015;372(24):2296–306. https://doi.org/10.1056/NEJMoa1503780.
62. Campbell BCV, Mitchell PJ, Yan B, et al. A multicenter, randomized, controlled study to investigate EXtending the time for thrombolysis in emergency neurological deficits with intra-arterial therapy (EXTEND-IA). Int J Stroke. 2014;9(1):126–32. https://doi.org/10.1111/ijs.12206.
63. Berkhemer OA, Fransen PSS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015;372(1):11–20. https://doi.org/10.1056/NEJMoa1411587.
64. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015;372(11):1019–30. https://doi.org/10.1056/NEJMoa1414905.
65. Peitsidis P, Kadir RA. Antifibrinolytic therapy with tranexamic acid in pregnancy and postpartum. Expert Opin Pharmacother. 2011;12(4):503–16. https://doi.org/10.1517/14656566.2011.545818.
66. Aaron S, Shyamkumar NK, Alexander S, et al. Mechanical thrombectomy for acute ischemic stroke in pregnancy using the penumbra system. Ann Indian Acad Neurol. 2016;19(2):261–3. https://doi.org/10.4103/0972-2327.173302.
67. Wiese KM, Talkad A, Mathews M, Wang D. Intravenous recombinant tissue plasminogen activator in a pregnant woman with cardioembolic stroke. Stroke. 2006;37(8):2168–9. https://doi.org/10.1161/01.STR.0000230286.95513.c2.
68. Tassi R, Acampa M, Marotta G, et al. Systemic thrombolysis for stroke in pregnancy. Am J

Emerg Med. 2013;31(2):448.e1–3. https://doi.org/10.1016/j.ajem.2012.05.040.
69. Murugappan A, Coplin WM, Al-Sadat AN, et al. Thrombolytic therapy of acute ischemic stroke during pregnancy. Neurology. 2006;66(5):768–70. https://doi.org/10.1212/01.wnl.0000201272.90216.15.
70. Mantoan Ritter L, Schuler A, Gangopadhyay R, et al. Successful thrombolysis of stroke with intravenous alteplase in the third trimester of pregnancy. J Neurol. 2014;261(3):632–4. https://doi.org/10.1007/s00415-014-7286-y.
71. Li Y, Margraf J, Kluck B, Jenny D, Castaldo J. Thrombolytic therapy for ischemic stroke secondary to paradoxical embolism in pregnancy: a case report and literature review. Neurologist. 2012;18(1):44–8. https://doi.org/10.1097/NRL.0b013e31823d7af0.
72. Leonhardt G, Gaul C, Nietsch HH, Buerke M, Schleussner E. Thrombolytic therapy in pregnancy. J Thromb Thrombolysis. 2006;21(3):271–6. https://doi.org/10.1007/s11239-006-5709-z.
73. Johnson DM, Kramer DC, Cohen E, Rochon M, Rosner M, Weinberger J. Thrombolytic therapy for acute stroke in late pregnancy with intra-arterial recombinant tissue plasminogen activator. Stroke. 2005;36(6):e53–5.
74. Hori H, Yamamoto F, Ito Y, Hashimoto Y, Hirano T, Uchino M. Intravenous recombinant tissue plasminogen activator therapy in a 14-week pregnant woman with embolic stroke due to protein S deficiency. Rinsho Shinkeigaku. 2013;53(3):212–6.
75. Elford K, Leader A, Wee R, Stys PK. Stroke in ovarian hyperstimulation syndrome in early pregnancy treated with intra-arterial rt-PA. Neurology. 2002;59(8):1270–2.
76. Dapprich M, Boessenecker W. Fibrinolysis with alteplase in a pregnant woman with stroke. Cerebrovasc Dis. 2002;13(4):290.
77. Boyko M, Iancu D, Lesiuk H, Dowlatshahi D, Shamy MCF. Decision making and the limits of evidence: A case study of acute stroke in pregnancy. Neurohospitalist. 2016;6(2):70–5. https://doi.org/10.1177/1941874415594120.
78. Ritchie J, Lokman M, Panikkar J. Thrombolysis for stroke in pregnancy at 39 weeks gestation with a subsequent normal delivery. BMJ Case Rep. 2015;2015 https://doi.org/10.1136/bcr-2015-209563.
79. Caso V, Falorni A, Bushnell CD, et al. Pregnancy, hormonal treatments for infertility, contraception, and menopause in women after ischemic stroke: A consensus document. Stroke. 2017;48(2):501–6. https://doi.org/10.1161/STROKEAHA.116.013964.
80. Bateman BT, Olbrecht VA, Berman MF, Minehart RD, Schwamm LH, Leffert LR. Peripartum subarachnoid hemorrhage: nationwide data and institutional experience. Anesthesiology. 2012;116(2):324–33. https://doi.org/10.1097/ALN.0b013e3182410b22.
81. Carcel C, Wang X, Sato S, et al. Degree and timing of intensive blood pressure lowering on hematoma growth in intracerebral hemorrhage: intensive blood pressure reduction in acute cerebral hemorrhage Trial-2 results. Stroke. 2016;47(6):1651–3. https://doi.org/10.1161/STROKEAHA.116.013326.
82. Qureshi AI, Palesch YY, Barsan WG, et al. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. N Engl J Med. 2016;375(11):1033–43. https://doi.org/10.1056/NEJMoa1603460.
83. Naidech AM. Diagnosis and management of spontaneous intracerebral hemorrhage. Continuum (Minneap Minn). 2015;21(5). Neurocritical Care:1288–98. https://doi.org/10.1212/CON.0000000000000222.
84. Demir BC, Ozerkan K, Ozbek SE, Yıldırım Eryılmaz N, Ocakoglu G. Comparison of magnesium sulfate and mannitol in treatment of eclamptic women with posterior reversible encephalopathy syndrome. Arch Gynecol Obstet. 2012;286(2):287–93. https://doi.org/10.1007/s00404-012-2268-8.
85. Handlogten KS, Sharpe EE, Brost BC, Parney IF, Pasternak JJ. Dexmedetomidine and Mannitol for awake craniotomy in a pregnant patient. Anesth Analg. 2015;120(5):1099–103. https://doi.org/10.1213/ANE.0000000000000710.
86. Freeman WD. Management of Intracranial Pressure. Continuum: Lifelong Learning in Neurology. 2015;21(5). Neurocritical Care:1299–323.
87. Parikh NS, Schweitzer AD, Young RJ, et al. Corticosteroid therapy and severity of vasogenic edema in posterior reversible encephalopathy syndrome. J Neurol Sci. 2017;380:11–5. https://doi.org/10.1016/j.jns.2017.06.044.
88. Gilmore E, Choi HA, Hirsch LJ, Claassen J. Seizures and CNS hemorrhage: spontaneous intracerebral and aneurysmal subarachnoid hemorrhage. Neurologist. 2010;16(3):165–75.
89. Freeman WD. Management of intracranial pressure. Continuum (Minneap Minn). 2015;21(5). Neurocritical Care:1299–323. https://doi.org/10.1212/CON.0000000000000235.
90. Eggert SM, Eggers KA. Subarachnoid haemorrhage following spinal anaesthesia in an obstetric patient. Br J Anaesth. 2001;86(3):442–4.
91. Suarez JI. Diagnosis and Management of Subarachnoid Hemorrhage. Continuum (Minneap Minn). 2015;21(5). Neurocritical Care:1263–87. https://doi.org/10.1212/CON.0000000000000217.
92. Belfort MA, Anthony J, Saade GR, Allen JCJ. A comparison of magnesium sulfate and nimodipine for the prevention of eclampsia. N Engl J Med. 2003;348(4):304–11.
93. Saposnik G, Barinagarrementeria F, Brown RD, et al. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011;42(4):1158–92. https://doi.org/10.1161/STR.0b013e31820a8364.
94. Coutinho JM, Ferro JM, Canhao P, et al. Cerebral venous and sinus thrombosis in women. Stroke. 2009;40(7):2356–61. https://doi.org/10.1161/STROKEAHA.108.543884.
95. Ghatge S, Uppugonduri S, Kamarzaman Z. Cerebral venous sinus thrombosis following accidental

dural puncture and epidural blood patch. Int J Obstet Anesth. 2008;17(3):267–70. https://doi.org/10.1016/j.ijoa.2008.01.001.
96. Katzin LW, Levine M, Singhal AB. Dural puncture headache, postpartum angiopathy, pre-eclampsia and cortical vein thrombosis after an uncomplicated pregnancy. Cephalalgia. 2007;27(5):461–4. https://doi.org/10.1111/j.1468-2982.2007.01285.x.
97. Lanska DJ, Kryscio RJ. Risk factors for peripartum and postpartum stroke and intracranial venous thrombosis. Stroke. 2000;31(6):1274–82. http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=10835444&retmode=ref&cmd=prlinks
98. Call GK, Fleming MC, Sealfon S, Levine H, Kistler JP, Fisher CM. Reversible cerebral segmental vasoconstriction. Stroke. 1988;19(9):1159–70. https://doi.org/10.1161/01.STR.19.9.1159.
99. Ducros A, Wolff V. The typical thunderclap headache of reversible cerebral vasoconstriction syndrome and its various triggers. Headache. 2016;56(4):657–73. https://doi.org/10.1111/head.12797.
100. Ducros A. Reversible cerebral vasoconstriction syndrome. Lancet Neurol. 2012;11(10):906–17. https://doi.org/10.1016/S1474-4422(12)70135-7.
101. Fugate JE, Wijdicks EFM, Parisi JE, et al. Fulminant postpartum cerebral vasoconstriction syndrome. Arch Neurol. 2012;69(1):111–7. https://doi.org/10.1001/archneurol.2011.811.
102. Singhal AB, Topcuoglu MA, Fok JW, et al. Reversible cerebral vasoconstriction syndromes and primary angiitis of the central nervous system: clinical, imaging, and angiographic comparison. Ann Neurol. 2016;79(6):882–94. https://doi.org/10.1002/ana.24652.
103. Wong SH, Dougan C, Chatterjee K, Fletcher NA, White RP. Recurrent thunderclap headaches and multilobar intracerebral haemorrhages: two cases of reversible cerebral vasoconstriction syndrome (RCVS). Cephalalgia. 2009;29(7):791–5. https://doi.org/10.1111/j.1468-2982.2008.01805.x.
104. Katz BS, Fugate JE, Ameriso SF, et al. Clinical worsening in reversible cerebral vasoconstriction syndrome. JAMA Neurol. 2014;71(1):68. https://doi.org/10.1001/jamaneurol.2013.4639.
105. Ducros A, Fiedler U, Porcher R, Boukobza M, Stapf C, Bousser M-G. Hemorrhagic manifestations of reversible cerebral vasoconstriction syndrome: frequency, features, and risk factors. Stroke. 2010;41(11):2505–11. https://doi.org/10.1161/STROKEAHA.109.572313.
106. Anzola GP, Brighenti R, Cobelli M, et al. Reversible cerebral vasoconstriction syndrome in puerperium: a prospective study. J Neurol Sci. 2017;375:130–6. https://doi.org/10.1016/j.jns.2017.01.056.
107. Hammer ES, Cipolla MJ. Cerebrovascular dysfunction in preeclamptic pregnancies. Curr Hypertens Rep. 2015;17(8):64. https://doi.org/10.1007/s11906-015-0575-8.
108. Ursell MR, Marras CL, Farb R, Rowed DW, Black SE, Perry JR. Recurrent intracranial hemorrhage due to postpartum cerebral angiopathy: implications for management. Stroke. 1998;29(9):1995–8.
109. Cipolla MJ. Cerebrovascular function in pregnancy and eclampsia. Hypertension. 2007;50(1):14–24. https://doi.org/10.1161/HYPERTENSIONAHA.106.079442.
110. Riskin-Mashiah S, Belfort MA, Saade GR, Herd JA. Cerebrovascular reactivity in normal pregnancy and preeclampsia. Obstet Gynecol. 2001;98(5). Pt 1:827–32.
111. Singhal AB. Postpartum angiopathy with reversible posterior leukoencephalopathy. Arch Neurol. 2004;61(3):411–6. https://doi.org/10.1001/archneur.61.3.411.
112. Cipolla MJ, Bishop N, Chan SL. Effect of pregnancy on autoregulation of cerebral blood flow in anterior versus posterior cerebrum. Hypertension. 2012;60(3):705–11. https://doi.org/10.1161/HYPERTENSIONAHA.112.198952.
113. Bushnell C, Chireau M. Preeclampsia and stroke: risks during and after pregnancy. Stroke Res Treat. 2011;2011(12):858134–9. https://doi.org/10.4061/2011/858134.
114. Feske SK. Stroke in pregnancy. Semin Neurol. 2007;27(5):442–52. https://doi.org/10.1055/s-2007-991126.
115. Song JK, Fisher S, Seifert TD, et al. Postpartum cerebral angiopathy: atypical features and treatment with intracranial balloon angioplasty. Neuroradiology. 2004;46(12):1022–6.https://doi.org/10.1007/s00234-003-1129-3.
116. Ducros A, Boukobza M, Porcher R, Sarov M, Valade D, Bousser M-G. The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome. A prospective series of 67 patients. Brain. 2007;130(Pt 12):3091–101. https://doi.org/10.1093/brain/awm256.
117. Chen S-P, Fuh J-L, Lirng J-F, Chang F-C, Wang S-J. Recurrent primary thunderclap headache and benign CNS angiopathy: spectra of the same disorder? Neurology. 2006;67(12):2164–9. https://doi.org/10.1212/01.wnl.0000249115.63436.6d.
118. Chen S-P, Fuh J-L, Wang S-J, et al. Magnetic resonance angiography in reversible cerebral vasoconstriction syndromes. Ann Neurol. 2010;67(5):648–56. https://doi.org/10.1002/ana.21951.
119. Singhal AB, Hajj-Ali RA, Topcuoglu MA, et al. Reversible cerebral vasoconstriction syndromes: analysis of 139 cases. Arch Neurol. 2011;68(8):1005–12. https://doi.org/10.1001/archneurol.2011.68.
120. Linn J, Fesl G, Ottomeyer C, et al. Intra-arterial application of nimodipine in reversible cerebral vasoconstriction syndrome: a diagnostic tool in select cases? Cephalalgia. 2011;31(10):1074–81. https://doi.org/10.1177/0333102410394673.
121. Cappelen-Smith C, Calic Z, Cordato D. Reversible cerebral vasoconstriction syndrome: recognition and

treatment. Curr Treat Options Neurol. 2017;19(6):21. https://doi.org/10.1007/s11940-017-0460-7.
122. Singhal AB, Topcuoglu MA. Glucocorticoid-associated worsening in reversible cerebral vasoconstriction syndrome. Neurology. 2017;88(3):228–36. https://doi.org/10.1212/WNL.0000000000003510.
123. Levin JH, Benavides J, Caddick C, et al. Transcranial Doppler ultrasonography as a non-invasive tool for diagnosis and monitoring of reversible cerebral vasoconstriction syndrome. R I Med J (2013). 2016;99(9):38–41.
124. Marsh EB, Ziai WC, Llinas RH. The need for a rational approach to vasoconstrictive syndromes: Transcranial Doppler and calcium channel blockade in reversible cerebral vasoconstriction syndrome. Case Rep Neurol. 2016;8(2):161–71. https://doi.org/10.1159/000447626.
125. Brewer J, Owens MY, Wallace K, et al. Posterior reversible encephalopathy syndrome in 46 of 47 patients with eclampsia. Am J Obstet Gynecol. 2013;208(6):468.e1–.e6. https://doi.org/10.1016/j.ajog.2013.02.015.
126. Mayama M, Uno K, Tano S, et al. Incidence of posterior reversible encephalopathy syndrome in eclamptic and patients with preeclampsia with neurologic symptoms. Am J Obstet Gynecol. 2016;215(2):239.e1–.e5. https://doi.org/10.1016/j.ajog.2016.02.039.
127. McDermott M, Miller EC, Rundek T, Hurn PD, Bushnell CD. Preeclampsia: association with posterior reversible encephalopathy syndrome and stroke. Stroke. 2018; https://doi.org/10.1161/STROKEAHA.117.018416.
128. Akins PT, Axelrod Y, Silverthorn JW, Guppy K, Banerjee A, Hawk MW. Management and outcomes of malignant posterior reversible encephalopathy syndrome. Clin Neurol Neurosurg. 2014;125:52–7. https://doi.org/10.1016/j.clineuro.2014.06.034.
129. Jauch EC, Saver JL, Adams HP, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44(3):870–947. https://doi.org/10.1161/STR.0b013e318284056a.
130. Mocco J, Rose JC, Komotar RJ, Mayer SA. Blood pressure management in patients with intracerebral and subarachnoid hemorrhage. Neurosurg Clin N Am. 2006;17:25–40. https://doi.org/10.1016/S1042-3680(06)80005-7.
131. Elias M, Abouleish E, Bhandari A. Arteriovenous malformation during pregnancy and labor--case review and management. Middle East J Anaesthesiol. 2001;16(2):231–7.
132. May AE, Fombon FN, Francis S. UK registry of high-risk obstetric anaesthesia: report on neurological disease. Int J Obstet Anesth. 2008;17(1):31–6. https://doi.org/10.1016/j.ijoa.2007.03.016.
133. Sibai BM, Coppage KH. Diagnosis and management of women with stroke during pregnancy/postpartum. Clin Perinatol. 2004;31(4):853–68–viii. https://doi.org/10.1016/j.clp.2004.06.003.
134. Leffert L, Butwick A, Carvalho B, et al. The Society for Obstetric Anesthesia and Perinatology Consensus Statement on the Anesthetic Management of Pregnant and Postpartum Women Receiving Thromboprophylaxis or Higher Dose Anticoagulants. Anesth Analg. 2018;126(3):928-944.
135. Leffert LR, Schwamm LH. Neuraxial anesthesia in parturients with intracranial pathology: a comprehensive review and reassessment of risk. Anesthesiology. 2013;119(3):703–18. https://doi.org/10.1097/ALN.0b013e31829374c2.
136. Cooperman LH. Succinylcholine-induced hyperkalemia in neuromuscular disease. JAMA. 1970;213(11):1867–71.
137. Alexander R, Olufolabi AJ, Booth J, El-Moalem HE, Glass PS. Dosing study of remifentanil and propofol for tracheal intubation without the use of muscle relaxants. Anaesthesia. 1999;54(11):1037–40.
138. Wang LP, Paech MJ. Neuroanesthesia for the pregnant woman. Anesth Analg. 2008;107(1):193–200. https://doi.org/10.1213/ane.0b013e31816c8888.
139. Tuncali B, Aksun M, Katircioglu K, Akkol I, Savaci S. Intraoperative fetal heart rate monitoring during emergency neurosurgery in a parturient. J Anesth. 2006;20(1):40–3. https://doi.org/10.1007/s00540-005-0359-4.
140. Bharti N, Kashyap L, Mohan VK. Anesthetic management of a parturient with cerebellopontine-angle meningioma. Int J Obstet Anesth. 2002;11(3):219–21.
141. Lazar RM, Fitzsimmons B-F, Marshall RS, et al. Reemergence of stroke deficits with midazolam challenge. Stroke. 2002;33(1):283–5.
142. Lazar RM, Fitzsimmons B-F, Marshall RS, Mohr JP, Berman MF. Midazolam challenge reinduces neurological deficits after transient ischemic attack. Stroke. 2003;34(3):794–6. https://doi.org/10.1161/01.STR.0000056540.04159.F3.
143. Lazar RM, Berman MF, Festa JR, Geller AE, Matejovsky TG, Marshall RS. GABAergic but not anti-cholinergic agents re-induce clinical deficits after stroke. J Neurol Sci. 2010;292(1–2):72–6. https://doi.org/10.1016/j.jns.2010.01.024.
144. Bagg S, Pombo AP, Hopman W. Effect of age on functional outcomes after stroke rehabilitation. Stroke. 2002;33(1):179–85.
145. Synhaeve NE, Arntz RM, van Alebeek ME, et al. Women have a poorer very long-term functional outcome after stroke among adults aged 18-50 years: the FUTURE study. J Neurol. 2016;263(6):1099–105. https://doi.org/10.1007/s00415-016-8042-2.
146. Al-Khindi T, MacDonald RL, Schweizer TA. Cognitive and functional outcome after aneurysmal subarachnoid hemorrhage. Stroke. 2010;41(8):e519–36. https://doi.org/10.1161/STROKEAHA.110.581975.
147. Maaijwee NAMM, Arntz RM, Rutten-Jacobs LCA, et al. Post-stroke fatigue and its association with poor functional outcome after stroke in young adults. J Neurol Neurosurg Psychiatry. 2015;86(10):1120–6. https://doi.org/10.1136/jnnp-2014-308784.

148. Kotila M, Numminen H, Waltimo O, Kaste M. Depression after stroke: results of the FINNSTROKE study. Stroke. 1998;29(2):368–72.
149. Chollet F, Tardy J, Albucher J-F, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. Lancet Neurol. 2011;10(2):123–30. https://doi.org/10.1016/S1474-4422(10)70314-8.
150. K Ward S, Turner A, A Hambridge J, et al. Group cognitive behavioural therapy for stroke survivors with depression and their carers. Top Stroke Rehabil. 2016;23(5):358–65. https://doi.org/10.1080/10749357.2016.1143706.
151. Bivard A, Lillicrap T, Krishnamurthy V, et al. MIDAS (Modafinil in debilitating fatigue after stroke): a randomized, double-blind, placebo-controlled, cross-over trial. Stroke. 2017;48(5):1293–8. https://doi.org/10.1161/STROKEAHA.116.016293.
152. Swartz RH, Bayley M, Lanctôt KL, et al. Post-stroke depression, obstructive sleep apnea, and cognitive impairment: rationale for, and barriers to, routine screening. Int J Stroke. 2016;11(5):509–18. https://doi.org/10.1177/1747493016641968.
153. Tse T, Binte Yusoff SZ, Churilov L, et al. Increased work and social engagement is associated with increased stroke specific quality of life in stroke survivors at 3 months and 12 months post-stroke: a longitudinal study of an Australian stroke cohort. Top Stroke Rehabil. 2017;8(3):1–10. https://doi.org/10.1080/10749357.2017.1318339.
154. Lamy C, Hamon JB, Coste J, Mas JL. Ischemic stroke in young women: risk of recurrence during subsequent pregnancies. French Study Group on Stroke in Pregnancy. Neurology. 2000;55(2):269–74.
155. Aguiar de Sousa D, Canhao P, Ferro JM. Safety of pregnancy after cerebral venous thrombosis: a systematic review. Stroke. 2016;47(3):713–8. https://doi.org/10.1161/STROKEAHA.115.011955.
156. Aguiar de Sousa D, Canhao P, Ferro JM. Safety of pregnancy after cerebral venous thrombosis: systematic review update. J Neurol. 2018;265(1):211–2. https://doi.org/10.1007/s00415-017-8666-x.
157. Newstead J, Dadelszen v P, Magee LA. Preeclampsia and future cardiovascular risk. Expert Rev Cardiovasc Ther. 2007;5(2):283–94. https://doi.org/10.1586/14779072.5.2.283.
158. Garovic VD, August P. Preeclampsia and the future risk of hypertension: the pregnant evidence. Curr Hypertens Rep. 2013;15(2):114–21. https://doi.org/10.1007/s11906-013-0329-4.
159. Amaral LM, Cunningham MW, Cornelius DC, LaMarca B. Preeclampsia: long-term consequences for vascular health. Vasc Health Risk Manag. 2015;11:403–15. https://doi.org/10.2147/VHRM.S64798.
160. Tranquilli AL, Landi B, Giannubilo SR, Sibai BM. Preeclampsia: no longer solely a pregnancy disease. Pregnancy Hypertens. 2012;2(4):350–7. https://doi.org/10.1016/j.preghy.2012.05.006.
161. Mounier-Vehier C, Madika A-L, Boudghene-Stambouli F, Ledieu G, Delsart P, Tsatsaris V. Hypertension in pregnancy and future maternal health. Presse Med. 2016;45(7–8 Pt 1):659–66. https://doi.org/10.1016/j.lpm.2016.05.017.
162. Kestenbaum B, Seliger SL, Easterling TR, et al. Cardiovascular and thromboembolic events following hypertensive pregnancy. Am J Kidney Dis. 2003;42(5):982–9.
163. Brown MC, Best KE, Pearce MS, Waugh J, Robson SC, Bell R. Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis. Eur J Epidemiol. 2013;28(1):1–19. https://doi.org/10.1007/s10654-013-9762-6.
164. Murphy MSQ, Smith GN. Pre-eclampsia and cardiovascular disease risk assessment in women. Am J Perinatol. 2016;33(8):723–31. https://doi.org/10.1055/s-0036-1572536.
165. Bellamy L, Casas J-P, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ. 2007;335(7627):974. https://doi.org/10.1136/bmj.39335.385301.BE.
166. Williams D. Long-term complications of preeclampsia. Semin Nephrol. 2011;31(1):111–22. https://doi.org/10.1016/j.semnephrol.2010.10.010.
167. Cheng S-B, Sharma S. Preeclampsia and health risks later in life: an immunological link. Semin Immunopathol. 2016;38(6):699–708. https://doi.org/10.1007/s00281-016-0579-8.

Neurological Crises

26

Chiara Robba, Valeria Spennati, Sharon Einav, and Federico Bilotta

Bullet Points

- Epilepsy in pregnancy should always be considered to be eclampsia unless or until this can be ruled out.
- Eclampsia often presents as epilepsy without other signs of preeclampsia.
- Women with epilepsy may modify or stop treatments due to fetal risk concerns.
- Stopping anti-epileptic drugs is associated with seizures, with severe maternal and fetal morbidity and even mortality, and should be discouraged.
- The most common causes of increasing maternal weakness are intracranial pathology and stroke (discussed in other chapters), magnesium overdose, and myasthenia gravis crisis.
- Myasthenia gravis may improve, worsen, or remain static in pregnancy with no relation to the patient's pre-pregnancy condition.

C. Robba · V. Spennati · F. Bilotta (✉)
Intensive Care Unit, Policlinico San Martino, Genova, Italy

Department of Neuroanaesthesia, University La Sapienza, Rome, Italy
e-mail: bilotta@tiscali.it

S. Einav
Intensive Care Unit, Shaare Zedek Medical Center, Jerusalem, Israel
e-mail: einav_s@szmc.org.il

26.1 Maternal Seizures

Pregnant women previously diagnosed with epilepsy frequently experience seizures during pregnancy. Status epilepticus occurs in 1.8% of pregnant women with epilepsy [1]. Pregnant women may be reluctant to take anti-epileptic drugs (AEDs) due to concerns regarding teratogenicity. All anticonvulsants cross the placenta. Chap. 38 discusses the risks associated with pharmacologic management of pregnant women for convulsions. AED therapy should be continued throughout pregnancy despite potential fetal risks. Patient education is crucial to ensure drug compliance. Any AED changes should be physician-guided [2]. Sudden unexpected death in epilepsy is usually associated with uncontrolled seizures [3].

The effect of maternal seizures on the fetus: Maternal seizures have been associated with an increased risk of low birth weight and preterm delivery [4]. Early case reports from [5], and from 1998 [6], noted fetal heart rate decelerations after maternal generalized tonic-clonic seizures, but these reports did not attribute clinical significance to this finding [5, 6]. There is a possibility that maternal seizures may cause redistribution of placental blood flow and post-ictal hypopnea and hypoxemia. However, later studies have also highlighted the notion that even if transient fetal hypoxia does occur, the clinical effect of hypoxia remains unclear [7, 8]. Non-convulsive seizures are consid-

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_26

ered less dangerous, but one case report [7] documented significant fetal bradycardia during complex partial seizures. Additional rare risks of maternal seizures to the fetus have been reported, including three cases of congenital malformations [9], one case of fetal intracranial hemorrhage [10], and two cases of subsequent fetal death [9, 10].

The differential diagnosis for seizures in pregnant women includes metabolic conditions such as hyponatremia, hypoglycemia, and intracranial pathologies such as space-occupying lesions, sinus vein thrombosis, posterior reversible encephalopathy syndrome, reversible cerebral vasoconstriction syndrome, and cardiac conditions such as arrhythmia, syncope, and Addisonian crisis [3].

Treatment. The first-line treatment for acute convulsion for any reason is management of airway obstruction and avoiding aspiration. Figure 26.1 presents a treatment and diagnostic algorithm for pregnant women with convulsions. Left lateral positioning is simple to implement and promote clearance of secretions as well as stabilization of patient hemodynamics. Airway control is best achieved with expert assistance, given the increased likeli-

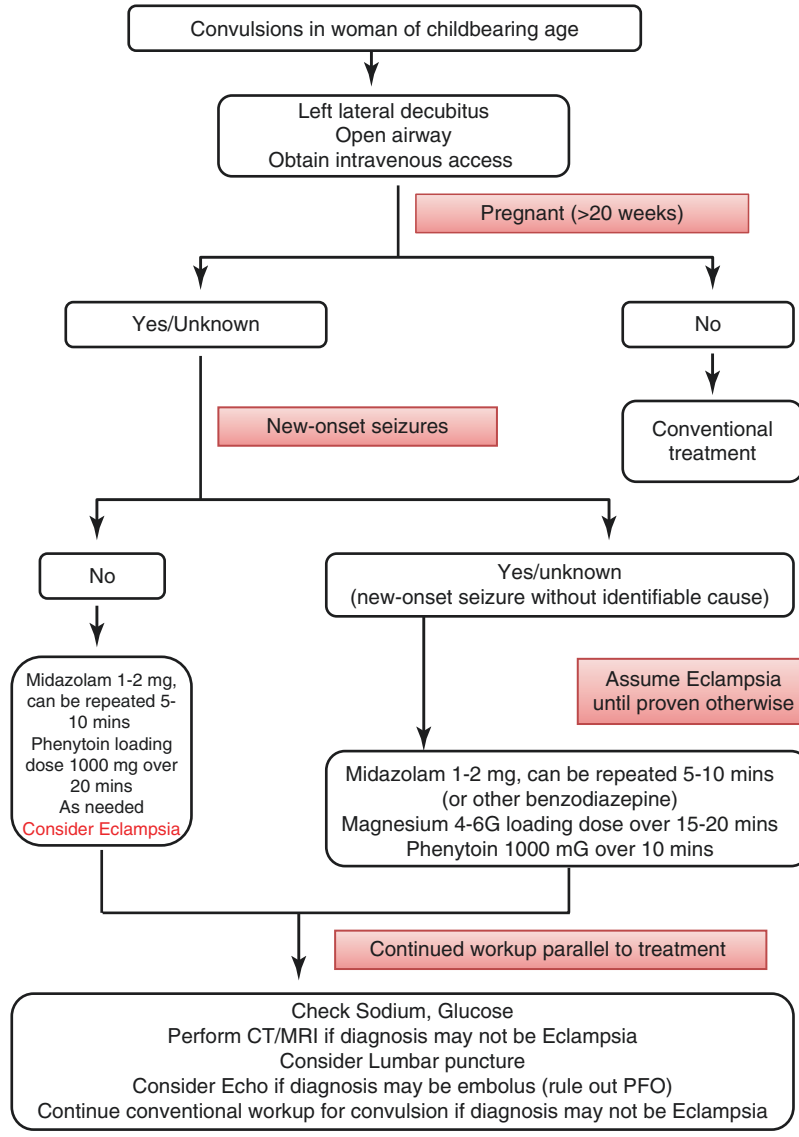


Fig. 26.1 Seizure's algorithm in pregnants

hood for challenging airway management among pregnant women, discussed in further detail in Chap. 21. Treatment with short-acting anticonvulsants should be initiated immediately. Benzodiazepines (preferably midazolam because of its relatively short half-life) are the drugs of choice because of their safety profile when considering maternal airway and breathing and fetal teratogenicity. If the need for intensive neurological examination arises, propofol (1 mg/kg) may be considered, but the potential benefit of using this ultra-short-acting drug must be weighed against the risk of maternal aspiration and loss of airway control.

The California Maternal Quality Care Collaborative (CMQCC) published a safety bundle with recommendations regarding eclampsia management [11].

Seizure-control medications can be administered as follows:

- *Midazolam*—Intravenous boluses 1–2 mg, can be repeated 5–10 min.
- *Lorazepam* 4 mg, can be repeated every 2–5 min.
- *Diazepam* 5–10 mg, can be repeated every 15–30 min.
- *Phenytoin*—Phenytoin loading dose 1000 mg over 20 min.
- *Sodium valproate*—Current advice is that valproate should not be used by women of childbearing potential, much less in the pregnant state, unless other treatments are ineffective or not tolerated [12].

Eclampsia should always be considered in women with seizures of childbearing age.

If relevant, magnesium therapy should be initiated in parallel (see Chap. 16).

Once convulsions have been controlled, vital signs, heart rate, blood pressure, and saturation should be assessed. Oxygen saturation below 92% may be treated with 2–3 L of oxygen administered via nasal cannula. An arterial blood gas should be obtained for assessment of the severity of metabolic derangement incurred by (or causing) the convulsion. Women with elevated lactate levels and/or any evidence of eclampsia should be admitted to a highly monitored environment following appropriate neurological workup, as these women represent a subset of the population more likely to be at risk for continued deterioration or repeat convulsions [13].

The option of an adjunct ketogenic diet should also be considered as a strategy for seizure control in pregnant epileptic women, although currently there are less than a handful of case studies on this topic in the literature [14]. A mice model of ketogenic diet during pregnancy suggested that such a diet may lead to alterations in embryonic organ growth (i.e., an increase in cardiac size and a decrease in brain and cord size) [15]. However, the potential effects of a ketogenic diet on the developing human fetus remain unknown at this time [16].

26.2 Maternal Weakness

The most common causes of increasing maternal weakness are intracranial pathology (Chap. 36), stroke (Chap. 25), magnesium overdose, and myasthenia gravis crisis.

Magnesium overdose is characterized by flushing, drowsiness, sweating, malaise, respiratory depression, and weakness. Treatment with magnesium should be discontinued immediately, and the diagnosis can be confirmed by laboratory testing as discussed in Chap. 16.

A neurologist should be consulted to aid with the diagnosis and management of these cases.

26.2.1 Myasthenia Gravis Crisis

Myasthenia gravis (MG) is an autoimmune disorder in which antibodies ravage nicotinic acetylcholine receptors at the junction between the nerve and muscle, thus disrupting nerve impulse transmission and impair muscle contracture. This disorder typically manifests as fluctuating weakness and rapid fatigue of voluntary muscles (e.g., periocular, limb, or oropharyngeal). The prevalence of MG has been estimated to be 1/5000 in the general population [17], and the incidence in women is double than in men. Symptoms may appear at any age, but the highest incidence is in the third decade of life [18].

Workup and diagnosis: Unless the existence of MG was known before pregnancy, clinical evidence of undue maternal weakness should prompt referral of the pregnant woman to diagnostic studies. These include electrodiagnostic studies and blood sampling for acetylcholine receptor (AChR)-binding antibodies and anti-muscle-specific kinase (MuSK) levels. The electrophysiology tests that demonstrate faulty neuromuscular transmission are repetitive nerve stimulation studies and the more sensitive single-fiber electromyography (SF-EMG). Both may safely be performed during pregnancy. Symptomatic weakness together with electrophysiology evidence of abnormal neuromuscular transmission or elevated serum levels of AChR or MuSK confirm the diagnosis.

Myasthenia gravis may be triggered or exacerbated by infection, changes in thyroid function, certain medications, emotional or physical stress, or menses [19]. In maternal cases, worsening of symptoms occurs most frequently either in the first trimester or postpartum [20]. Thymoma is an uncommon cause of MG in women of childbearing age, particularly if AChR antibody testing is negative [21, 22]. The decision to perform thymic imaging depends on the importance of a definitive diagnosis and on the likelihood of a positive finding (which is low in antibody-negative women). In most cases, imaging may be postponed until after delivery, since thymectomy is unlikely to confer clinical benefit during pregnancy. Nevertheless, if considered imperative, chest computerized tomography (CT) imaging without contrast may be performed, as this test confers minimal risk to the fetus. Though chest magnetic resonance imaging (MRI) does not involve radiation, MRI is inferior to CT for visualization of the anterior mediastinum.

Follow-up on MG during pregnancy: The effect of pregnancy on the course of MG is unpredictable [20, 23]. The severity of weakness at the beginning of pregnancy does not forecast either remission or exacerbation; some women may improve, while others may worsen or remain in the same condition. MG may be unmasked or worsened in approximately one-third of patients during pregnancy [20], thus close monitoring of maternal condition is mandatory, as respiratory crises may occur. Postpartum disease exacerbations are more prevalent after the first delivery [24]. While treatment is less complicated at this time, a high level of suspicion is required, as symptoms such as fatigue may be attributed to the presence of new challenges at home rather than to disease exacerbation.

Respiratory failure manifesting as severe hypoventilation usually occurs due to extreme respiratory muscle weakness combined with restriction of diaphragmatic excursion, by the rapidly enlarging uterus. Bedside spirometry tests that may assist in identifying impending respiratory failure in patients without obvious respiratory distress include forced vital capacity and maximal inspiratory and maximal expiratory pressures. However, as the predictive values of all of these tests are based on studies in the non-pregnant population, it is reasonable to consider sequential testing in pregnant women.

Treatment of MG crisis during pregnancy: Treatment of the pregnant woman presenting with MG requires multidisciplinary input throughout pregnancy and the peripartum period [25]. During MG crisis, the mainstays of therapy are similar to those of the non-pregnant state, including supportive ventilation with concomitant infection control, plasma exchange, intravenous gammaglobulins (IVIG), and immune-modulating therapies.

Indications for mechanical ventilation include clinical signs of respiratory distress, progressive hypercapnic respiratory acidosis despite therapy and inadequate secretion clearance (e.g., recurrent episodes of acute hypoxemia due to mucus plugging). Endotracheal intubation should preferably be performed semi-electively rather than emergently in order to maximize situational control and minimize complications. In the general population, serial measurements showing a decrease in forced vital capacity below 15–20 mL/kg or a mean inspiratory pressure between 0 and −30 cmH_2O are considered possible triggers for intubation, but these measurements may not be valid for pregnant women. Serial measurement deterioration is likely a better measure in this population. If required, intubation is best facili-

tated by short-term neuromuscular blockers. Following endotracheal intubation, any form of adaptive support ventilation is probably more conducive to preserving residual muscle strength rather than implementing full sedation without spontaneous respiratory effort.

During pregnancy, myasthenia gravis exacerbations are ideally treated with steroids (oral prednisone 60–80 mg once daily or the intravenous equivalent). Intravenous cholinesterase inhibitors are best avoided unless delivery is imminent, since these medications may trigger uterine contractions. Steroids are less invasive than plasma exchange and probably more beneficial to the fetus than intravenous immunoglobulin (IVIG). Furthermore, the onset of steroid effect is relatively rapid compared to other immune-modulating medications (hours vs. days), and the effect of steroids is sustained for the duration of treatment, whereas plasma exchange and IVIG confer a more fleeting benefit [26]. However, inadequate maternal response to steroid therapy should lead to consideration of alternative treatment options. Cyclosporine is considered relatively safe for pregnant women [27, 28]. Azathioprine may be used as the next line of treatment during maternal crises despite the presence of the fetus. However, this medication is controversial; in Europe it is the nonsteroidal immune suppressive medication of choice for MG in pregnancy [26]. One retrospective case series of gravid women with inflammatory bowel disease reported no fetal congenital abnormalities despite azathioprine use [29]. It has been hypothesized that although azathioprine does cross the placenta, the fetal liver lacks the enzyme that converts the drug to its active metabolites, thus this enzyme deficiency seems to be protective [30]. However, there are also reports of impaired fetal hemopoiesis and perhaps also its complications due to this therapy [31]. In the United States, azathioprine is considered a high-risk medication during pregnancy. Mycophenolate mofetil and methotrexate significantly increase the risk of teratogenicity and should therefore not be used unless the life of the mother is at risk and alternative treatments are unavailable [25].

As described above, plasma exchange and IVIG are both temporizing measures. In the general MG population, IVIG has been associated with efficacy similar to that of plasma exchange [32]. A single case series describing the use of IVIG during pregnancy has shown some promise [33]; therefore, among the two options, this mode of therapy should be considered preferable. Variable degrees of success have been described with plasma exchange used for other immune disorders during pregnancy [34–37], but there is no data on this mode of therapy during pregnancy, and it is clearly a more invasive procedure. Thus, plasmapheresis should likely not be the initial choice of therapy in the gravid state. In general, decisions regarding the use of these measures should balance potential maternal benefit with the likelihood of both maternal and fetal complications.

In women with MG and preeclampsia, magnesium sulfate should be used with extreme caution, since it may exacerbate neuromuscular weakness [38] as noted above. If eclampsia does occur, barbiturates or phenytoin usually provide adequate treatment (see Chap. 6).

Labor and delivery: Unlike striated muscle, the uterine smooth muscle is unaffected by acetylcholine receptor antibodies. Spontaneous vaginal delivery is therefore encouraged in women with MG, as labor contractions are preserved. However, early-onset fatigue and extreme weakness may occur during the second stage of labor when striated muscle is involved, requiring assisted delivery. If anesthesia is required, neuraxial blockade is preferred to general anesthesia (due to its lesser systemic effects) and has been used safely for delivery in women with MG [39, 40]. Regardless of the severity of maternal MG, all neonates must be received and treated by an expert neonatal team, as upon birth they too may manifest transient weakness [23].

26.3 Summary

Neurological crises in pregnant women may be related to preexisting conditions, such as epilepsy or myasthenia gravis, or to obstetric conditions, primarily eclampsia. The two most common neurological crises likely to be encountered by the

clinician treating a critically ill pregnant woman are seizures and severe weakness. This chapter discussed the differential diagnoses and treatment recommendations that should be considered in these clinical conditions.

References

1. EURAP Study Group. Seizure control and treatment in pregnancy: observations from the EURAP epilepsy pregnancy registry. Neurology. 2006;66(3):354–60.
2. RCOG. Epilepsy in pregnancy: Green-top Guideline No 68. 2016. Last accessed Nov 14, 2019 at https://www.rcog.org.uk/globalassets/documents/guidelines/green-top-guidelines/gtg68_epilepsy.pdf
3. Knight M, Kenyon S, Brocklehurst P, Neilson J, Shakespeare J, Kurinczuk JJ (Eds.) on behalf of MBRRACE-UK. Saving lives, improving mothers' care: lessons learned to inform future maternity care from the UK and Ireland confidential enquiries into maternal deaths and morbidity 2009–12. Oxford: National Perinatal Epidemiology Unit, University of Oxford 2014. Last accessed Nov 14, 2019 at https://www.npeu.ox.ac.uk/downloads/files/mbrrace-uk/reports/Saving%20Lives%20Improving%20Mothers%20Care%20report%202014%20Full.pdf.
4. Chen YH, Chiou HY, Lin HC, Lin HL. Effect of seizures during gestation on pregnancy outcomes in women with epilepsy. Arch Neurol. 2009;66(8):979–84.
5. Teramo K, Hiilesmaa V, Bardy A, Saarikoski S. Fetal heart rate during a maternal grand mal epileptic seizure. J Perinat Med. 1979;7(1):3–6.
6. Nei M, Daly S, Liporace J. A maternal complex partial seizure in labor can affect fetal heart rate. Neurology. 1998;51:904–6.
7. Sahoo S, Klein P. Maternal complex partial seizure associated with fetal distress. Arch Neurol. 2005;62(8):1304–5.
8. Sveberg L, Svalheim S, Taubøll E. The impact of seizures on pregnancy and delivery. Seizure. 2015;28:35–8.
9. Battino D, Tomson T, Bonizzoni E, Craig J, Lindhout D, Sabers A, Perucca E, Vajda F, EURAP Study Group. Seizure control and treatment changes in pregnancy: observations from the EURAP epilepsy pregnancy registry. Epilepsia. 2013;54(9):1621–7.
10. Minkoff H, Schaffer RM, Delke I, Grunebaum AN. Diagnosis of intracranial hemorrhage in utero after a maternal seizure. Obstet Gynecol. 1985;65(3). Suppl:22S–4S.
11. CMQCC California Maternal Quality Care Collaborative Toolkits. https://www.cmqcc.org/resources-tool-kits/toolkits. Accessed 29th July 2019.
12. Shakespeare J, Sisodiya SM; On behalf of the Royal College of General Practitioners and Association of British Neurologists and Royal College of Physicians. Guidance Document on Valproate Use in Women and Girls of Childbearing Years. 2019. Last accessed Nov 17, 2019 at https://www.rcog.org.uk/globalassets/documents/guidelines/valproate-guidance-march-2019.pdf
13. Albright CM, Ali TN, Lopes V, Rouse DJ, Anderson BL. Lactic acid measurement to identify risk of morbidity from sepsis in pregnancy. Am J Perinatol. 2015;32(5):481–6.
14. van der Louw EJ, Williams TJ, et al. Ketogenic diet therapy for epilepsy during pregnancy: a case series. Seizure. 2017;45:198–201.
15. Sussman D, van Eede M, Wong MD, Adamson SL, Henkelman M. Effects of a ketogenic diet during pregnancy on embryonic growth in the mouse. BMC Pregnancy Childbirth. 2013;13:109.
16. Williams TJ, Cervenka MC. The role for ketogenic diets in epilepsy and status epilepticus in adults. Clin Neurophysiol Pract. 2017;2:154–60.
17. Mays J, Butts CL. Intercommunication between the neuroendocrine and immune systems: focus on myasthenia gravis. Neuroimmunomodulation. 2011;18(5):320–7.
18. Drachman DB. Myasthenia gravis. N Engl J Med. 1994;330(25):1797–810.
19. Howard JF (ed). Myasthenia gravis: a manual for the health care provider. 2009. Last accessed Nov 17, 2019 at https://myasthenia.org/Portals/0/Provider%20Manual_ibook%20version.pdf
20. Batocchi AP, Majolini L, Evoli A, Lino MM, Minisci C, Tonali P. Course and treatment of myasthenia gravis during pregnancy. Neurology. 1999;52(3):447–52.
21. Massey JM, De Jesus-Acosta C. Pregnancy and myasthenia gravis. Continuum (Minneap Minn). 2014;20(1). Neurology of Pregnancy:115–27.
22. Choi Decroos E, Hobson-Webb LD, Juel VC, Massey JM, Sanders DB. Do acetylcholine receptor and striated muscle antibodies predict the presence of thymoma in patients with myasthenia gravis? Muscle Nerve. 2014;49(1):30–4.
23. Djelmis J, Sostarko M, Mayer D, Ivanisevic M. Myasthenia gravis in pregnancy: report on 69 cases. Eur J Obstet Gynecol Reprod Biol. 2002;104(1):21–5.
24. Boldingh MI, Maniaol AH, Brunborg C, Weedon-Fekjær H, Verschuuren JJ, Tallaksen CM. Increased risk for clinical onset of myasthenia gravis during the postpartum period. Neurology. 2016;87(20):2139–45.
25. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: executive summary. Neurology. 2016;87(4):419–25.
26. Bansal R, Goyal MK, Modi M. Management of myasthenia gravis during pregnancy. Indian J Pharmacol. 2018;50(6):302–8.
27. Radomski JS, Ahlswede BA, Jarrell BE, Mannion J, Cater J, Moritz MJ, Armenti VT. Outcomes of 500 pregnancies in 335 female kidney, liver, and heart transplant recipients. Transplant Proc. 1995;27(1):1089–90.

28. Bar Oz B, Hackman R, Einarson T, Koren G. Pregnancy outcome after cyclosporine therapy during pregnancy: a meta-analysis. Transplantation. 2001;71(8):1051–5.
29. Alstead EM, Ritchie JK, Lennard-Jones JE, Farthing MJ, Clark ML. Safety of azathioprine in pregnancy in inflammatory bowel disease. Gastroenterology. 1990;99(2):443–6.
30. Ferrero S, Pretta S, Nicoletti A, Petrera P, Ragni N. Myasthenia gravis: management issues during pregnancy. Eur J Obstet Gynecol Reprod Biol. 2005;121(2):129–38.
31. Davison JM, Dellagrammatikas H, Parkin JM. Maternal azathioprine therapy and depressed haemopoiesis in the babies of renal allograft patients. Br J Obstet Gynaecol. 1985;92(3):233–9.
32. Gajdos P, Chevret S, Toyka KV. Intravenous immunoglobulin for myasthenia gravis. Cochrane Database Syst Rev. 2012;12:CD002277.
33. Gamez J, Salvado M, Casellas M, Manrique S, Castillo F. Intravenous immunoglobulin as monotherapy for myasthenia gravis during pregnancy. J Neurol Sci. 2017;383:118–22.
34. Saad AF, Roman J, Wyble A, Pacheco LD. Pregnancy-associated atypical hemolytic-uremic syndrome. AJP Rep. 2016;6(1):e125–8.
35. Mayer-Pickel K, Horn S, Lang U, Cervar-Zivkovic M. Response to plasmapheresis measured by angiogenic factors in a woman with antiphospholipid syndrome in pregnancy. Case Rep Obstet Gynecol. 2015;2015:123408.
36. Nwogu LC, Moise KJ Jr, Klein KL, Tint H, Castillo B, Bai Y. Successful management of severe red blood cell alloimmunization in pregnancy with a combination of therapeutic plasma exchange, intravenous immune globulin, and intrauterine transfusion. Transfusion. 2018;58(3):677–84.
37. Kronbichler A, Brezina B, Quintana LF, Jayne DR. Efficacy of plasma exchange and immunoadsorption in systemic lupus erythematosus and antiphospholipid syndrome: a systematic review. Autoimmun Rev. 2016;15(1):38–49.
38. Sikka P, Joshi B, Aggarwal N, Suri V, Bhagat H. Distinguishing myasthenia exacerbation from severe preeclampsia: a diagnostic and therapeutic challenge. J Clin Diagn Res. 2015;9(8):QD05–6.
39. Almeida C, Coutinho E, Moreira D, Santos E, Aguiar J. Myasthenia gravis and pregnancy: anaesthetic management—a series of cases. Eur J Anaesthesiol. 2010;27(11):985–90.
40. Chabert L, Benhamou D. Myasthenia gravis, pregnancy and delivery: a series of ten cases]. [Article in French]. Ann Fr Anesth Reanim. 2004;23(5):459–64.

Part VII

Maternal Cardiac Arrest

Maternal Resuscitation

27

Laura Peltola and Felicity Plaat

Bullet Points

- Maternal cardiac arrest is a rare event.
- Inadequate care contributes to fatal outcomes.
- The gravid uterus can significantly impede resuscitation.
- The standard adult hand position should be used for chest compression with minimal interruptions.
- Early airway protection is required with active and aggressive treatment of hypoxia.
- Anticipate a difficult airway.
- Manual uterine displacement is the recommended method to relieve aortocaval compression and should be maintained throughout resuscitation and after return of spontaneous circulation.
- Early defibrillation with standard adult energies should be provided if the rhythm is shockable.
- Use standard adult resuscitation drugs and doses.
- Perimortem caesarean delivery should be performed early and at the site of collapse.

27.1 Introduction

Cardiac arrest in pregnancy is rare, but the incidence may be increasing in some countries [1]. Recent publications suggest a low incidence in developed countries; 1:16,000 deliveries in the United Kingdom (UK) [1] and 1:12,000 deliveries in the United States (USA) [2]. These figures rise dramatically if resource-poor areas of the world are included.

Just over a decade ago, the prevailing view was that cardiac arrest in pregnant women resulted in such poor outcomes that resuscitation was likely to be futile [3]. Studies from across the world revealed lack of knowledge of resuscitation of the pregnant woman amongst frontline healthcare providers [4]. Such findings led authors of one study to conclude: 'In the current situation, even if a pregnant woman were to suffer a cardiac arrest in front of a trained physician, this might not improve her likelihood of survival' [5]. The situation has appeared to improve: survival from an in-hospital cardiac arrest in a pregnant woman is now more likely than in non-pregnant women of reproductive age [6, 7], with survival rates ranging

L. Peltola · F. Plaat (✉)
Department of Anaesthesia, Queen Charlotte's & Chelsea Hospital, London, UK
e-mail: peltola.laura@googlemail.com; felicityplaat@nhs.net

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_27

Table 27.1 Cerebral performance categories (CPC) scale

CPC 1	Good cerebral performance (Normal life)	Conscious, alert, able to work. Possible minor neurological or psychological deficits
CPC 2	Moderate cerebral disability (disabled but independent)	Conscious, independent in activities of daily life. Able to work in sheltered environment
CPC 3	Severe cerebral disability (conscious but disabled and dependent)	Conscious, dependent on others for daily support. Ranges from ambulatory state to severe dementia or paralysis
CPC 4	Coma or vegetative state (unconscious)	Unconscious, no cognition. No verbal or psychological interaction with environment
CPC 5	Brain death	Apnoea, areflexia

between 54% and 65% [1–3, 8]. Of those women who survive, most survive with good neurological outcomes, with 78.4% mothers and 52.3% neonates having cerebral performance category outcomes of 1–2 [8] (Table 27.1). Nevertheless, in the UK, analysis of maternal deaths occurring between 2012 and 2014 suggested that a fatal outcome might have been avoided with different care in 42% of cases [9].

The first stand-alone guidelines for the treatment of cardiac arrest in pregnancy were published in 2014 by The Society of Obstetric Anesthesia and Perinatology (SOAP) [10], closely followed in 2015 by the American Heart Association (AHA) scientific statement on maternal resuscitation [11]. These guidelines are based on small case series, simulation studies, expert opinion and extrapolated data from the non-pregnant cardiac arrest population [12, 13]. This chapter examines the current evidence for the management of non-traumatic maternal cardiac arrest.

27.2 Physiological Changes in Pregnancy

Maternal resuscitation is unlikely to succeed unless modified to encompass the physiological and anatomical changes of pregnancy. The most significant changes are those affected by the gravid uterus on cardiac output and the efficacy of cardiac compressions. Splinting of the diaphragm necessitates exertion of greater force to generate an adequate ejection fraction during chest compression. Obstruction of the inferior vena cava leads to a decrease in maternal venous return, further compromising cardiac output. In the supine position, from approximately 12 weeks gestation, the gravid uterus causes inferior vena cava compression and to a lesser extent compression of the aorto caval compression (ACC). At term, the vena cava is completely occluded in the supine position in 90% of healthy pregnant women, with significant effects on stroke volume (SV) and cardiac output (CO) [14, 15]. During CPR, ACC reduces the CO that can be generated by approximately 90% compared with that achieved in non-pregnant patients [16].

There is also an increased risk of aspiration during pregnancy; therefore, the airway requires early protection. Hypoxia and acidosis occur earlier due to a combination of reduced functional residual capacity, increased maternal oxygen consumption and increased intrapulmonary shunting. The oxygen dissociation curve is shifted to the right, so higher partial pressures of oxygen are required to achieve a given saturation [11, 16, 17]. All of these justify early consideration of intubation. However, tracheal intubation is more difficult and outright failure more common. Therefore, tracheal intubation is best performed by an experienced operator (see below).

27.3 Resuscitation

All healthcare personnel caring for pregnant women should be trained to diagnose cardiac arrest and initiate basic life support (BLS). The contents of the AHA cardiac arrest in pregnancy in-hospital BLS algorithm (under AHA copyright) can be accessed via the following link (supplied

by AHA) http://circ.ahajournals.org/content/circulationaha/132/18/1747/F2.large.jpg [11].

27.4 Cardiac Compressions and Defibrillation

Cardiac compressions should be delivered with the standard hand position for adults on the centre of the chest, as imaging studies have established that there is no displacement of the heart in pregnancy [11, 18, 19]. Table 27.2 lists the characteristics of effective cardiac compressions. The quality of compressions deteriorates rapidly even in the most expert hands and the provider should change every 2 min [20, 21].

Shockable rhythms (i.e. ventricular tachycardia, ventricular fibrillation) are rare in the obstetric population [2]. However, when they occur, they require immediate defibrillation as chances of success deteriorate with time [14]. Defibrillation should not be withheld because of concerns regarding the effect of defibrillation on the foetus [11, 12]. Minimal energy is transmitted to the foetus.

Defibrillation should be performed within 3 min of collapse in a hospital setting [10, 11, 21]. Pads should be placed in the anterolateral position, with the anterior pad beneath the right clavicle and the left lateral pad under the breast tissue in the V6 position, mid-axillary line [11, 19]. Biaxillary pads may also be used [19]. (See accompanying PowerPoint slides for the Resuscitation Council (UK) adult advanced life support algorithm, reproduced with kind permission of the Resuscitation Council (UK)). Standard adult energies should be used as thoracic impedance is unchanged in pregnancy [12].

There is conflicting advice about fetal monitoring. Theoretically the risk is greatest if fetal scalp electrodes are applied [17]. Some authorities advise their removal prior to defibrillation to avoid the risk of electrocution. The AHA, however, considers monitoring safe and arcing unlikely [11]. A pragmatic approach is to remove fetal monitoring if this does not delay defibrillation [10]. Fetal monitoring should certainly not be applied during maternal resuscitation.

Table 27.2 Characteristics of effective cardiac compressions [10, 19, 21]

Rate: 100–120 compressions per minute
Depth: 5–6 cm
Ratio of compressions to breaths: 30:2
Full release of pressure on the chest during upstrokes
Minimal interruptions, <5 s
Regular changes of CPR provider, ideally every 2 min
Continued compression during application and charging of defibrillator
No evidence for routine use of mechanical chest compression devices

27.5 Airway, Oxygenation and Ventilation

A difficult airway should be anticipated. Indeed, hypoxia resulting from difficulties with intubation may be the cause of the arrest [11]. Only two attempts at intubation should be made and only by an experienced operator [22, 23]. If intubation cannot be achieved or an operator with the requisite skills is not available, a supraglottic airway device (SGA) should be inserted—again using a maximum of two attempts—to ensure oxygenation [23]. As a last resort, front of neck access should be attempted. Surgical cricothyroidotomy is the recommended technique [24] (Fig. 27.1).

The use of cricoid pressure remains controversial and does not necessarily protect from aspiration [17]. The European Resuscitation Guidelines [20] state that in a cardiac arrest the use of cricoid pressure is not routinely recommended. The AHA and the SOAP concur that there is no evidence for use of cricoid pressure during CPR [10, 11, 21], while the Resuscitation Council (UK) makes no mention of cricoid pressure. There is consensus that cricoid pressure should be removed early if there is difficulty maintaining oxygenation or intubating [10, 11, 20, 23].

Ventilation may be challenging due to limited diaphragmatic and chest wall excursion secondary to the gravid uterus and increased breast tissue. Smaller tidal volumes may be required [14, 17]. Hyperventilation should be avoided as excessive ventilation has been shown to exacerbate circulatory compromise in low-flow states

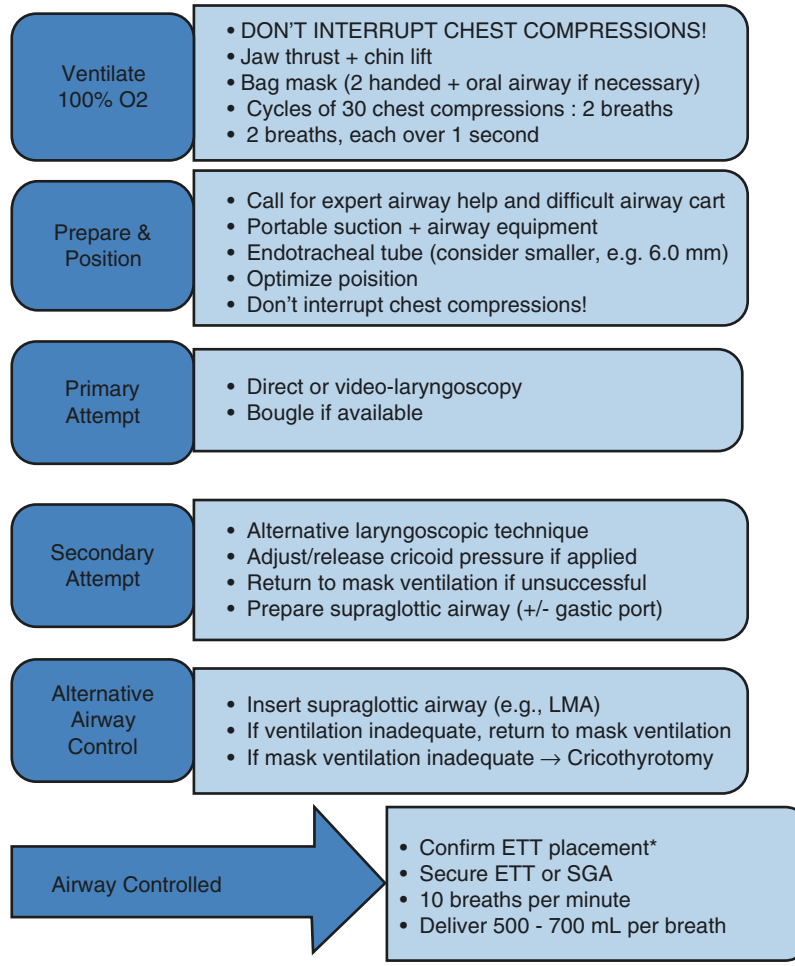


Fig. 27.1 The Society of Obstetric Anesthesia and Perinatology consensus airway algorithm for cardiac arrest in pregnancy, reproduced with kind permission [10]

[25]. Respiratory alkalosis also contributes to uterine vasoconstriction and therefore fetal hypoxia and acidosis [11, 26].

27.6 Circulation

If possible, two large bore (> = 16G) intravenous access lines should be secured above the level of the diaphragm [13, 16, 19]. Intraosseous (IO) access is an alternative [17]. In patients with severe preeclampsia (PET) and eclampsia, fluid resuscitation should be undertaken with caution due to an increased risk of precipitating pulmonary edema [16]. Blood and blood products should be given as early as possible during hypovolemic collapse due to hemorrhage.

27.7 Relieving Aortocaval Compression

Relief of ACC must be maintained throughout resuscitation and at return of spontaneous circulation (ROSC) [11]. Manual uterine displacement (MUD) is the recommended method for relieving ACC during CPR [10, 11, 19]. A 15° left lateral tilt with the woman lying on a firm surface such as an operating table, Cardiff wedge or someone's knees is a widely recommended method for reducing ACC [16]. However, randomised controlled trials in healthy women undergoing Caesarean section demonstrate that there is less hypotension and the vasopressor requirements are lower when the uterus is manually displaced, compared to tilting the table [27].

Furthermore, tilting to an 15° is difficult to achieve, and it appears that ACC can occur at excessive lateral tilt [11, 17]. Tilting the table also reduces the force of cardiac compressions [28]. Finally, airway management, defibrillation and perimortem caesarean delivery (PMCD) are all easier with the patient supine [12, 17].

Manual displacement can be undertaken from either side of the patient [10]. With the operator on the left, the uterus is lifted up and to the left, off the maternal vessels. From the right side, the uterus should be pushed up and to the left [11]. The aim is to apply leftward pressure to the right upper uterine border thereby displacing the uterus 1.5 inches laterally from the midline [27].

27.8 Monitoring

The use of continuous capnography is strongly recommended. Capnography provides information regarding airway patency, appropriate ventilation, efficacy of CPR and can indicate ROSC [11, 17, 19]. Clinical diagnosis of 'chest wall excursion' does not comprise evidence of actual ventilation. The chances of ROSC are improved when end tidal carbon dioxide ($ETCO_2$) is maintained above 1.3 kPa (>10 mmHg) [11]. If capnography is not immediately available, resuscitation efforts should not be delayed [10].

The use of ultrasound may be helpful to confirm pregnancy and in the diagnosis of potential reversible causes of cardiac arrest [12].

27.9 Drugs

Although pharmacodynamics are altered in pregnancy, there is insufficient evidence to recommend drug dose alterations. Standard adult drug doses should be used [29]. No drugs should be withheld due to concerns regarding potential harm to the fetus, not least because all the evidence suggests that the best outcome for the fetus is associated with return of maternal spontaneous circulation [11].

27.10 Reversible Causes

In the obstetric population, pregnancy specific causes of collapse should be considered in addition to those in the general population. (See accompanying PowerPoint slides for the 4 Hs and 4 Ts, reproduced with kind permission of the Resuscitation Council (UK).).

Hemorrhage is a common cause of cardiac arrest in pregnancy. As the uterus has a blood flow of approximately 700 mL/min at term, life-threatening hypovolemia can develop rapidly [30]. Uterine atony is the most common cause of postpartum hemorrhage and early use of uterotonics should be part of the resuscitation strategy. Oxytocin should be used with caution due to its vasodilatory and negative inotropic effects [10, 11]. The specifics of obstetric and surgical management are outside the scope of this chapter. However, early recourse to hysterectomy may be life-saving. Blood and coagulation products, including tranexamic acid, should be given as early as possible.

Hypoxia features frequently in maternal cardiac arrest. The causes of hypoxia include loss of airway, intracerebral events, anesthetic complications, pulmonary embolism, pneumonia, pulmonary edema, venous air embolus and influenza [11]. Cardiac arrest following respiratory depression secondary to opiates appears to be associated with particularly poor outcomes, with 73% of such patients dying or sustaining permanent brain injury [31].

Ischemic heart disease heart in pregnancy is increasingly common [9, 12]. An incidence of 0.7 myocardial infarctions (MI) per 100,000 maternities is likely to be an underestimation [32]. The mortality from MI in the peripartum period is double that of a MI in non-pregnant women of a similar age [33]. Presentation may be atypical, with epigastric pain and vomiting [13] and such cases may be misdiagnosed as reflux. Percutaneous coronary intervention (PCI) is the first line treatment for ST Elevation MI (STEMI), and thrombolysis should be considered when PCI is not available [13].

If thromboembolism is suspected to be the cause of cardiac arrest, thrombolysis may be indicated as

part of resuscitation. The literature supports safe use of thrombolysis in pregnancy [34, 35]. Most published data of thrombolysis in pregnancy is for streptokinase, but urokinase and recombinant tissue plasminogen activator have also been safely used in pregnancy [34]. Tenecteplase has yet to be studied in pregnancy [34].

Regarding amniotic fluid embolism (AFE), although one-quarter of women who suffer AFE will experience a cardiac arrest, over half survive [2]. The mainstay of treatment is supportive [12, 36]. However, the successful use of extracorporeal life support has been reported for AFE [37, 38] as well as for other causes of maternal cardiac arrest (See Chap. 14).

A recent study found that 24% of maternal cardiac arrests were solely attributable to anesthesia [1]. The majority of these (63%) were due to high blocks following de novo spinals. Seventy-five percent of the patients were obese. In contrast to the cohort who suffered cardiac arrest from other causes, there were no deaths, presumably because all these were witnessed and resuscitation promptly instituted. However, other evidence suggests complications of general anesthesia such as aspiration to be responsible for 7% maternal cardiac arrests [2].

Magnesium sulphate, local anesthetic (LA) agents, opiates, and anaphylactic and blood transfusion reactions are other causes of cardiac arrest in the obstetric population. The use recent UK data shows that of 20% intralipid solution to treat LA toxicity in pregnancy has not been evaluated, but its use in severe hyperemesis appears safe [10, 39, 40]. Magnesium toxicity is more common in the presence of renal dysfunction [11]. Hypermagnesemia should be treated with intravenous 10% calcium chloride.

27.11 Perimortem Caesarean Delivery

Perimortem caesarean delivery (PMCD), or 'resuscitative hysterotomy' [41] refers to caesarean delivery performed after CPR has commenced [17].

The gravid uterus may hinder maternal resuscitation, and emptying it can therefore improve the chances of survival for both mother and fetus [3, 11, 13]. Relief of ACC is likely to reduce the oxygen consumption and improve the thoracic compliance of the compromised mother [14, 16, 17]. In one case series, 66% of women achieved ROSC immediately following PMCD [3]. PMCD should not be delayed to confirm fetal viability [42]. Although ultrasound is a more accurate tool than palpation for estimating gestational age, the equipment and expertise for this may not be immediately available and should not delay the procedure [13] Furthermore, as noted above, neonatal survival directly correlates with maternal survival [1].

Limited evidence suggests that PMCD should be carried out if ROSC is not achieved within 4 min of arrest in women with a uterine fundus at or above the umbilicus despite relief of ACC and effective cardiac compressions [17, 19, 42, 43]. Practically, PMCD should be considered as soon as cardiac arrest is confirmed [11]. Although irreversible hypoxic brain damage starts to occur within 4 min in a patient without cardiac output [11, 16], there is evidence that PMCD may benefit both mother and fetus even when initiated more than 5 minutes from cardiac arrest. A significant difference between the arrest to delivery interval has been found between survivors and non-survivors of maternal cardiac arrest (10.0 ± 7.2 min vs 22.6 ± 13.3 minutes, respectively ($p < 0.001$)) [8]. The recommended timeframe of 5 minutes appears difficult to achieve, and this may lead to a reluctance to embark on PMCD at all [8, 44, 45]. Furthermore, one review found that only 7% of PMCDs were carried out within the recommended time frame [8]. However, the most recent UK data shows that 61% of PMCDs were achieved within less than 5 minutes [1]. There is no evidence of harm caused by PMCD [3, 8, 11]. It is therefore recommended that PMCD be undertaken regardless of the time since cardiac arrest, as long as maternal resuscitation itself is not considered futile.

Maternal survival is greater when PMCD is performed at the site of collapse, compared with transferring to the operating theatre (72% vs 36%, respectively) [1]. This difference can probably be attributed to the quality of resuscitation provided during maternal transfer [45, 46].

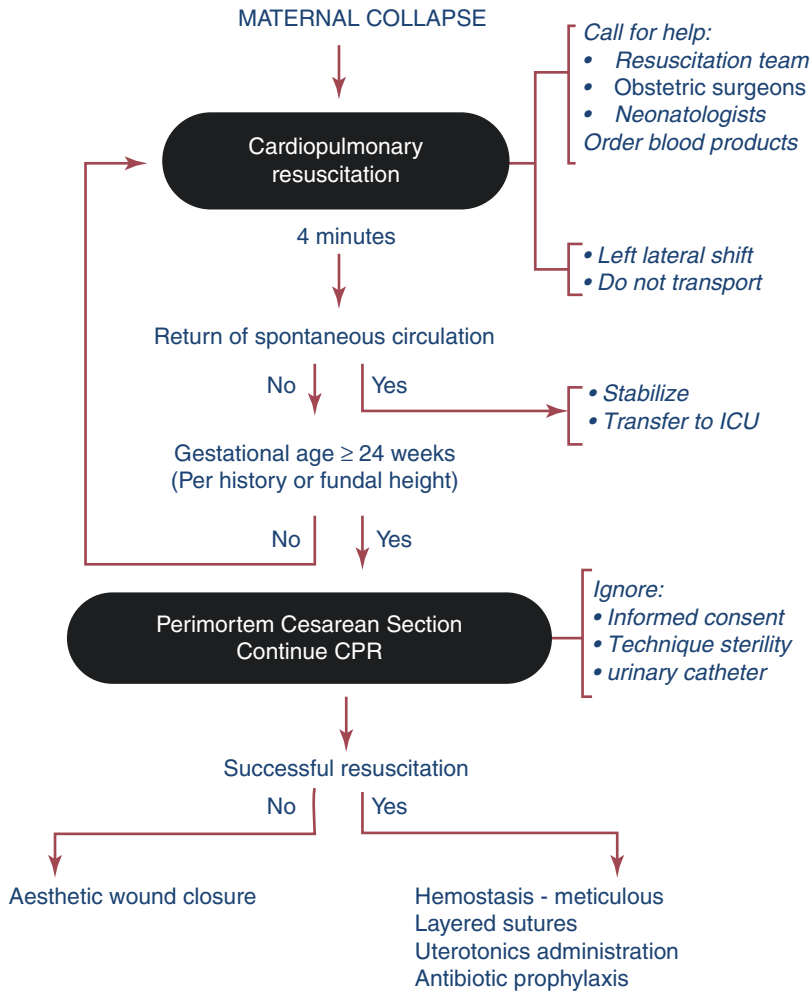


Fig. 27.2 A perimortem caesarean delivery decision-making flow diagram, reproduced with kind permission [48]

CPR with MUD should be continued during the procedure [10, 16, 46, 47]. Minimal equipment is required in order to conduct PMCD. This equipment should be kept on all cardiac arrest trolleys in areas where maternal collapse may occur [14]. A urinary catheter does not need to be inserted prior to PMCD [48]. An aseptic technique is also not required as this would delay delivery [11]. The incision used is at the discretion of the operator. A classical incision may offer better visualisation of the abdomen and pelvis, but the Pfannenstiel may be a more familiar approach [16]. No anaesthetic is required until ROSC. Triggering the major obstetric hemorrhage (MOH) protocol should be considered at the time of PMCD in anticipation of bleeding should ROSC be achieved, especially if an AFE is suspected [42]. With the abdomen open, direct cardiac massage is also possible [14, 16, 17].

If ROSC is achieved and the mother is stable, transfer to the operating theatre can be undertaken in order to complete surgery and improve hemostasis. Antibiotics and uterotonics may also be considered. Figure 27.2 illustrates a PMCD flow diagram.

27.12 Vaginal Delivery

If the cervix is fully dilated, the fetal head is at an appropriate station, and it is likely that delivery can be accomplished within 5 minutes, assisted vaginal delivery for emptying the uterus may be

feasible. Resuscitation should not be interrupted during delivery [11, 17].

27.13 When to Stop

Current guidance states that resuscitation should be continued while the patient remains in a shockable rhythm, or until all resources and attempts to achieve ROSC have been exhausted [17]. The decision to stop should be made by a senior obstetrician and anaesthetist in consultation with the arrest team and should be unanimous if possible [16].

27.14 Aftermath

Family members should be kept fully informed during resuscitation. Although the literature currently supports having family members present at the time of resuscitation, there is no literature on the topic in the maternal population. Given the potential need to perform urgent surgery, this concept may not hold true for this special population. After the resuscitation, staff debriefing should be undertaken by a competent professional [16]. There is little literature on survivors of maternal cardiac arrest or PMCD, but it is likely that both mother and child will require a period of intensive care.

27.15 Human Factors and Teamwork

In every resuscitation, a team leader should be identified. Systematic delegation of tasks, regular reassessment of progress and the use of checklists and visual aids are recommended [10]. Closed loop communication is most effective in the emergency setting. Therefore, instructions should be issued directly to a specific team member, and their performance should be verbally reported to the team leader.

Simulation studies and reviews of clinical practice indicate that care during obstetric resuscitations is often suboptimal [9, 49]. Regular multidisciplinary simulation and practice drills are strongly recommended to improve team performance [10, 47, 50].

All maternity staff should complete annual formal training in life support and the management of maternal collapse [16]. There is evidence that the MOET (Managing Obstetric Emergencies and Trauma) training course in obstetric resuscitation has led to greater use of PMCD during maternal cardiac arrest both in the UK [1, 14, 16] and Europe [44].

27.16 Conclusion

Management of obstetric cardiac arrest should prioritise the mother. Successful management of the mother maximises the chances for the fetus. Effective CPR should be commenced immediately with minimal interruptions of chest compressions and early defibrillation of shockable rhythms. Hypoxia must be treated quickly and a difficult airway anticipated. Manual uterine displacement should be maintained throughout resuscitation. Early PMCD is associated with improved chance of ROSC and maternal survival [3, 10, 11]. Early senior and multidisciplinary involvement from obstetricians, anaesthetists, neonatologists, intensivists and cardiologists are essential [10, 16].

References

1. Beckett VA, Knight M, Sharpe P. The CAPS study: incidence, management and outcomes of cardiac arrest in pregnancy in the UK: a prospective, descriptive study. BJOG. 2017;124:1374–81.
2. Mhyre JM, Tsen LC, Einav S, Kuklina EV, Leffert LR, Bateman BT. Cardiac arrest during hospitalization for delivery in the United States, 1998-2011. Anesthesiology. 2014;120(4):810–8.
3. Katz V, Balderston K, DeFreest M. Perimortem cesarean delivery: were our assumptions correct? Am J Obstet Gynecol. 2005;192(6):1916–20. discussion 1920-1
4. Cohen SE, Andes LC, Carvalho B. Assessment of knowledge regarding cardiopulmonary resuscitation of pregnant women. Int J Obstet Anesth. 2008;17:20–5.
5. Einav S, Matot I, Berkenstadt H, Bromiker R, Weiniger CF. A survey of labour ward clinicians'

knowledge of maternal cardiac arrest and resuscitation. Int J Obstet Anesth. 2008;17(3):238–42.
6. Mogos MF, Salemi JL, Spooner KK, McFarlin BL, Salihu HM. Differences in mortality between pregnant and nonpregnant women after cardiopulmonary resuscitation. Obstet Gynecol. 2016;128(4):880–8.
7. Lavecchia M, Abenhaim HA. Cardiopulmonary resuscitation of pregnant women in the emergency department. Resuscitation. 2015;91:104–7.
8. Einav S, Kaufman N, Sela HY. Maternal cardiac arrest and perimortem caesarean delivery: evidence or expert-based? Resuscitation. 2012;83(10):1191–200.
9. Knight M, Nair M, Tuffnell D, Kenyon S, Shakespeare J, Brocklehurst P, on behalf of MBRRACE-UK, et al. Saving lives, improving mothers' care—surveillance of maternal deaths in the UK 2012-14 and lessons learned to inform maternity care from the UK and Ireland confidential enquiries into maternal deaths and morbidity 2009–14. Oxford: National Perinatal Epidemiology Unit, University of Oxford; 2016.
10. Lipman S, Cohen S, Einav S, Jeejeebhoy F, Mhyre JM, Morrison LJ, et al. The Society for Obstetric Anesthesia and Perinatology consensus statement on the Management of Cardiac Arrest in Pregnancy. Anesth Analg. 2014;118(5):1003–16.
11. Jeejeebhoy FM, Zelop CM, Lipman S, Carvalho B, Joglar J, Mhyre JM, et al. Cardiac arrest in pregnancy: a scientific statement from the American Heart Association. Circulation. 2015;132(18):1747–73.
12. Soar J, Perkins GD, Abbas G, Alfonzo A, Barelli A, BIerens JJLM, et al. European Resuscitation Council Guidelines for Resuscitation 2010 Section 8. Cardiac arrest in special circumstances: electrolyte abnormalities, poisoning, drowning, accidental hypothermia, hyperthermia, asthma, anaphylaxis, cardiac surgery, trauma, pregnancy, electrocution. Resuscitation. 2010;81(10):1400–33.
13. Truhlář A, Deakin CD, Soar J, Khalifa GEA, Alfonzo A, Bierens JJLM, et al. European Resuscitation Council Guidelines for Resuscitation 2015: section 4. Cardiac arrest in special circumstances. Resuscitation. 2015;95:148–201.
14. Paterson Brown S, Howell C. Chapter 4 cardiopulmonary resuscitation in the non-pregnant and pregnant patient. In: Managing obstetric emergencies and trauma: the MOET course manual. 3rd ed. Cambridge: Cambridge University Press; 2014. ISBN: 978-1-1076-7534-6, http://www.alsg.org/en/files/KCh42011.pdf [Accessed 07 June 2017].
15. Higuchi H, Takagi S, Zhang K, Furui I, Ozaki M. Effect of lateral tilt angle on the volume of the abdominal aorta and inferior vena cava in pregnant and nonpregnant women determined by magnetic resonance imaging. Anesthesiology. 2015;122(2):286–93.
16. Johnston TA, Grady K. Maternal collapse in pregnancy and the puerperium. The Royal College of Obstetricians and Gynaecologists Green-top Guideline No. 56. London (UK): RCOG, 2011. https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg56/ [Accessed: 07 June 2017].
17. Zelop CM, Hepner DL, Ramin SM, Walls RM Cardiopulmonary arrest in pregnancy. Uptodate 2017. http://www.uptodate.com/contents/cardiopulmonary-arrest-in-pregnancy [Accessed 07 June 2017].
18. Holmes S, Kirkpatrick ID, Zelop CM, Jassal DS. MRI evaluation of maternal cardiac displacement in pregnancy: implications for cardiopulmonary resuscitation. Am J Obstet Gynecol. 2015;213(3):401.e1–401. e5
19. Soar J, Deakin C, Lockey A, Nolan J, Perkins G. Advanced life support. 7th ed; 2016. ISBN: 978 1 903812 30 3, https://www.resus.org.uk/resuscitation-guidelines/adult-advanced-life-support/ [Accessed 07 June 2017]
20. Soar J, Nolan JP, Bottiger BW, Perkins GD, Lott C, Carli P, et al. European Resuscitation Council Guidelines for Resuscitation 2015: section 3. Adult advanced life support. Resuscitation. 2015;95:100–47.
21. Neumar RW, Otto CW, Link MS, Kronick SL, Shuster M, Callaway CW, et al. Part 8: adult advanced cardiovascular life support: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2010;122:S729–67.
22. Balki M, Cooke ME, Dunington S, Salman A, Goldszmidt E. Unanticipated difficult airway in obstetric patients: development of a new algorithm for formative assessment in high-fidelity simulation. Anesthesiology. 2012;117:883–97.
23. Mushambi MC, Kinsella SM, Popat M, Swales H, Ramaswamy KK, Winton AL, et al. Obstetric Anaesthetists' Association and Difficult Airway Society guidelines for the management of difficult and failed tracheal intubation in obstetrics. Anaesthesia. 2015;70(11):1286–306.
24. Frerk C, Mitchell VS, McNarry AF, Mendonca C, Bhagrath R, Patel A, et al. Difficult Airway Society 2015 guidelines for management of unanticipated difficult intubation in adults. Br J Anaesth. 2015;115(6):827–48.
25. Pepe PE, Roppolo LP, Fowler RL. The detrimental effects of ventilation during low-blood-flow states. Curr Opin Crit Care. 2005;11(3):212–8.
26. Levinson G, Shnider SM, DeLorimier AA, Steffenson JL. Effects of maternal hyperventilation on uterine blood flow and fetal oxygenation and acid-base status. Anesthesiology. 1974;40(4):340–7.
27. Kundra P, Khanna S, Habeebullah S, Ravishankar M. Manual displacement of the uterus during caesarean section. Anaesthesia. 2007;62(5):460–5.
28. Rees GA, Willis BA. Resuscitation in late pregnancy. Anaesthesia. 1988;43(5):347–9.
29. Vanden Hoek TL, Morrison LJ, Shuster M, Donnino M, Sinz E, Lavonas EJ, et al. Part 12: cardiac arrest in special situations: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2010;122(18 Suppl 3):S829–61.
30. Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee. http://www.transfusionguidelines.org/

transfusion-handbook/9-effective-transfusion-in-obstetric-practice/9-4-major-obstetric-haemorrhage [Accessed 12 July 2017].
31. Archer GW Jr, Marx GF. Arterial oxygen tension during apnoea in parturient women. Br J Anaesth. 1974;46(5):358–60.
32. Bush N, Nelson-Piercy C, Spark P, Kurinczuk JJ, Brocklehurst P, Knight M, UKOSS. Myocardial infarction in pregnancy and postpartum in the UK. Eur J Prev Cardiol. 2013;20(1):12–20.
33. Roth A, Elkayam U. Acute myocardial infarction associated with pregnancy. J Am Coll Cardiol. 2008;52(3):171–80.
34. Ahearn GS, Hadjiliadis D, Govert JA, Tapson VF. Massive pulmonary embolism during pregnancy successfully treated with recombinant tissue plasminogen activator: a case report and review of treatment options. Arch Intern Med. 2002;162:1221–7.
35. Knight M. UKOSS. Antenatal pulmonary embolism: risk factors, management and outcomes. BJOG. 2008;115:453–61.
36. Knight M, Kurinczuk JJ, Tufnell D, Brocklehurst P. The UK obstetric surveillance system for rare disorders of pregnancy. BJOG. 2005;112(3):263–5.
37. Stanten RD, Iverson LI, Daugharty TM, Lovett SM, Terry C, Blumenstock E. Amniotic fluid embolism causing catastrophic pulmonary vasoconstriction: diagnosis by transesophageal echocardiogram and treatment by cardiopulmonary bypass. Obstet Gynecol. 2003;102(3):496–8.
38. Shen HP, Chang WC, Yeh LS, Ho M. Amniotic fluid embolism treated with emergency extracorporeal membrane oxygenation: a case report. J Reprod Med. 2009;54:706–8.
39. Rayburn W, Wolk R, Mercer N, Roberts J. Parental nutrition in obstetrics and gynecology. Obstet Gynecol Surv. 1986;41:200–14.
40. Bern S, Weinbery G. Local anesthetic toxicity and lipid resuscitation in pregnancy. Curr Opin Anaesthesiol. 2011;24(3):262–7.
41. Rose CH, Faksh A, Traynor KD, Cabrera D, Arendt KW, Brost BC. Challenging the 4- to 5-minute rule: from perimortem caesarean to resuscitative hysterotomy. Am J Obstet Gynecol. 2015;213(5):653–6.
42. Knight M, Kenyon S, Brocklehurst P, Neilson J, Shakespeare J, Kurinczuk JJ on behalf of MBRRACE-UK (eds). Saving Lives, Improving Mothers' Care—Lessons learned to inform future maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009–12. Oxford: National Perinatal Epidemiology Unit, University of Oxford 2014.
43. Svinos H. BET 1: emergency caesarean section in cardiac arrest before the third trimester. Emerg Med J. 2008;25:764–5.
44. Dijkman A, Huisman CM, Smit M, Schutte JM, Zwart JJ, van Roosmalen JJ, et al. Cardiac arrest in pregnancy: increasing use of perimortem caesarean section due to emergency skills training? BJOG. 2010;117(3):282–7.
45. Lipman S, Daniels K, Cohen SE, Carvalho B. Labor room setting compared with the operating room for simulated perimortem cesarean delivery: a randomized controlled trial. Obstet Gynecol. 2011;118(5):1090–4.
46. Lipman SS, Wong JY, Arafeh J, Cohen SE, Carvalho B. Transport decreases the quality of cardiopulmonary resuscitation during simulated maternal cardiac arrest. Anesth Analg. 2013;116(1):162–7.
47. Lipman SS, Daniels KI, Arafeh J, Halamek LP. The case for OBLS: a simulation-based obstetric life support program. Semin Perinatol. 2011;35(2):74–9.
48. Drukker L, Hants Y, Einav S, Sela HY, Grisaru-Granovsky S. Perimortem cesarean section for maternal and fetal salvage: concise review and protocol. Acta Obstet Gynecol Scand. 2014;93(10):965–72.
49. Lipman SS, Daniels KI, Carvalho B, Arafeh J, Harney K, Puck A, Cohen SE, Druzin M. Deficits in the provision of cardiopulmonary resuscitation during simulated obstetric crises. Am J Obstet Gynecol. 2010;203(2):179.e1–5.
50. Al-Foudri H, Kevelighan E, Catling S. CEMACH 2003–5 saving mothers' lives: lessons for anaesthetists. Continuing education in anaesthesia. Crit Care Med. 2010;10:81–7.

28

Intensive Care Management of the Pregnant Patient after Cardiac Arrest

Markus B. Skrifvars

Bullet Points

- Cardiac arrest is uncommon in pregnant patients. Therefore, few intensivists have experience with post-cardiac arrest care in pregnancy.
- Pregnant post-cardiac arrest patients should receive tailored intensive care considering the state of pregnancy, general principles of post-cardiac arrest care and the disease causing the arrest.
- Cardiac causes commonly lead to ventricular fibrillation or ventricular tachycardia and may result from a myocardial infarction, cardiomyopathy or myocarditis.
- Non-cardiac causes such as hypovolemia related to bleeding, hypoxia, thromboembolism, maternal fluid embolism and air embolism as well as intracranial bleeding are possible causes of cardiac arrests with a non-shockable rhythm such as pulseless electrical activity or asystole.
- Immediately after return of spontaneous circulation, the patient should be assessed according to an ABCD approach.
- The airway should be secured in all patients after cardiac arrest unless they are conscious and have stable vital signs. Endotracheal intubation may be difficult and should be done with diligence.
- Hypoxia, extreme hyperoxia as well as hypo- and hypercarbia should be avoided. Mechanical ventilation should be undertaken utilising a lung-protective strategy.
- Blood pressure may be high immediately after return of spontaneous circulation if the patient has received adrenaline during cardiopulmonary resuscitation but afterwards patients may require intravenous fluid and/or vasopressors. The blood pressure target should be between 65 and 70 mmHg.
- Manage patient temperature targeting to 33–36 °C. In patients with bleeding or severe shock, targeting to 36° may be preferable.
- Use short-acting sedative agents such as propofol and remifentanil to facilitate early extubation in the neurologically improving patient.

M. B. Skrifvars (✉)
Department of Emergency Care and Services, Helsinki University Hospital and University of Helsinki, Helsinki, Finland
e-mail: markus.skrifvars@hus.fi

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_28

- Avoid hyper- and hypoglycaemia using insulin if needed. If the patient is not arousable within 48–72 h, a multimodal approach should be used to determine prognosis and guide future care. Include a thorough neurological examination, electroencephalography, a computed tomography of the brain, somatosensory evoked potentials and biomarkers.
- Recovery from cardiac arrest takes time and may require rehabilitation and support for both patient and family.

28.1 Introduction and Epidemiology

Given the rarity of cardiac arrest in pregnancy, most intensivists will have limited practical experience in post-cardiac arrest care of maternal patients. The United Kingdom cardiac arrest in pregnancy study (CAPS) published in 2017 identified 66 maternal deaths occurring in 1 year, equalling an incidence of 2.78 cases per 100,000 maternities [1]. Most of these deaths occurred in the hospital, and many were related to an anaesthetic procedure. The 12-month FINNRESUSCI study conducted in Finland (two large emergency medical systems and all Finnish intensive care units) identified no pregnant women among the 548 cardiac arrest patients who survived to intensive care unit (ICU) admission [2, 3]. In the United States, related at least in part to the opioid crisis, critical cardiovascular events such as cardiac arrests are increasing during pregnancy [4]. This trend may lead to a rise in the number of pregnant women with cardiac arrest who will require ICU care in the future.

All randomised controlled trials on post-resuscitation care have excluded pregnant patients [5–8]. Thus, the discussion regarding management of pregnant patients after cardiac arrest in this chapter is based on interpretation of the applicability, benefits and possible harms of the available therapeutic interventions given the state of the pregnancy, as well as on generally accepted principles of critical care management of the pregnant patient.

28.2 Pathophysiology of the Post-Cardiac Arrest Syndrome

Non-pregnant patients who initially survived cardiac arrest to be admitted to an ICU die mostly due to brain injury and less commonly due to cardiac injury [9, 10]. The main cause of brain injury is global hypoxia, which initiates a series of events that result in various degrees of hypoxic-ischaemic brain injury (HIBI) or hypoxic-ischaemic encephalopathy (HIE) [11, 12]. The damage occurring after cardiac arrest is usually described as a ‘two-hit model’. The primary injury occurs during cardiac standstill and is highly dependent on both the no-flow time (the period the patient is in cardiac arrest and does not receive any basic life support) and the low-flow time (the period of chest compression, during which there is some circulation) [13]. The development of HIBI appears to be predominantly related to the length of the no-flow state, accentuating the importance of immediate basic life support. The magnitude of pre-arrest hypoxia and hypotension also seem to be important [14]. Patients with cardiac arrest related to hypoxia (suffocation, hanging) appear to develop a severe form of HIBI and have a worse prognosis [15]. There are limited data about the cause of death in pregnant patients treated in the ICU after cardiac arrest, and there is little likelihood of data on this topic forthcoming soon. At this time, it is therefore reasonable to assume that these findings may be relevant in the pregnant population as well.

If return of spontaneous circulation (ROSC) is achieved, the second hit develops over the following 24–48 h [16]. The pathophysiology behind the second hit neurological injury is complex but includes reperfusion injury, disturbed autoregulation, local brain hypoxia and brain tissue oedema [11, 17]. Fever is a common feature and multiple studies have suggested harm from fever after cardiac arrest. During the first 24 h, cerebral blood flow decreases and oxygen deficit develops [18, 19]. In severe cases, catastrophic cerebral oedema may develop, leading to brain death. Patients may also develop a generalised systemic inflammatory response similar to that observed in sepsis, with elevation of inflammatory marker and cytokine levels [20, 21]. This

inflammatory response tends to manifest in patients who also develop extracranial organ failure [22, 23]. Myocardial dysfunction, which typically occurs during the first 24 h following ROSC and then tends to abate, is probably an important cause of this organ failure [24]. Treatment in cases with an evolving inflammatory response remains mainly supportive [22]. High-volume haemofiltration has been tried as a means of reducing inflammatory cytokine levels with inconclusive results [25].

28.3 Stage of Pregnancy and Change in Physiology Relevant to the ICU Physician

The stage of pregnancy will influence the type of ICU care provided after cardiac arrest [26]. During early pregnancy (up to a gestational age of 20 weeks), post-resuscitation treatment of the pregnant woman should adhere to the principles of post-resuscitation management for the general population [12]. At this time, the most profound physiological changes of pregnancy have yet to occur, and the fetus is not viable. Thus, the strategy should be to maximise the likelihood of benefit for the mother and, by proxy, that of the fetus. After 20 weeks of gestation, the physiological changes of pregnancy become more apparent and therefore merit greater consideration when planning care.

28.4 Immediate Management after Return of Spontaneous Circulation

Immediately after return of spontaneous circulation (ROSC) the woman should be surveyed according to an ABCD type approach.

Airway: Evidence shows that most women undergoing in-hospital resuscitation are intubated during the cardiac arrest [27]. However, the importance of intubation during CPR has recently been challenged [27]. Therefore, more patients may undergo cariopulmonary resuscitaiton (CPR) with only bag-valve-mask ventilation or airway devices in the future. After ROSC, the airway must be secured, with the sole exception of the completely conscious patient who has experienced a very brief cardiac arrest. Pregnant women also have an increased risk of regurgitation, placing even greater importance on securing of the airway with an endotracheal tube (ETT). Since endotracheal intubation is more difficult in pregnant women than in the general population, this should be performed in a controlled manner. Ideally, an airway checklist should be used (Table 28.1) [28]. Correct placement of the endotracheal tube is best confirmed by combining visual inspection of chest rise, fogging of the tube, continuous capnography and assessment of tube location by auscultation (i.e. absence of auditory sound over the stomach indicating oesophageal intubation followed by auditory signs indicating entry to air into the lungs during inspirium) [29]. Initially the tube should be placed and secured at a depth of 21–23 cm. Placement at the correct depth is then verified by chest radiography or direct fiberoscopy (see also Chap. 21).

Breathing: Most pregnant/post-partum women after cardiac arrest will likely require ventilator support. While there is no direct evidence to support this assumption, controlled mechanical ventilation may be less damaging than manual ventilation with unknown and probably dynamic parameters. Thus, mechanical ventilation is best initiated early after ROSC. Minute ventilation increases up to 50% during pregnancy [30]. Initial ventilation settings should take this change into consideration. As a rule of thumb, the aim should be for 14–16 breaths per minute, a tidal volume of between 400 and 500 mL (6–8 mL/kg ideal body weight) and a positive end-expiratory pressure (PEEP) of 6 cmH_2O.

During CPR, all patients receive 100% oxygen, and there is no accurate way to monitor the adequacy of oxygenation. After ROSC, oxygenation should be monitored using pulse oximetry (peripheral oxygen saturation) and by sampling of arterial blood gases. The fraction of inspired oxygen (FiO2) should be titrated to achieve an oxygen saturation of 94–98% [29]. If the woman is still undergoing bag-valve-mask ventilation, FiO2 may be adjusted by regulating fresh oxygen flow [31]. The FiO2 achieved will depend on minute

Table 28.1 Checklist to be used for safe management of the airway outside the operating room. All parts of the list are addressed by the whole team prior to initiating the procedure (modified from a list used since 2011 in the ED of Helsinki University Hospital and developed by RN M Kemppainen, RN A Rantanen, MD S Urtamo, MD J Puolakka)

Aim	Action
Preoxygenation	O_2 flow of >15 L, ensure the reservoir bag of the bag-valve-mask is full
Intravenous access	Ideally two iv lines with fluid running
Patient monitoring	1. Peripheral oxygenation saturation 2. Electrocardiography 3. Invasive blood pressure if possible, or non-invasive measurement set to measure every 2 min 4. Capnography connected to the bag-valve-mask with curve shown on screen (ensure it functions by using it during preoxygenation) 5. Assign one person to follow vital signs during the procedure
Medications	1. Anesthetic drugs 2. Norepinephrine infusion prepared and connected to an intravenous line 3. A bolus of vasopressor (diluted norepinephrine or diluted epinephrine) prepared in a 5 ml syringe
Airway equipment	1. Endotracheal tube - prepare two sizes and a 10 ml syringe for filling cuff 2. Laryngoscope ready and checked 3. Stylet or bougie ready to be used with lubricant 4. Tape or lace for securing the endotracheal tube 5. Suction ready and checked 6. Plan for difficult intubation. Consider and prepare a videolaryngoscope and an supraglottic airway
Prepare the patient	1. Optimise patient positioning, use the 'sniffing position' 2. Optimise work conditions for the person performing intubation 3. Clarify the person allocated to each of the following roles: (a) Performance of cricoid pressure (if required) (b) Moving the larynx into an optimal position (c) Positioning the side of the patients' mouth to facilitate tube insertion 4. Decide on a strategy of there is a circulatory collapse and the patient requires cardiopulmonary resuscitation

ventilation; with an oxygen flow of 4 L/min, the FiO2 approximates 50% [31]. Most women will not require prolonged ventilation with 100% oxygen. However, if arrest had occurred secondary to hypoxia (e.g. suffocation, acute asthma, pulmonary embolism or aspiration), ongoing treatment with high FiO2 may be required to maintain appropriate oxygen saturation. If the cause of the arrest was cardiac and CPR was promptly initiated, less oxygen will probably be required. In this situation, prolonged use of 100% oxygen will result in extreme hyperoxia [32].

Ventilation should be adjusted to achieve a PaCO2 of around 32–34 mmHg, which is normal during pregnancy [30]. Hyperventilation (PaCO2 < 32 mmHg) is harmful both during and after cardiac arrest in the non-pregnant patient [33, 34]. In pregnant women, hyperventilation may also cause vasoconstriction with a resultant decrease in uterine blood flow, which may lead to foetal distress [35]. End-tidal CO2 level monitored by capnography may provide some guidance for setting ventilation after the woman has stabilised. However, in the first hours after cardiac arrest, there may be a large arterial-alveolar difference due to faulty tissue perfusion (including the lungs). Thus, setting the correct minute ventilation requires frequent arterial blood gas sampling in the first hours of ventilation [36]. This will also aid in adjusting FiO2.

28.4.1 Circulation

During the first 20 min after ROSC, the risk of re-arrest is high. Efforts should be invested in ensuring adequate monitoring of patient vital signs. This should include continuous

electrocardiography (ECG), blood pressure and capnography. A sudden drop in end-tidal CO2 suggests impending re-arrest; this can be verified by identifying lack of a palpable pulse and loss of an organised cardiac rhythm on the ECG. The treating staff should be prepared to identify and rapidly manage re-arrest should this occur. If the woman had a shockable initial rhythm and sequences of shock-resistant ventricular fibrillation/tachycardia (VF/VT), these arrhythmias may recur. In such cases, a defibrillator must remain available nearby. If the woman was resuscitated from a non-shockable rhythm such as pulseless electrical activity (PEA) or asystole, recurrent PEA or severe hypotension are more likely. These can only be identified if blood pressure is measured continuously parallel to monitoring of electrocardiography. A high-monitoring environment and invasive blood pressure measurement are preferred as these will facilitate the response to possible maternal re-arrest.

Adrenaline received during resuscitation can sometimes greatly elevate systemic blood pressures. The half-life of adrenaline approximates 5 min, therefore the treating clinician should be alert to the option of hypotension occurring shortly (within 5–10 min) after ROSC [12]. The likelihood of such occurrence may even be higher in women whose cause of arrest was hypovolemia (e.g. hemorrhage).

Disability: A brief neurological examination should be undertaken after ROSC. If the woman has received adrenaline or atropine her pupils may be dilated. If the patient is restless or combative, a sedative agent or opiate should be administered. Generally, extubation should not be performed shortly after ROSC; the added work of spontaneous breathing may augment post-arrest intracellular energy deficit, and the patient may not be able to protect her airway, resulting in gastric aspiration. Sedation must be tailored first and foremost to maternal condition, as foetal well-being hinges on maternal well-being. Additional considerations affecting the choice of sedation are the stage of pregnancy and the pregnancy management plan. If immediate delivery is planned, an obstetric anaesthesiologist and a neonatologist should be involved in the decision-making process at this stage. For example, if caesarean delivery is being planned, sedation should be kept to a minimum in order to diminish the likelihood of neonatal respiratory depression. See below the discussion regarding sedation options.

28.5 Logistics of ICU Care

Comatose post-ROSC patients commonly require intensive care for a minimum of 48–72 h. Observational data from non-pregnant out of hospital cardiac arrest patients suggests that transfer from the scene of the arrest to a specialised cardiac arrest centre may be associated with better outcomes than transfer to the nearest hospital [37–39]. Pregnant and peripartum women who have arrested outside the hospital, and achieved ROSC should be transferred to a hospital with both intensive care and obstetric expertise. The details of the arrest and the clinical condition of the patient after ROSC should be ascertained from the emergency medical service (in case of out-of-hospital arrest) or the resuscitation team (in case of in-hospital arrest) and diligently documented. These details are of paramount importance for decisions at a later stage of intensive care (Table 28.1). A protocol should ideally be used in all intensive care units when managing patients after cardiac arrest [40]. This is particularly true for pregnant women, as care is being delivered to two patients rather than one.

28.6 Determining the Cause of the Arrest

Important information regarding cardiac arrest management will provide clues on arrest cause, and should be collected from the CPR providers, either the emergency medical service providers or members of the in-hospital cardiac arrest team (Table 28.2). Acute myocardial infarction is the most common cause for cardiac arrest in non-pregnant patients, but it is less common in pregnant patients [41]. In pregnant women, heart failure due to exacerbation of pre-existing heart

Table 28.2 Pre- and intra-arrest factors that should be ascertained from the emergency medical service (in case of out-of-hospital arrest) or the resuscitation team (in case of in-hospital arrest) and diligently documented. These details are of paramount importance for decisions at a later stage of intensive care

Factor	Relevance and how to avoid pitfalls
Relevant symptoms prior to the arrest	May provide insight regarding the etiology of the arrest Headache may suggest an intracranial process. Dyspnea may suggest heart failure or pulmonary embolism. Chest pain may suggest myocardial infarction or arterial dissection
Clinical status prior to the arrest	Seizure in late pregnancy is most commonly pre-eclampsia. Other possible causes are intracranial pathologies such as subarachnoid hemorrhage, other forms of intracerebral hemorrhage or sinus vein thrombosis. Cardiac arrest in such cases may be related to a sudden increase in intracerebral pressure or severe hypoxia due to respiratory depression
Was the arrest witnessed?	Unwitnessed arrest has a much worse prognosis both in and out of hospital
Did the patients receive bystander-initiated life support?	Chest compression is pivotal for survival and may not have been delivered in a timely manner. Even in-hospital cardiac arrest may not be recognised or responded to appropriately. Obstetric department staff rarely encounter patients in cardiac arrest
Initial rhythm	May suggest the most likely cause of arrest and is also an important predictor of survival. The reported initial rhythm is best verified against real-time pre-hospital/event electrocardiography printouts
Duration of the arrest	The actual time of the arrest may be difficult to ascertain. It is therefore common practice to use the time the call was placed to the dispatch centre or to the cardiac arrest team as “time zero”
Clinical findings after return of spontaneous circulation	Persistent hypertension (notwithstanding intra-arrest use of adrenaline) suggests eclampsia or an intracranial process Ongoing hypotension suggests bleeding Ongoing hypoxia suggests pulmonary embolisms or massive aspiration

disease, cardiomyopathy or myocarditis are more common [42] and may cause a primary cardiac arrhythmia. However, myocardial infarction has also been reported during pregnancy [43]. Ventricular fibrillation may also be related to certain electrolyte disturbances and intoxications [44].

The diagnostic workup of patients resuscitated from a shockable rhythm should start with a 12-lead ECG. In cases of prolonged CPR with use of adrenaline, changes suggesting ischaemia may be seen immediately after ROSC. Therefore decisions should be made based on the findings of an ECG obtained 20 min from ROSC [42].

If ongoing ST-segment elevation is observed, additional investigations should be undertaken without delay regardless of pregnancy [43, 45]. The value of measuring cardiac enzyme levels early after cardiac arrest remains unclear even in the general population [46]. An echocardiogram (ECHO) may reveal regional wall motion abnormalities, valvular abnormalities (e.g. aortic stenosis, mitral regurgitation), cardiomyopathy or severe cardiac failure. Computed tomography may be required to rule out alternative causes (e.g. aortic or coronary dissection). If indicated, iodinated contrast media may be used despite ongoing pregnancy. To date, no teratogenic effects have been clearly attributed to exposure to the newer generation of low-osmolality contrast media during pregnancy [47].

The option of coronary artery disease as the cause of cardiac arrest is commonly overlooked even in non-pregnant women [48]. While pregnant women are younger, aortic dissection, coronary artery dissection and clinically significant atherosclerotic coronary artery disease have all been described during pregnancy [49]. Maternal mortality from myocardial infarction ranges between 5% and 37% even in developed countries [47, 50, 51]. Therefore, regardless of pregnancy, the mother should receive appropriate workup and treatment. In the presence of ongoing ST-elevation (and in some cases with non-ST elevation myocardial infarction), early coronary angiography may be indicated [52].

Coronary rupture has been reported during performance of coronary angiography in pregnant women, and foetal exposure to ionising radiation should be minimised, therefore such catheterisation should only be performed by an experienced invasive cardiologist. In such cases, the risk-benefit ratio must always be weighed together with the family on an individual basis, the understanding being that the benefit of the mother comes before that of the fetus.

Subarachnoid hemorrhage (SAH) may also cause ventricular fibrillation in rare instances. If the ECG and ECHO results are normal, computed tomography imaging of the brain is indicated. The presence of a headache preceding the arrest is often described in SAH-related cardiac arrest. However, the absence of a pre-arrest headache does not rule out SAH [53].

For pregnant women with PEA as their initial non-perfusing rhythm, the mnemonic BEAUCHOPS (bleeding, embolism, anaesthetic complications, uterine atony, cardiac disease, hypertension due to eclampsia, other causes and sepsis) summarises the etiological factors that should be considered (Table 28.3) [54]. Efforts should be made to identify and treat these causes as well as the causes of PEA observed in the general population even during resuscitation [55]. If this has not been completed before ROSC, the likely etiology should be ascertained with further

Table 28.3 Identifying the cause of the arrest and tailoring investigations and management in the ICU according to the mnemonic 'BEAUCHOPS'

Cause of the arrest	Diagnostic considerations	Management priorities immediately after ROSC	Management priorities during the first 24–48 h
Bleeding	Hemoglobin level, coagulation status, focused assessment with s*onography* for trauma (FAST), whole body computed tomography, temperature, arterial blood gases and electrolytes	Identify active bleeding identify and control the source of bleeding, correct coagulation profile, transfuse, warm the patient and correct acid-base and electrolyte disorders throughout surgery/ radiological intervention	Identify possible rebleeding. Manage coagulation and venous thromboembolism prophylaxis
Embolism	Echocardiography Computed tomography coronary angiography Duplex ultrasound of the lower limbs	Thrombolysis/surgical embolectomy and/or extracorporeal membrane oxygenator	Anticoagulation with heparin infusion or low molecular weight heparin
Anaesthetic complications	Identify possible trigger and Document the relevant clinical details of the event	Stabilisation	Stabilisation
Uterine atony	Obstetric consultation, vaginal ultrasound, clinical examination	Immediate surgery	Stabilisation
Hypertension due to eclampsia	Clinical history, urinary screening for protein, electroencephalography, kidney and liver function tests	Computed tomography of the brain to rule out complications, managment of convulsions and blood pressure stabilization	Identify relevant organ failure (liver, kidneys), infuse magnesium, control blood pressure
Other cause	Clinical history suggesting overdose, drug screen. In case of trauma appropriate CT scan (head, neck, thorax, abdomen, pelvis)	Relevant antidote if such exists (e.g. naloxone) arterial blood gas (seek findings suggestive of intoxications), anion gap calculation Identify active bleeding in trauma patients	Stabilisation. Renal replacement in certain intoxications Trauma treatment according to standard management strategies
Sepsis	Blood, sputum and urinary cultures, cerebrospinal fluid in specific cases, chest radiography, targeted computed tomography scan	Antibiotics	Antibiotics and obtain source control

investigations after ROSC and treatment should be targeted accordingly (Table 28.2). Initial workup should include 12-lead ECG, arterial blood gas analysis with lactate, haemoglobin and electrolytes and chest radiography. A computed tomography scan of the brain, thorax, abdomen, and pelvis should be considered. CT angiogram must be undertaken if pulmonary embolism or arterial dissection is suspected and in select cases with suspected coronary heart disease. A drug and toxicology screen is in order when there is reason to suspect drug abuse or foul play and when no other obvious cause of arrest has been identified.

The circumstances surrounding the arrest will also be important for prognostication purposes (Table 28.2) [56] and must therefore be accurately documented in the hospital charts. If the CA occurs in the hospital during delivery (either vaginal or C-section), hemorrhage, eclampsia and maternal fluid and air embolism need to be kept in mind. Maternal amniotic fluid embolism is a dramatic event which occurs most commonly immediately after delivery of the placenta [57].

28.7 Mechanical Ventilation

Most patients with cardiac arrest who have been admitted to intensive care remain ventilated for 24–72 h [58]. The goals of positive pressure mechanical ventilation are to provide stable oxygenation and ventilation while protecting the lungs from secondary damage [59].

Oxygenation targets: Maternal hypoxemia (PaO2 < 75 mmHg) should be avoided by means of moderate PEEP and, if required, increased FiO2 [32]. Maternal arterial oxygen in the range of 75–100 mmHg appears to suffice for fetal oxygenation [60, 61]. Retrospective studies have associated extreme hyperoxia (PaO2 > 300 mmHg) in the first days after ROSC with higher death rates and poorer neurological outcomes [62, 63]. Hyperoxia is most commonly observed with inadvertent prolonged use of 100% oxygen [32]. Whether targeting moderate hyperoxia is protective or harmful in cardiac arrest patients is currently unclear [58]. Therefore, until more data is forthcoming. Hyperoxia should be avoided after cardiac arrest.

Ventilation targets: In late pregnancy (>28 weeks), the normal PaCO2 is in the range of 30–32 mmHg, which is lower than in the non-pregnant patient [26]. This is multifactorial, but is in part related to hyperventilation induced by progesterone and beginning after the first trimester. In cardiac arrest patients, the evidence is conflicting regarding optimal PaCO2 targets. It is generally accepted that hyperventilation should be avoided as it can induce arterial vasoconstriction in the brain [58, 64, 65]. As noted above, in pregnant women, hyperventilation may also cause uterine artery vasoconstriction, thereby decreasing blood flow to the fetus [26]. Mild hypercapnia has been shown to increase brain oxygenation [66, 67]. Current investigations in non-pregnant patients after ROSC are therefore focusing on the option of targeting mild hypercapnia. However, in the pregnant patient, even mild hypercapnia may cause acidosis which may be harmful for the fetus and cannot be recommended for pregnant patients at the present time [54, 60]. As there is no conclusive evidence regarding carbon dioxide targets, targeting normoventilation is likely most safe.

Lung protection: Lung-protective ventilation with avoidance of excessive tidal volumes is recommended in patients with ARDS. One study showed an increase in mortality with tidal volumes (TV) exceeding 8 mL/kg (predicted ideal body weight) [68]. Thus, in general, TVs of 5–6 mL/kg should be used and the frequency titrated to achieve the desired PaCO2. This might be slightly more challenging in the pregnant patient than in the general population given the metabolic increase. The indications for and method of lung-protective ventilation are discussed in greater detail in Chap. 23.

28.8 Targeted Temperature Management

Targeting of systemic temperatures to 33–36 °C for at least 24 h is recommended in non-pregnant cardiac arrest patients [12]. Recent evidence support the use of TTM also in patients resuscitated from non-shockable and in-hospital CA [69].

However, all clinical trials thus far have focused mainly on patients with an assumed cardiac cause for the arrest and have excluded pregnant women. There is little or no data on whether targeted temperature management (TTM) is efficacious in arrests occurring due to non-cardiac causes (e.g. pulmonary embolism, hypoxia, hemorrhage), although the ultimate mechanism of brain injury is likely to be similar (hypoperfusion mixed with increasing hypoxemia over time). In addition, the evidence suggests TTM may be beneficial mainly for patients resuscitated from a shockable initial rhythm [70].

TTM in pregnant and peripartum women: The two main concerns regarding the use of TTM in pregnant and peripartum women after ROSC are the risk of maternal hemorrhage and the potential for fetal damage especially if targeting 33 °C. Nonetheless, case reports have come out in recent years describing successful treatment of pregnant women with TTM which have suggested feasibility and lack of side effects [71]. Cardiac conduction may be modified during hypothermia with prolongation of the QT interval, QRS and PR segments all being observed. This reduction in heart rates usually only occurs within the lower range of temperatures used for TTM [72]. One case reported appearance of maternal bradycardia at 33 °C accompanied by signs of fetal distress [73]. Therefore, TTM of pregnant women must be accompanied by close monitoring and controlling of maternal heart rate and continuous monitoring of fetal heart rate. The decision as to which temperature (33 or 36 degrees) to target should be made on a case-by-case basis while taking into account the possible benefits and risks.

Systemic temperatures below 32 °C may also affect the coagulation cascade and platelet function [74]. This issue is of concern particularly in the peripartum period when there is an increased risk of maternal bleeding regardless of the mode of delivery. Theoretically, the risk of bleeding increases as systemic temperatures decrease. In non-pregnant patients after ROSC, there do not appear to be major differences in outcome when treated with 33 °C versus 36 °C. Therefore, in women after ROSC who are at risk of hemorrhage, a temperature of 36 °C should be targeted. At this time the literature describes only two women who arrested post-partum and were treated with TTM after achieving ROSC; of these, one exhibited coagulopathy [75]. However, the characteristics of the case were suggestive of amniotic fluid embolism which may itself be accompanied by coagulopathy. TTM after cardiac arrest is generally not associated with an increased risk of bleeding [5, 6]. Therefore, this treatment should be provided if it may improve maternal outcome. However, more attention should be directed towards selection of the individuals for treatment and to monitoring to prevent bleeding complications.

Pre-hospital induction of hypothermia with cold fluids during the arrest [76] or after ROSC is not beneficial [77, 78]. Targeted temperature management should therefore be started in the ICU and should continue for at least 24 h (Table 28.3). Outcomes are not better with treatment for 48 h compared to 24 h [5]. At the end of the TTM treatment period, the woman should be rewarmed slowly to 36.5–37 °C. Fever occurs commonly and may be treated with paracetamol. Any rebound hyperthermia may be treated invasively or non-invasively [5]. Temperatures exceeding 38.5 °C should be prevented especially in the comatose patients with signs of hypoxic-ischaemic brain injury.

28.9 Sedation

In the first 24 h after ROSC, sedation should be kept deep in most cases; waking the patient up in order to perform neurological assessment is best avoided [79]. Most patients are encephalopathic, and the lack of a positive neurological response does not influence treatment decisions. A wake-up test may cause hypertension and arrhythmias and increase intracerebral pressure. Exceptions to this rule include patients with a very brief cardiac arrest, cases with alcohol intoxication or drug overdose, or those needing frequent clinical neurological assessments when findings may change immediate clinical management (e.g. when there are focal findings on the brain CT

scan). After 24 h, sedation should be titrated using a sedation scale [80, 81].

Traditionally patients treated with TTM after ROSC were sedated using continuous infusions of midazolam and fentanyl [8]. At this time, short-acting agents such as propofol and remifentanil are preferred as they have been shown to shorten the time to extubation in this population [82]. Propofol is more likely to cause hypotension than midazolam [83, 84]. Thus, despite literature associating this drug with delirium and poorer outcomes, midazolam remains favoured by some for haemodynamically unstable patients [79]. Dexmedetomidine is another option for pregnant post-cardiac arrest women. Dexmedetomidine causes less hypertension and tachycardia than midazolam and has therefore been used in women with eclampsia for control of hypertension [85, 86]. However, in non-pregnant patients undergoing TTM (33 °C), the use of dexmedetomidine has been associated with bradycardia [87]. Dexmedetomidine has also been proposed for sedation during rewarming as shivering may occur at this stage of treatment, although conclusive evidence to support such practice is still lacking [88]. The metabolism of many sedative drugs (e.g. propofol, midazolam, morphine) is prolonged at systemic temperatures below the norm, therefore dosing may require adjustment dependent on the temperatures targeted and the phase of treatment [83].

28.10 Blood Pressure Management

The optimal blood pressure after cardiac arrest is not well defined. Studies have shown that disturbed cerebral autoregulation and decreases in cerebral blood flow contributes to poor outcome in patients post cardiac arrest [84]. Especially in patients with chronic hypertension, the autoregulation curve is shifted to the right, and patients could benefit from higher blood pressure [89]. Patients with eclampsia also appear to have disturbed autoregulation [90]. Nonetheless recent evidence does not support targeting mean arterial blood pressures higher than 65–70 mmHg after return of spontaneous circulation [91–93]. Marked hypotension with blood pressure less than 60 mmHg appears harmful [94] and should be avoided during the first 48 h. Signs of adequate blood pressure include adequate urinary output and decreasing lactate [12]. The one exception to this rule may be the woman with active bleeding where there is some evidence to support carefully monitored hypotensive resuscitation until bleeding has been controlled [94, 95].

Hypotension should generally be treated with either intravenous fluids or vasopressors, depending on the possible cause of the arrest. Hypovolemic shock (i.e. if the cause of arrest was hemorrhage or loss of intravascular volume for any other reason) should continue to be treated with fluids or blood products. Cardiogenic shock (i.e. infarction, arrhythmia, myocarditis) should be treated with vasopressors. Distributive shock (sepsis, anaphylaxis) may require treatment with both. In obstructive shock (e.g. pulmonary embolism, pneumothorax, tamponade), the woman will be less responsive to treatment with either fluids or vasopressors. In this situation the cause of the arrest must be reversed rapidly to maintain circulation, this may include thrombolysis or insertion of a chest drain.

There is limited evidence to direct the choice of vasopressors after cardiac arrest. However, vasoplegia is often seen after ROSC, particularly in patients who have entered the metabolic stage of cardiac arrest (i.e. in prolonged resuscitation). Norepinephrine is a good treatment option, but large amounts of fluid may also need to be infused. Norepinephrine increases mean arterial blood pressure without resulting in tachycardia [91, 92]. Based on data from patients with cardiogenic shock, treatment with norepinephrine is preferred over treatment with epinephrine which may cause severe tachycardia and recurrent shock [96]. Also see Chap. 38 regarding drug treatment during pregnancy. The response to treatment is best judged by lactate clearance and urinary output (0.5–1 mL/kg) [93, 97, 98]. The possibility of recurring cardiac ischemia should be kept in mind and serial echocardiography imaging to assess cardiac and valve function and left ventricular filling pressures may be indicated. Anecdotal evidence supports the short-term use

of inhaled nitric oxide and milrinone in the patient treated after cardiac arrest related to maternal fluid embolism [56].

28.11 Fluid and Glucose Management

Extrapolation from non-pregnant patients suggests that hypotonic fluids should be avoided during the first 24–48 h unless the patient has documented hypernatremia, and fluids containing glucose should be avoided unless the patient has a documented hypoglycaemia [99–102]. Apart from these two specific situations, there is limited evidence regarding the choice of fluid after cardiac arrest (see also Chap. 7 regarding fluid therapy). If there is clear evidence of cerebral edema, targeting a blood sodium level of 140–145 mmol/L appears well justified [17]. Hypertonic saline or mannitol may also be used in severe brain edema cases, although conclusive evidence of their benefit is lacking [17].

Hyperglycemia is commonly found in patients admitted after cardiac arrest and is associated with worse outcomes [103]. Lenient normoglycemia (i.e. blood glucose <10 mmol/L) is best targeted [104, 105]. Strict normoglycemia increases the likelihood of iatrogenically induced hypoglycemia without increasing benefit [7, 105].

28.12 Management of Seizures

Ideally, patients after cardiac arrest should be monitored with continuous electroencephalography (EEG) to allow early identification of epileptic activity. When such monitoring is unavailable, intermittent EEG is also an option. Seizures (and more often myoclonus) often occur in non-pregnant patients after ROSC and are usually related to HIBI [106]. In pregnant or peripartum women, the possibility of pre-eclampsia and eclampsia should also be kept in mind [26]. Differentiating between these two conditions may be difficult. However, HIBI usually occurs after prolonged CPR and tends to appear more than 24 h after ROSC. Epileptic activity and seizures related to HIBI are strongly associated with no- and low-flow times [106].

There is no evidence to support prophylactic seizure prevention after ROSC [12, 107, 108]. The presence of epileptic activity is associated with a poor prognosis, but some patients are amenable to treatment once such activity has appeared. Phenytoin is not particularly effective in treatment of myoclonus or more severe epileptic activity related to HIBI [109]. Sodium valproate is contraindicated in pregnancy given the risk of birth defects. Therefore, in pregnant women with seizure activity after ROSC, levetiracetam is probably the drug of choice [110, 111]. Levetiracetam is eliminated by the kidneys and has linear pharmacokinetics and low protein binding, all of which increase its safety profile for both mother and fetus. Seizures related to eclampsia should also be treated with magnesium and strict control of blood pressure (See also Chap. 16).

28.13 General Intensive Care Management

If the gestational age is greater than 20 weeks, and the fetus is still in situ, placing the woman in the supine position is accompanied by the risk of aortocaval compression. Aortocaval compression may decrease venous return, causing hypotension and even shock or re-arrest. Therefore, after ROSC, the pregnant woman should be placed in a left lateral tilt position. Because of the option of inferior cava compression, central venous lines should be placed above the diaphragm [26, 54]. The risk of thrombosis is increased in pregnancy. However, coagulation disturbances have been described after cardiac arrest and have been associated with worse outcome [112]. Whether these coagulation disturbances require correction and to what degree such correction is possible and/or may change outcome remains unclear [113]. It is therefore wise to test coagulation periodically in order to balance the risk of administering prophylaxis for deep vein thrombosis with the need to correct coagulation abnormalities on an individual basis.

Aspiration may occur both during and after cardiac arrest, especially with prolonged periods of bag-valve-mask ventilation. Although gastric content may be sterile in non-hospitalised patients, treatment with an antibiotic is justified. In general in patients undergoing TTM after cardiac arrest, prophylactic uses of antibiotics has been shown to decrease the incidence of ventilator associated pneumonia [114]. The antibiotic chosen should depend on the cause of the arrest (e.g. hemorrhage vs. pneumonia) as well as local practices and bacterial resistance patterns. If the cause of arrest was not infectious, a second generation cephalosporin (e.g. cefuroxime) has been shown to suffice in unconscious traumatic brain injury patients [115]. Although there is limited evidence to support such practice, if the woman remains hypoxemic and aspiration is suspected, fiberoptic bronchoscopy and pulmonary lavage may be considered in order to remove residual gastric content and/or sputum[116].

Gastric ulcer prophylaxis is commonly used in intensive care, although conclusive evidence to support such practice is lacking [117]. Pregnant and peripartum women also have an increased risk of regurgitation, the symptoms of which may be alleviated with proton-pump inhibitors. Comatose hemodynamically unstable patients have a higher risk of developing gastrointestinal hemorrhage. Patients after myocardial infarction and/or percutaneous coronary intervention commonly receive antiplatelet agents and anticoagulants, further increasing the risk gastrointestinal hemorrhage.

28.14 Extracorporeal Membrane Oxygenation (ECMO) and Mechanical Assist Devices

The role of ECMO in management of cardiac arrest is unclear, especially in pregnant patients [118]. One centre has reported good results with the use ECMO in pregnant patients but only half of the women described were placed on ECMO during or immediately after CPR (see also Chap. 14). In the patient with extreme shock or hypoxia after return of spontaneous circulation, consideration should be given to treatment in an ECMO center (so-called ECMO watch) [56]. In non-pregnant patients, there is some evidence supporting the use of an intra-aortic balloon pump (IABP) [119–121], but there is no data on its applicability in pregnant patients. Furthermore, in late pregnancy, placing the patient in a lateral decubitus position may be difficult with an IABP. Caesarean section may also be considered if there is a chance that surgery will facilitate rather than complicate further care of the mother.

28.15 Prognostication

Patients after ROSC are usually kept sedated for 24–36 h, after which sedation is stopped, provided patient condition so allows. Continued sedation may be required in severe hypoxia, severe disseminated intravascular coagulopathy with ongoing hemorrhage or when brain edema or other pathological intracranial processes have been diagnosed [12, 79]. Ongoing coma or partial consciousness after termination of sedation suggests hypoxic-ischaemic encephalopathy (HIE). Factors increasing the risk of HIE are the absence of bystander-initiated life support and prolonged delays to return of spontaneous circulation [29]. HIE in general does not occur with ROSC delays briefer than 5 min.

If the patient fails to awaken, consultation with a neurologist is warranted and a multimodal prognostication approach should be applied [122]. Based on test results, the family can be approached with recommendations for further treatment, or in some cases, treatment withdrawal. All unconscious patients should undergo a thorough clinical examination. Important features include the presence/absence of brainstem reflexes (e.g. pupil size and reactivity, gag reflex) and cortical responses. An electroencephalography should again be obtained, as at this time it may identify more severe forms of HIE. Computed tomography of the brain is warranted to rule out intracranial pathology (e.g. severe brain oedema in HIE, hemorrhage). In some cases, magnetic resonance imaging of the brain may provide additional information on the severity of HIE and on the presence of lesions in areas of the brainstem which are seen less clearly in computed tomogra-

phy. Blood levels of specific brain biomarkers may also be used for prognostication after cardiac arrest. In non-pregnant patients, neuron-specific enolase (NSE) is most widely used and has been validated [123–125]; an increase in NSE between 24 and 48 h and elevated NSE 48 h after ROSC suggest severe HIE [125]. At a gestational age of 37 weeks, healthy pregnant women have normal NSE levels. However, NSE levels are physiologically elevated in the early weeks of pregnancy (up to 10 weeks) due to extracerebral sources (e.g. the corpus luteum). Women developing pre-eclampsia have ongoing elevated levels of NSE throughout pregnancy and up to a year later, whereas in healthy women, the levels tend to decline to normal during pregnancy [126, 127]. Furthermore, hemolysis causes elevation of NSE levels [128, 129]. Therefore, NSE should not be used for prognostication in early pregnancy, in women with pre-eclampsia, or in pregnant or post-partum women with disseminated intravascular coagulation, amniotic fluid embolism or those who have undergone massive transfusion due to bleeding.

28.16 Further Care and Rehabilitation

Recovery after cardiac arrest can take time [130, 131]. Data on long-term survival varies greatly, but survival to hospital discharge is generally higher in pregnant patients than in non-pregnant patients [132, 133]. Beyond somatic recovery, psychological symptoms and even post-traumatic stress disorder are not uncommon after cardiac arrest [134–137]. Patients may feel guilt, bewilderment and depression. The possible addition of having lost a child or having to care for a child after severe illness is likely to make things even more difficult. Follow-up and counselling is therefore much needed.

28.17 Conclusions

Care of the pregnant patient after cardiac arrest is challenging. Maternal cardiac arrest during pregnancy, and the peripartum period is fortunately rare. However, this rarity makes it difficult for clinicians and staff to attain clinical experience with this condition. Adequate preparation, education, simulation-based training and adherence to a high standard of intensive care are likely to facilitate efficient performance when needed.

References

1. Beckett VA, Knight M, Sharpe P. The CAPS study: incidence, management and outcomes of cardiac arrest in pregnancy in the UK: a prospective, descriptive study. BJOG. 2017;124(9):1374–81.
2. Vaahersalo J, Hiltunen P, Tiainen M, Oksanen T, Kaukonen KM, Kurola J, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest in Finnish intensive care units: the FINNRESUSCI study. Intensive Care Med. 2013;39(5):826–37.
3. Hiltunen P, Kuisma M, Silfvast T, Rutanen J, Vaahersalo J, Kurola J, et al. Regional variation and outcome of out-of-hospital cardiac arrest (ohca) in Finland—the Finnresusci study. Scand J Trauma Resusc Emerg Med. 2012;20:80.
4. Salihu HM, Salemi JL, Aggarwal A, Steele BF, Pepper RC, Mogos MF, et al. Opioid drug use and acute cardiac events among pregnant women in the United States. Am J Med. 2018;131(1):64–71.
5. Kirkegaard H, Soreide E, de Haas I, Pettila V, Taccone FS, Arus U, et al. Targeted temperature management for 48 vs 24 hours and neurologic outcome after out-of-hospital cardiac arrest: a randomized clinical trial. JAMA. 2017;318(4):341–50.
6. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. N Engl J Med. 2013;369(23):2197–206.
7. Oksanen T, Skrifvars MB, Varpula T, Kuitunen A, Pettila V, Nurmi J, et al. Strict versus moderate glucose control after resuscitation from ventricular fibrillation. Intensive Care Med. 2007;33(12):2093–100.
8. Hypothermia after Cardiac Arrest Study G. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med. 2002;346(8):549–56.
9. Laver S, Farrow C, Turner D, Nolan J. Mode of death after admission to an intensive care unit following cardiac arrest. Intensive Care Med. 2004;30(11):2126–8.
10. Lemiale V, Dumas F, Mongardon N, Giovanetti O, Charpentier J, Chiche JD, et al. Intensive care unit mortality after cardiac arrest: the relative contribution of shock and brain injury in a large cohort. Intensive Care Med. 2013;39(11):1972–80.
11. Sekhon MS, Ainslie PN, Griesdale DE. Clinical pathophysiology of hypoxic ischemic brain injury after cardiac arrest: a "two-hit" model. Crit Care. 2017;21(1):90.

12. Nolan JP, Soar J, Cariou A, Cronberg T, Moulaert VR, Deakin CD, et al. European resuscitation council and European Society of Intensive Care Medicine 2015 guidelines for post-resuscitation care. Intensive Care Med. 2015;41(12):2039–56.
13. Adrie C, Cariou A, Mourvillier B, Laurent I, Dabbane H, Hantala F, et al. Predicting survival with good neurological recovery at hospital admission after successful resuscitation of out-of-hospital cardiac arrest: the OHCA score. Eur Heart J. 2006;27(23):2840–5.
14. Skrifvars MB, Nurmi J, Ikola K, Saarinen K, Castren M. Reduced survival following resuscitation in patients with documented clinically abnormal observations prior to in-hospital cardiac arrest. Resuscitation. 2006;70(2):215–22.
15. Penney DJ, Stewart AH, Parr MJ. Prognostic outcome indicators following hanging injuries. Resuscitation. 2002;54(1):27–9.
16. Sekhon MS, Griesdale DE. Individualized perfusion targets in hypoxic ischemic brain injury after cardiac arrest. Crit Care. 2017;21(1):259.
17. Hayman EG, Patel AP, Kimberly WT, Sheth KN, Simard JM. Cerebral Edema after cardiopulmonary resuscitation: a therapeutic target following cardiac arrest? Neurocrit Care. 2017;28(3):276.
18. Edgren E, Enblad P, Grenvik A, Lilja A, Valind S, Wiklund L, et al. Cerebral blood flow and metabolism after cardiopulmonary resuscitation. Resuscitation. 2003;57(2):161–70.
19. Buunk G, van der Hoeven JG, Meinders AE. Prognostic significance of the difference between mixed venous and jugular bulb oxygen saturation. Resuscitation. 1999;41(3):257–62.
20. Adrie C, Laurent I, Monchi M, Cariou A, Dhainaou JF, Spaulding C. Postresuscitation disease after cardiac arrest: a sepsis-like syndrome? Curr Opin Crit Care. 2004;10(3):208–12.
21. Vaahersalo J, Skrifvars MB, Pulkki K, Stridsberg M, Rosjo H, Hovilehto S, et al. Admission interleukin-6 is associated with post resuscitation organ dysfunction and predicts long-term neurological outcome after out-of-hospital ventricular fibrillation. Resuscitation. 2014;85(11):1573–9.
22. Roberts BW, Trzeciak S. Systemic inflammatory response after cardiac arrest: potential target for therapy? Crit Care Med. 2015;43(6):1336–7.
23. Roberts BW, Kilgannon JH, Chansky ME, Mittal N, Wooden J, Parrillo JE, et al. Multiple organ dysfunction after return of spontaneous circulation in postcardiac arrest syndrome. Crit Care Med. 2013;41(6):1492–501.
24. Laurent I, Monchi M, Chiche JD, Joly LM, Spaulding C, Bourgeois B, et al. Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. J Am Coll Cardiol. 2002;40(12):2110–6.
25. Laurent I, Adrie C, Vinsonneau C, Cariou A, Chiche JD, Ohanessian A, et al. High-volume hemofiltration after out-of-hospital cardiac arrest: a randomized study. J Am Coll Cardiol. 2005;46(3):432–7.
26. Lapinsky SE, Kruczynski K, Slutsky AS. Critical care in the pregnant patient. Am J Respir Crit Care Med. 1995;152(2):427–55.
27. Andersen LW, Granfeldt A, Callaway CW, Bradley SM, Soar J, Nolan JP, et al. Association between tracheal intubation during adult in-hospital cardiac arrest and survival. JAMA. 2017;317(5):494–506.
28. Djabatey EA, Barclay PM. Difficult and failed intubation in 3430 obstetric general anaesthetics. Anaesthesia. 2009;64(11):1168–71.
29. Soar J, Nolan JP, Bottiger BW, Perkins GD, Lott C, Carli P, et al. European resuscitation council guidelines for resuscitation 2015: section 3. Adult advanced life support. Resuscitation. 2015;95:100–47.
30. Elkus R, Popovich J Jr. Respiratory physiology in pregnancy. Clin Chest Med. 1992;13(4):555–65.
31. Young P, Pilcher J, Patel M, Cameron L, Braithwaite I, Weatherall M, et al. Delivery of titrated oxygen via a self-inflating resuscitation bag. Resuscitation. 2013;84(3):391–4.
32. Nelskyla A, Parr MJ, Skrifvars MB. Prevalence and factors correlating with hyperoxia exposure following cardiac arrest--an observational single Centre study. Scand J Trauma Resusc Emerg Med. 2013;21:35.
33. Aufderheide TP, Sigurdsson G, Pirrallo RG, Yannopoulos D, McKnite S, von Briesen C, et al. Hyperventilation-induced hypotension during cardiopulmonary resuscitation. Circulation. 2004;109(16):1960–5.
34. Aufderheide TP, Lurie KG. Death by hyperventilation: a common and life-threatening problem during cardiopulmonary resuscitation. Crit Care Med. 2004;32(9 Suppl):S345–51.
35. Levinson G, Shnider SM, DeLorimier AA, Steffenson JL. Effects of maternal hyperventilation on uterine blood flow and fetal oxygenation and acid-base status. Anesthesiology. 1974;40(4):340–7.
36. Roberts BW, Kilgannon JH, Chansky ME, Trzeciak S. Association between initial prescribed minute ventilation and post-resuscitation partial pressure of arterial carbon dioxide in patients with post-cardiac arrest syndrome. Ann Intensive Care. 2014;4(1):9.
37. Elmer J, Rittenberger JC, Coppler PJ, Guyette FX, Doshi AA, Callaway CW, et al. Long-term survival benefit from treatment at a specialty center after cardiac arrest. Resuscitation. 2016;108:48–53.
38. Soholm H, Wachtell K, Nielsen SL, Bro-Jeppesen J, Pedersen F, Wanscher M, et al. Tertiary centres have improved survival compared to other hospitals in the Copenhagen area after out-of-hospital cardiac arrest. Resuscitation. 2013;84(2):162–7.
39. Spaite DW, Stiell IG, Bobrow BJ, de Boer M, Maloney J, Denninghoff K, et al. Effect of transport interval on out-of-hospital cardiac arrest survival in the OPALS study: implications for triaging patients to specialized cardiac arrest centers. Ann Emerg Med. 2009;54(2):248–55.
40. Sunde K, Pytte M, Jacobsen D, Mangschau A, Jensen LP, Smedsrud C, et al. Implementation of

a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. Resuscitation. 2007;73(1):29–39.
41. Yannopoulos D, Bartos JA, Raveendran G, Conterato M, Frascone RJ, Trembley A, et al. Coronary artery disease in patients with out-of-hospital refractory ventricular fibrillation cardiac arrest. J Am Coll Cardiol. 2017;70(9):1109–17.
42. Lellouche N, Sacher F, Jorrot P, Cariou A, Spaulding C, Aurore A, et al. Sudden cardiac arrest: ECG repolarization after resuscitation. J Cardiovasc Electrophysiol. 2011;22(2):131–6.
43. Dumas F, Cariou A, Manzo-Silberman S, Grimaldi D, Vivien B, Rosencher J, et al. Immediate percutaneous coronary intervention is associated with better survival after out-of-hospital cardiac arrest: insights from the PROCAT (Parisian Region Out of hospital Cardiac ArresT) registry. Circ Cardiovasc Interv. 2010;3(3):200–7.
44. Kontio T, Salo A, Kantola T, Toivonen L, Skrifvars MB. Successful use of therapeutic hypothermia after cardiac arrest due to amitriptyline and venlafaxine intoxication. Ther Hypothermia Temp Manag. 2015;5(2):104–9.
45. Spaulding CM, Joly LM, Rosenberg A, Monchi M, Weber SN, Dhainaut JF, et al. Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. N Engl J Med. 1997;336(23):1629–33.
46. Dumas F, Manzo-Silberman S, Fichet J, Mami Z, Zuber B, Vivien B, et al. Can early cardiac troponin I measurement help to predict recent coronary occlusion in out-of-hospital cardiac arrest survivors? Crit Care Med. 2012;40(6):1777–84.
47. Ladner HE, Danielsen B, Gilbert WM. Acute myocardial infarction in pregnancy and the puerperium: a population-based study. Obstet Gynecol. 2005;105(3):480–4.
48. Winther-Jensen M, Hassager C, Kjaergaard J, Bro-Jeppesen J, Thomsen JH, Lippert FK, et al. Women have a worse prognosis and undergo fewer coronary angiographies after out-of-hospital cardiac arrest than men. Eur Heart J Acute Cardiovasc Care. 2017:2048872617696368.
49. Pierce T, Hovnanian M, Hedgire S, Ghoshhajra B. Imaging of cardiovascular disease in pregnancy and the peripartum period. Curr Treat Options Cardiovasc Med. 2017;19(12):94.
50. James AH, Jamison MG, Biswas MS, Brancazio LR, Swamy GK, Myers ER. Acute myocardial infarction in pregnancy: a United States population-based study. Circulation. 2006;113(12):1564–71.
51. Roth A, Elkayam U. Acute myocardial infarction associated with pregnancy. J Am Coll Cardiol. 2008;52(3):171–80.
52. Dumas F, Bougouin W, Geri G, Lamhaut L, Rosencher J, Pene F, et al. Emergency percutaneous coronary intervention in post-cardiac arrest patients without ST-segment elevation pattern: insights from the PROCAT II registry. JACC Cardiovasc Interv. 2016;9(10):1011–8.
53. Skrifvars MB, Parr MJ. Incidence, predisposing factors, management and survival following cardiac arrest due to subarachnoid haemorrhage: a review of the literature. Scand J Trauma Resusc Emerg Med. 2012;20:75.
54. Jeejeebhoy FM, Morrison LJ. Maternal cardiac arrest: a practical and comprehensive review. Emerg Med Int. 2013;2013:274814.
55. Saarinen S, Nurmi J, Toivio T, Fredman D, Virkkunen I, Castren M. Does appropriate treatment of the primary underlying cause of PEA during resuscitation improve patients' survival? Resuscitation. 2012;83(7):819–22.
56. Bernstein SN, Cudemus-Deseda GA, Ortiz VE, Goodman A, Jassar AS. Case 33-2019: a 35-year-old woman with cardiopulmonary arrest during Cesarean section. N Engl J Med. 2019;381(17):1664–73.
57. Conde-Agudelo A, Romero R. Amniotic fluid embolism: an evidence-based review. Am J Obstet Gynecol. 2009;201(5):445 e1–13.
58. Vaahersalo J, Bendel S, Reinikainen M, Kurola J, Tiainen M, Raj R, et al. Arterial blood gas tensions after resuscitation from out-of-hospital cardiac arrest: associations with long-term neurologic outcome. Crit Care Med. 2014;42(6):1463–70.
59. Herlitz J, Castren M, Friberg H, Nolan J, Skrifvars M, Sunde K, et al. Post resuscitation care: what are the therapeutic alternatives and what do we know? Resuscitation. 2006;69(1):15–22.
60. Hill CC, Pickinpaugh J. Physiologic changes in pregnancy. Surg Clin North Am. 2008;88(2):391–401. vii
61. Catanzarite V, Willms D, Wong D, Landers C, Cousins L, Schrimmer D. Acute respiratory distress syndrome in pregnancy and the puerperium: causes, courses, and outcomes. Obstet Gynecol. 2001;97(5 Pt 1):760–4.
62. Kilgannon JH, Jones AE, Parrillo JE, Dellinger RP, Milcarek B, Hunter K, et al. Relationship between supranormal oxygen tension and outcome after resuscitation from cardiac arrest. Circulation. 2011;123(23):2717–22.
63. Kilgannon JH, Jones AE, Shapiro NI, Angelos MG, Milcarek B, Hunter K, et al. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. JAMA. 2010;303(21):2165–71.
64. Falkenbach P, Kamarainen A, Makela A, Kurola J, Varpula T, Ala-Kokko T, et al. Incidence of iatrogenic dyscarbia during mild therapeutic hypothermia after successful resuscitation from out-of-hospital cardiac arrest. Resuscitation. 2009;80(9):990–3.
65. Pynnonen L, Falkenbach P, Kamarainen A, Lonnrot K, Yli-Hankala A, Tenhunen J. Therapeutic hypothermia after cardiac arrest—cerebral perfusion and metabolism during upper and lower threshold normocapnia. Resuscitation. 2011;82(9):1174–9.
66. Eastwood GM, Tanaka A, Bellomo R. Cerebral oxygenation in mechanically ventilated early car-

diac arrest survivors: the impact of hypercapnia. Resuscitation. 2016;102:11–6.
67. Eastwood GM, Schneider AG, Suzuki S, Peck L, Young H, Tanaka A, et al. Targeted therapeutic mild hypercapnia after cardiac arrest: a phase II multicentre randomised controlled trial (the CCC trial). Resuscitation. 2016;104:83–90.
68. Beitler JR, Ghafouri TB, Jinadasa SP, Mueller A, Hsu L, Anderson RJ, et al. Favorable neurocognitive outcome with low tidal volume ventilation after cardiac arrest. Am J Respir Crit Care Med. 2017;195(9):1198–206.
69. Lascarrou JB, Merdji H, Le Gouge A, Colin G, Grillet G, Girardie P, et al. Targeted temperature management for cardiac arrest with nonshockable rhythm. N Engl J Med. 2019;381:2327.
70. Freund B, Kaplan PW. A review of the utility of a hypothermia protocol in cardiac arrests due to nonshockable rhythms. Cardiol J. 2017;24(3):324–33.
71. Rittenberger JC, Kelly E, Jang D, Greer K, Heffner A. Successful outcome utilizing hypothermia after cardiac arrest in pregnancy: a case report. Crit Care Med. 2008;36(4):1354–6.
72. Chavez LO, Leon M, Einav S, Varon J. Editor's choice—inside the cold heart: a review of therapeutic hypothermia cardioprotection. Eur Heart J Acute Cardiovasc Care. 2017;6(2):130–41.
73. Wible EF, Kass JS, Lopez GA. A report of fetal demise during therapeutic hypothermia after cardiac arrest. Neurocrit Care. 2010;13(2):239–42.
74. Stockmann H, Krannich A, Schroeder T, Storm C. Therapeutic temperature management after cardiac arrest and the risk of bleeding: systematic review and meta-analysis. Resuscitation. 2014;85(11):1494–503.
75. Song KH, Lee BK, Jeung KW, Lee SM. Safely completed therapeutic hypothermia in postpartum cardiac arrest survivors. Am J Emerg Med. 2015;33(6):861 e5–6.
76. Bernard SA, Smith K, Finn J, Hein C, Grantham H, Bray JE, et al. Induction of therapeutic hypothermia during out-of-hospital cardiac arrest using a rapid infusion of cold saline: the RINSE trial (rapid infusion of cold normal saline). Circulation. 2016;134(11):797–805.
77. Kim F, Nichol G, Maynard C, Hallstrom A, Kudenchuk PJ, Rea T, et al. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: a randomized clinical trial. JAMA. 2014;311(1):45–52.
78. Bernard SA, Smith K, Cameron P, Masci K, Taylor DM, Cooper DJ, et al. Induction of therapeutic hypothermia by paramedics after resuscitation from out-of-hospital ventricular fibrillation cardiac arrest: a randomized controlled trial. Circulation. 2010;122(7):737–42.
79. Dell'Anna AM, Taccone FS, Halenarova K, Citerio G. Sedation after cardiac arrest and during therapeutic hypothermia. Minerva Anestesiol. 2014;80(8):954–62.
80. Ely EW, Truman B, Shintani A, Thomason JW, Wheeler AP, Gordon S, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond agitation-sedation scale (RASS). JAMA. 2003;289(22):2983–91.
81. De Jonghe B, Cook D, Appere-De-Vecchi C, Guyatt G, Meade M, Outin H. Using and understanding sedation scoring systems: a systematic review. Intensive Care Med. 2000;26(3):275–85.
82. Bjelland TW, Dale O, Kaisen K, Haugen BO, Lydersen S, Strand K, et al. Propofol and remifentanil versus midazolam and fentanyl for sedation during therapeutic hypothermia after cardiac arrest: a randomised trial. Intensive Care Med. 2012;38(6):959–67.
83. Bjelland TW, Klepstad P, Haugen BO, Nilsen T, Dale O. Effects of hypothermia on the disposition of morphine, midazolam, fentanyl, and propofol in intensive care unit patients. Drug Metab Dispos. 2013;41(1):214–23.
84. Ameloot K, Genbrugge C, Meex I, Jans F, Boer W, Vander Laenen M, et al. An observational near-infrared spectroscopy study on cerebral autoregulation in post-cardiac arrest patients: time to drop 'one-size-fits-all' hemodynamic targets? Resuscitation. 2015;90:121–6.
85. Rashid MR, Najeeb R, Mushtaq S, Habib R. Comparative evaluation of midazolam, dexmedetomidine, and propofol as intensive care unit sedatives in postoperative electively ventilated eclamptic patients. J Anaesthesiol Clin Pharmacol. 2017;33(3):331–6.
86. Esmaoglu A, Ulgey A, Akin A, Boyaci A. Comparison between dexmedetomidine and midazolam for sedation of eclampsia patients in the intensive care unit. J Crit Care. 2009;24(4):551–5.
87. Tobias JD. Bradycardia during dexmedetomidine and therapeutic hypothermia. J Intensive Care Med. 2008;23(6):403–8.
88. Callaway CW, Elmer J, Guyette FX, Molyneaux BJ, Anderson KB, Empey PE, et al. Dexmedetomidine reduces shivering during mild hypothermia in waking subjects. PLoS One. 2015;10(8):e0129709.
89. Ameloot K, Meex I, Genbrugge C, Jans F, Boer W, Verhaert D, et al. Hemodynamic targets during therapeutic hypothermia after cardiac arrest: a prospective observational study. Resuscitation. 2015;91:56–62.
90. Jones-Muhammad M, Warrington JP. Cerebral blood flow regulation in pregnancy, hypertension, and hypertensive disorders of pregnancy. Brain Sci. 2019;9(9):224.
91. Jakkula P, Pettila V, Skrifvars MB, Hastbacka J, Loisa P, Tiainen M, et al. Targeting low-normal or high-normal mean arterial pressure after cardiac arrest and resuscitation: a randomised pilot trial. Intensive Care Med. 2018;44(12):2091–101.
92. Ameloot K, De Deyne C, Eertmans W, Ferdinande B, Dupont M, Palmers PJ, et al. Early goal-directed haemodynamic optimization of cerebral oxygenation in comatose survivors after cardiac arrest: the

Neuroprotect post-cardiac arrest trial. Eur Heart J. 2019;40(22):1804–14.
93. Dell'Anna AM, Sandroni C, Lamanna I, Belloni I, Donadello K, Creteur J, et al. Prognostic implications of blood lactate concentrations after cardiac arrest: a retrospective study. Ann Intensive Care. 2017;7(1):101.
94. Dutton RP, Mackenzie CF, Scalea TM. Hypotensive resuscitation during active hemorrhage: impact on in-hospital mortality. J Trauma. 2002;52(6):1141–6.
95. Sapsford W. Should the 'C' in 'ABCDE' be altered to reflect the trend towards hypotensive resuscitation? Scand J Surg. 2008;97(1):4–11. discussion 2-3
96. Levy B, Clere-Jehl R, Legras A, Morichau-Beauchant T, Leone M, Frederique G, et al. Epinephrine versus norepinephrine for cardiogenic shock after acute myocardial infarction. J Am Coll Cardiol. 2018;72(2):173–82.
97. Taccone FS, Donadello K, Dell'Anna AM. Lactate measurement after cardiac arrest: tissue hypoxia or adaptive response?*. Crit Care Med. 2014;42(8):1942–3.
98. Vincent JL, Quintairos ESA, Couto L Jr, Taccone FS. The value of blood lactate kinetics in critically ill patients: a systematic review. Crit Care. 2016;20(1):257.
99. Olson JE, Banks M, Dimlich RV, Evers J. Blood-brain barrier water permeability and brain osmolyte content during edema development. Acad Emerg Med. 1997;4(7):662–73.
100. Olson JE, Evers JA, Banks M. Brain osmolyte content and blood-brain barrier water permeability surface area product in osmotic edema. Acta Neurochir Suppl (Wien). 1994;60:571–3.
101. D'Alecy LG, Lundy EF, Barton KJ, Zelenock GB. Dextrose containing intravenous fluid impairs outcome and increases death after eight minutes of cardiac arrest and resuscitation in dogs. Surgery. 1986;100(3):505–11.
102. Peng TJ, Andersen LW, Saindon BZ, Giberson TA, Kim WY, Berg K, et al. The administration of dextrose during in-hospital cardiac arrest is associated with increased mortality and neurologic morbidity. Crit Care. 2015;19:160.
103. Skrifvars MB, Pettila V, Rosenberg PH, Castren M. A multiple logistic regression analysis of in-hospital factors related to survival at six months in patients resuscitated from out-of-hospital ventricular fibrillation. Resuscitation. 2003;59(3):319–28.
104. Investigators N-SS, Finfer S, Chittock DR, Su SY, Blair D, Foster D, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360(13):1283–97.
105. Investigators N-SS, Finfer S, Liu B, Chittock DR, Norton R, Myburgh JA, et al. Hypoglycemia and risk of death in critically ill patients. N Engl J Med. 2012;367(12):1108–18.
106. Moonen C, Lemmens R, Van Paesschen W, Wilmer A, Eertmans W, Ferdinande B, et al. The impact of global hemodynamics, oxygen and carbon dioxide on epileptiform EEG activity in comatose survivors of out-of-hospital cardiac arrest. Resuscitation. 2018;123:92–7.
107. Longstreth WT Jr, Fahrenbruch CE, Olsufka M, Walsh TR, Copass MK, Cobb LA. Randomized clinical trial of magnesium, diazepam, or both after out-of-hospital cardiac arrest. Neurology. 2002;59(4):506–14.
108. Brain Resuscitation Clinical Trial ISG. Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest. N Engl J Med. 1986;314(7):397–403.
109. Caviness JN, Brown P. Myoclonus: current concepts and recent advances. Lancet Neurol. 2004;3(10):598–607.
110. Wyszynski DF, Nambisan M, Surve T, Alsdorf RM, Smith CR, Holmes LB, et al. Increased rate of major malformations in offspring exposed to valproate during pregnancy. Neurology. 2005;64(6):961–5.
111. Alsdorf R, Wyszynski DF. Teratogenicity of sodium valproate. Expert Opin Drug Saf. 2005;4(2):345–53.
112. Kim J, Kim K, Lee JH, Jo YH, Kim T, Rhee JE, et al. Prognostic implication of initial coagulopathy in out-of-hospital cardiac arrest. Resuscitation. 2013;84(1):48–53.
113. Skrifvars M, Pettila V. Disseminated intravascular coagulation is bad news for patients following cardiac arrest. Resuscitation. 2013;84(1):9–10.
114. Francois B, Cariou A, Clere-Jehl R, Dequin PF, Renon-Carron F, Daix T, et al. Prevention of early ventilator-associated pneumonia after cardiac arrest. N Engl J Med. 2019;381(19):1831–42.
115. Esnault P, Nguyen C, Bordes J, D'Aranda E, Montcriol A, Contargyris C, et al. Early-onset ventilator-associated pneumonia in patients with severe traumatic brain injury: incidence, risk factors, and consequences in cerebral oxygenation and outcome. Neurocrit Care. 2017;27:187.
116. Loftus TJ, Lemon SJ, Nguyen LL, Voils SA, Brakenridge SC, Jordan JR, et al. Early bronchoalveolar lavage for intubated trauma patients with TBI or chest trauma. J Crit Care. 2017;39:78–82.
117. Krag M, Perner A, Wetterslev J, Moller MH. Stress ulcer prophylaxis in adult neurocritical care patients—no firm evidence for benefit or harm. Crit Care. 2016;20:22.
118. Biderman P, Carmi U, Setton E, Fainblut M, Bachar O, Einav S. Maternal salvage with extracorporeal life support: lessons learned in a single center. Anesth Analg. 2017;125(4):1275–80.
119. Fengler K, Fuernau G, Desch S, Eitel I, Neumann FJ, Olbrich HG, et al. Gender differences in patients with cardiogenic shock complicating myocardial infarction: a substudy of the IABP-SHOCK II-trial. Clin Res Cardiol. 2015;104(1):71–8.
120. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, et al. Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK

II): final 12 month results of a randomised, open-label trial. Lancet. 2013;382(9905):1638–45.
121. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med. 2012;367(14):1287–96.
122. Sandroni C, Cariou A, Cavallaro F, Cronberg T, Friberg H, Hoedemaekers C, et al. Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European resuscitation council and the European Society of Intensive Care Medicine. Resuscitation. 2014;85(12):1779–89.
123. Cronberg T, Rundgren M, Westhall E, Englund E, Siemund R, Rosen I, et al. Neuron-specific enolase correlates with other prognostic markers after cardiac arrest. Neurology. 2011;77(7):623–30.
124. Rundgren M, Karlsson T, Nielsen N, Cronberg T, Johnsson P, Friberg H. Neuron specific enolase and S-100B as predictors of outcome after cardiac arrest and induced hypothermia. Resuscitation. 2009;80(7):784–9.
125. Oksanen T, Tiainen M, Skrifvars MB, Varpula T, Kuitunen A, Castren M, et al. Predictive power of serum NSE and OHCA score regarding 6-month neurologic outcome after out-of-hospital ventricular fibrillation and therapeutic hypothermia. Resuscitation. 2009;80(2):165–70.
126. Bergman L, Akerud H. Plasma levels of the cerebral biomarker, neuron-specific enolase, are elevated during pregnancy in women developing preeclampsia. Reprod Sci. 2016;23(3):395–400.
127. Bergman L, Akerud H, Wikstrom AK, Larsson M, Naessen T, Akhter T. Cerebral biomarkers in women with preeclampsia are still elevated 1 year postpartum. Am J Hypertens. 2016;29(12):1374–9.
128. Geisen U, Benk C, Beyersdorf F, Klemm R, Trummer G, Ozbek B, et al. Neuron-specific enolase correlates to laboratory markers of haemolysis in patients on long-term circulatory support. Eur J Cardiothorac Surg. 2015;48(3):416–20. discussion 20
129. Gao F, Harris DN, Sapsed-Byrne S, Sharp S. Neurone-specific enolase and Sangtec 100 assays during cardiac surgery: part III—dose haemolysis affect their accuracy? Perfusion. 1997;12(3):171–7.
130. Mateen FJ, Josephs KA, Trenerry MR, Felmlee-Devine MD, Weaver AL, Carone M, et al. Long-term cognitive outcomes following out-of-hospital cardiac arrest: a population-based study. Neurology. 2011;77(15):1438–45.
131. Cowan MJ, Pike KC, Budzynski HK. Psychosocial nursing therapy following sudden cardiac arrest: impact on two-year survival. Nurs Res. 2001;50(2):68–76.
132. Balki M, Liu S, Leon JA, Baghirzada L. Epidemiology of cardiac arrest during hospitalization for delivery in Canada: a Nationwide study. Anesth Analg. 2017;124(3):890–7.
133. Mhyre JM, Tsen LC, Einav S, Kuklina EV, Leffert LR, Bateman BT. Cardiac arrest during hospitalization for delivery in the United States, 1998–2011. Anesthesiology. 2014;120(4):810–8.
134. Cronberg T, Lilja G, Horn J, Kjaergaard J, Wise MP, Pellis T, et al. Neurologic function and health-related quality of life in patients following targeted temperature management at 33°C vs 36°C after out-of-hospital cardiac arrest: a randomized clinical trial. JAMA Neurol. 2015;72(6):634–41.
135. Israelsson J, Bremer A, Herlitz J, Axelsson AB, Cronberg T, Djarv T, et al. Health status and psychological distress among in-hospital cardiac arrest survivors in relation to gender. Resuscitation. 2017;114:27–33.
136. Lilja G. Follow-up of cardiac arrest survivors: why, how, and when? A practical approach. Semin Neurol. 2017;37(1):88–93.
137. Lilja G, Nilsson G, Nielsen N, Friberg H, Hassager C, Koopmans M, et al. Anxiety and depression among out-of-hospital cardiac arrest survivors. Resuscitation. 2015;97:68–75.

29 The Brain-Dead Mother in Intensive Care Unit: Ethics, Physiology and Management

Paul McConnell and Rosaleen Baruah

Bullet Points

- Criteria for diagnosis of brain death vary between countries.
- Maternal brain death is a rare event.
- Legal and ethical principles governing the care of the brain-dead mother will vary depending on the jurisdiction of the hospital.
- Brain death must be confirmed using the accepted guidelines of the country in which the practitioner is working.
- Providing ongoing somatic support to the mother after confirmation of brain death may be appropriate, for example, to facilitate organ donation if this had been the mother's expressed wish in life.
- The ethical arguments for and against continuing a pregnancy are complex, will vary depending on the cultural and religious norms of the country in which the mother is a patient and must be examined on a case to case basis.
- Brain death can cause widespread and severe physiological derangement to the pregnant patient and the fetus.
- A systematic and thorough approach should be taken to the care of the pregnant brain-dead patient. This will require a multi-specialty approach.
- Supporting the family of the brain-dead mother and ensuring that medical and nursing staff receive adequate psychological support are essential.
- Developments in delivery of intensive care and medical device technology may make prolongation of pregnancy in the brain-dead mother technically more achievable in the future.

29.1 Introduction: Concepts and Controversies in Defining Death

Defining death is more difficult than it first appears to be. Traditionally, death was diagnosed based on cardiorespiratory criteria (e.g. lack of a perfusing cardiac rhythm/pulselessness and/or lack of respiration). Recent research raises significant questions regarding this definition given evidence of metabolism and even gene activation and function in the days following death [1]. In the philosophical sense, death is thought of as the

P. McConnell (✉)
Anaesthesia and Intensive Care Medicine, Royal Alexandra Hospital, Paisley, UK
e-mail: paulmcconnell@doctors.org.uk

R. Baruah
NHS Lothian, Edinburgh, UK

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_29

irreversible loss of personhood [2]. However, this definition ignores the intricacies and practicalities of quantifying and demonstrating fulfilment of such a criterion.

The concept of brain death was first introduced in 1959 [3]. It is now recognised in many parts of the world, though individual criteria may vary between countries [4]. In such places that brain death is recognised, it is considered inappropriate to continue organ support following a diagnosis of brain death. At the same time, it is often considered acceptable to provide temporary organ support in order to facilitate the successful removal of organs for transplantation [5]. Stemming from this is the concept of continuing organ support in a brain death parturient to facilitate the delivery of a live fetus [6]. While theoretically possible, this may prove challenging; large case series have shown that despite organ support, most patients with brain death will inevitably progress to cardiac asystole [7]. In fact, brain death leans on the assumption that irreversible loss of brainstem function rapidly leads to cardiorespiratory somatic death. With temporising organ support, this deterioration may be delayed, but there remains irreversible cessation of brain function and loss of consciousness [8]. Published reports of supposed survival after a diagnosis of brain death have always been due to failure to follow the correct testing criteria or misunderstanding the concept of brain death [9]. Both the American Academy of Neurology [10] and the Australia and New Zealand Intensive Care Society [11] report no return of cognition in any person who fulfilled the criteria of brain death.

29.2 Epidemiology of Maternal Brain Death

Death due to neurological causes is extremely rare during pregnancy, with an incidence approximating 1:100,000 pregnancies (data from 2012 to 2014 in the UK) [12]. The most common causes of maternal brainstem death are subarachnoid hemorrhage and trauma [12]. However, meningoencephalitis [13, 14], intracranial mass lesions [2] and cerebral venous sinus thrombosis [15] have all been implicated.

Even more uncommon are cases of maternal death fulfilling criteria for brain death. A case series examining 252 brain-dead patients over a 6-year period found only five pregnant women [16]. Most rare are cases of severe maternal neurological injury in which ongoing organ support to continue pregnancy is an issue; in most cases, severe neurological injury will result in fetal death [15]. Though there is no lower limit of fetal age for providing somatic maternal support, an Irish review from 2008 found that in the reported literature, no fetus had survived if the maternal injury took place earlier than 15 weeks [17]. A later review of the published literature found only 30 cases of brain-dead pregnant women reported between 1982 and 2010 [18]. In this case series, the mean gestational age at maternal brainstem death was 22 weeks, and the mean age at delivery was 29.5 weeks, suggesting that when this situation arises, somatic support is often given to the mother for the sake of the unborn child. Of the continuing pregnancies, 12 produced viable infants who survived the neonatal period [18]. The longest duration of maternal support documented is 107 days which allowed the delivery of a live infant at 32 weeks' gestation [19].

29.3 Brain Death Testing

Any attempt to diagnose brain death must follow the guideline of the country the practitioner is working in regardless of the ongoing pregnancy. As a rule, all countries that accept the concept of brain death require that the following criteria be fulfilled [20].

1. An established and defined etiology for the condition which has led to the irreversible loss of the capacity for consciousness combined with the irreversible loss of capacity to breathe due to profound structural brain damage.
2. Exclusion of underlying reversible conditions (pharmacological, environmental, metabolic, endocrine or cardiovascular) which may mimic brain death or confound clinical examination.
3. A clinical examination demonstrating a profound, unchanging coma, apnea and the absence of brainstem reflexes.

The timing of clinical examination is usually at the discretion of the clinician, provided they are satisfied that an appropriate period of time has elapsed to ensure that the condition is irreversible. In certain countries (e.g. United Kingdom, Australia) [20], more than one practitioner is required to perform non-simultaneous testing before a diagnosis of brain death can be made.

Most jurisdictions will allow a diagnosis of brainstem death to be made clinically. However, some require confirmatory investigations [21]. Multiple tests have been used as adjuvant, confirmatory tests in brain death. Some tests demonstrate loss of bioelectrical activity (e.g. electroencephalography, evoked potentials), while others demonstrate cessation of cerebral circulation (e.g. four vessel intraarterial catheter angiography, contrast computed tomography angiography (CCTA), magnetic resonance angiography (MRA), single photon emission computed tomography (SPECT), positron emission tomography (PET) and transcranial Doppler) [20, 22].

The use of ancillary testing in addition to a full clinical examination is controversial. However, such tests may provide important information when fulfilling the components of clinical testing is impossible (e.g. extensive facial injuries preventing adequate clinical assessment, high cervical cord injury preventing full exclusion of alternative causes of apnoea) [23]. In case of a pregnant potentially brain-dead patient, the information these will provide must also be weighed against exposing the fetus to ionizing radiation should the pregnancy continue.

29.4 Ethical and Legal Considerations

The conundrums generated by maternal brain death provoke much controversy and emotion. As seen in the case of the 'Erlanger baby' [24], a great divide exists between those who believe in a fetal right to life and those who perceive extended somatic support as medical experimentation depriving the mother the right to die with dignity. Central to this issue is the question of whom we are treating—mother or unborn child. In other words, what status does the mother have, and what rights (if any) does the fetus have in this situation? These ethical questions must in turn be framed in the practicalities of whether we believe our treatments will be beneficial in the first instance.

The maternal rights rely very much on the condition we denote to the mother. Finnerty et al. [25] believed it was possible to ascribe three distinct statuses to the mother in such a situation: that of a terminally ill patient; that of a voluntary organ donor; and that of a cadaveric incubator. If the mother being treated is viewed as one of the former two, then her previous wishes and 'best interests' should supersede. However, to consider the brain-dead woman as 'terminally ill' fails to recognise that she is in fact dead. To treat her as anything but a dead person will blur the line between neurologic and somatic death even further, potentially causing the family greater distress [26]. If the mother is being treated as a "cadaveric incubator", fetal rights are the most important. However, in such case, the FIGO (International Federation of Gynecology and Obstetrics) committee for the study of ethical aspects of human reproduction and women's health have explicitly stated that 'fetal rescue does not exonerate health-care givers from the duty to respect (the) right of the primary patient, the woman' [27].

The issue of fetal rights is complicated again, as their extent is very much dependant on the jurisdiction. Countries such as Sweden, Germany, France and Austria confer no rights to the fetus, and both fetus and mother are considered a single entity. This may be contrasted with the Republic of Ireland where the fetus holds rights as a full person. At the latter end of the spectrum, if there is a realistic possibility of successful delivery, there would be no question of not continuing the pregnancy [17].

Given the complexities and multiple issues arising, it is easiest to deal with this subject with a four pillar 'principlism' approach, despite the criticisms of this method [28].

29.4.1 Beneficence

The concept of beneficence fosters the belief that any possible good that can be snatched from this

dire situation should be taken advantage of and that saving a life should be pursued at all costs. However, this simplistic view fails to recognise that the aforesaid 'life' may not always be good. Consideration must also be given to fetal injury and viability and the duration of therapy. Even countries conferring the fetus rights as a full person should not mandate continuation of an early pregnancy if the chances of a successful delivery are deemed minimal [17].

29.4.2 Non-Maleficence

Occurring in tandem with beneficence, one must act to minimise harm. In the case of the mother, one could initially assume that the dead can no longer be harmed. However, through our actions on the deceased, her memory may be harmed in the eyes of her family and loved ones; these may be forced to observe continued interventions and perceive harm and suffering. Harm may also be perceived ethically if the actions of the medical staff contradict previous wishes and decisions of the patient. Such harm may be incurred by delivery of organ support and abuse of liberty interests, particularly if there is no apparent benefit to that person.

The notion of fetal harm is more quantifiable. One must consider the injuries sustained during the traumatic event causing brain death itself and the effects of ongoing maternal organ support. The gestational age is an important factor. Should maternal brain death occur early in the pregnancy, consideration must be given to the likelihood of a successful pregnancy outcome versus mere slowing of the dying process of the fetus. Care and consideration must also be given to the institution of any therapies or invasive monitoring (e.g. pharmacological agents with a risk of teratogenesis, amniocentesis).

Looking beyond the mother and child, there may be quantifiable harm for medical and nursing staff caring for the mother. Looking after a patient whose care may be thought of as futile leads to an increase in the incidence of emotional exhaustion in ICU nursing staff, which is a key component of burnout [29].

29.4.3 Autonomy

The principle of autonomy demands that the wishes of the mother be considered. It would be extremely unusual for a mother to have an advance decision which fully covers and encapsulates the nuances of this situation [30]. One must therefore act in the best interests of the patient by attempting to elicit from her nearest relatives what her views would have been regarding prolonged organ support and the continuation of pregnancy. These best interests must address her wishes as a whole, paying attention to previous statements and examining and encompassing wider spiritual, social and psychological beliefs. Assuming that the mother would automatically wish the pregnancy to continue just because she was not actively seeking an abortion prior to injury does not suffice. Her decision to not have an abortion may have been based on a belief that she would enjoy a life with her child rather than merely wishing life for her child.

29.4.4 Justice

By far though the least discussed aspect of somatic support following brain death is the cost implication of providing high level critical care for potentially weeks to month in an experimental situation with uncertain outcomes. While parallels are drawn between somatic support to facilitate organ donation and somatic support to facilitate fetal delivery and survival, from a resource allocation perspective, the two scenarios are very different. Organ donation is a short (usually less than 24 h) period of intensive care followed by a procedure which may have the potential to improve multiple lives with well-described outcomes and cost benefits. Somatic support for fetal delivery has a limited evidence base and will occupy an intensive care bed for a prolonged period. This is not necessarily a contraindication to providing it, but the chances of success, particularly looking at gestational age and maternal physiological stability, must be carefully considered, particularly in a public system where resources may be limited. As stated

previously, the impact of prolonged care of the brain-dead mother on the long-term well-being of staff within the unit must also be considered. Given the uncertainties of success, provision must be made to support the psychological welfare of health-care providers, lest this emotive case impacts on their well-being and their ability to care for their other patients [29].

29.5 Physiological Changes in Brain Death and Organ Support

Once the decision has been taken to undertake somatic support of a brain-dead pregnant woman in the hope of keeping the pregnancy, treatment should be directed to optimization of fetal outcome. As in most cases involving brain death, maternal haemodynamic instability, respiratory arrest, panhypopituitarism, temperature lability and reduced energy expenditure are frequently observed. However, in such cases the goal of somatic support is not merely the retrieval of viable organs after a short hiatus (usually less than 24 h) but rather the support of a fetus for weeks or longer. The destruction of the cerebral centres responsible for many homeostatic functions and autoregulation leads to profound physiological collapse in addition to the apnea occurring in brain death. Only a minority of brain-dead patients remain hemodynamically stable without critical care intervention [31]. The care of the brain-dead patient as a potential organ donor is well described [31].

As noted above, the evidence regarding success of somatic maternal support despite fulfilment of brain death criteria is limited. Hence any decision to embark on prolonged fetal support following maternal brain death must be a carefully weighed decision that goes beyond a simple 'life at all costs' dogma. In such cases, some of the therapies conventionally used in brain-dead patients may have unknown (or even potentially harmful) effects. Hence certain additional considerations relating to fetal well-being must be observed, and careful thought must be given to any treatment [32]. It must also be recognised that given the lack of research and experience in this area, the medical management of such a case is currently considered an experimental therapy [32].

29.5.1 Cardiovascular Changes and Management

Brain death is initially accompanied by a massive sympathetic release. This causes severe hypertension, which may in one-third of cases be associated with bradycardia (Cushing's reflex). Following exhaustion of sympathetic reserves, there is often a sustained period of hypotension which will require vasopressor support. This sympathetic reduction in afterload can be compounded by adrenal insufficiency (occurring in 85% of brain-dead patients), direct damage to the cerebral vasomotor centres and a generalised systemic inflammatory response. Cardiovascular depression is further compounded by secondary disorders such as hypovolemia resulting from excessive diuresis due to diabetes insipidus, cerebral salt wasting or hyperglycaemia (see below) and decreased myocardial contractility due to acidosis and hypothermia [33].

In cases involving a pregnant brain-dead patient, preservation of uterine/placental blood flow is the most important treatment priority [34]. Given the lack of autoregulation in the uterine circulation, hemodynamic support is essential to maintain placental perfusion and ultimately fetal survival. Consideration must first be given to the position in which the brain-dead pregnant patient is nursed. Compression of the inferior vena cava by the gravid uterus may reduce cardiac output (see Chap. 9). Therefore, whenever possible, the mother should be maintained in a left lateral recumbent position.

Additional management must be geared towards maintaining end organ (and therefore placental) perfusion. This may be accomplished using a combination of intravenous fluids, inotropic agents and vasopressors. Hypovolemia secondary to disorders of diuresis should be corrected with crystalloids and colloids. However it should be remembered that the relative hypoalbuminemia and low oncotic pressures of pregnancy [35]

may predispose the mother to pulmonary edema. The choice of vasopressor and inotropic agents is difficult. Current transplant management favours the use of vasopressin in combination with epinephrine to minimise other vasopressor requirements [36] in conjunction with invasive blood pressure and fetal cardiac output monitoring. It should however be remembered that in non-pregnant patients, vasopressin my cause uterine vasoconstriction [37]. Previous successful regimes have used a combination of dopamine and dobutamine [6, 14, 38]. Where resistance to vasopressor therapy is seen, treatment with steroids for adrenal insufficiency must be considered. A target mean arterial pressure of 80–110 has been quoted in reviews [18, 38].

29.5.2 Respiratory Changes and Management

With the patient apneic, invasive ventilation must be ongoing. Respiratory support should be conducted in line with usual evidence-based intensive care practice, avoiding excessive tidal volumes and pressures (see Chap. 23). There are, however, some additional considerations to ensure optimal fetal outcome. Profound respiratory acidosis should be avoided, as animal studies demonstrated that this practice results in uterine hypoperfusion [32]. In fact, $PaCO_2$ should be maintained around 30–35 mmHg [39]. Normal pregnancy produces a mild to moderate respiratory alkalosis, and fetal acidosis may result from a high maternal $PaCO_2$ [34]. Hypoxia should be avoided, though the fetus is relatively protected against this (as fetal hemoglobin has a much higher affinity for oxygen) and oxygen saturations should be maintained at greater than 90% [18, 32]. The minimal amount of oxygen to achieve this saturation should be used, as prolonged ventilation at high FiO_2 may induce or exacerbate pulmonary damage [40]. While viable delivery and neonatal survival have been described following prolonged maternal ventilation, the effects on the fetus remain unknown [27].

29.5.3 Endocrine Changes and Management

Failure of the hypothalamic-pituitary axis occurs commonly in brain death and results in panhypopituitarism. More than 70% of brain death cases demonstrate diabetes insipidus [34]. The ensuing pathological diuresis may result in profound hypovolemia, compounding cardiovascular instability. In addition to the administration of hypotonic fluids, desmopressin/DDAVP should be administered to control the polyuria and hypernatremia [18, 32].

Adrenal failure is also well described [6, 18, 32] and may also contribute to hypotension. Blood should be sampled for cortisol levels after brain death has been declared in order to determine the need to commence steroid replacement [32]. Concerns remain surrounding the effect of long-term steroid administration on the developing fetus. Therefore either prednisolone or methylprednisolone should be used as replacement to minimise placental crossing [18, 41].

Hyperglycemia may also occur due to a combination of stress-related peripheral insulin resistance, pregnancy and steroid administration [18, 32]. Hyperglycemia should be treated with insulin to restore normoglycemia.

Thyroid dysfunction occurs but is less common than diabetes insipidus, as the blood flow to the anterior pituitary may be better preserved than that of the posterior pituitary [36]. Thyroid function tests should also be taken after declaration of brain death in order to determine whether there is need for thyroid hormone replacement. Routine thyroid hormone replacement is not recommended in brain death [36, 42]; however, treatment with tri-iodothyronine has been given empirically in certain cases [39].

29.5.4 Temperature Regulation

Brain death induces a poikilothermic state [5], and the majority of patients become hypothermic. Hypothalamic damage and sepsis may also induce hyperthermia. Both hypothermia and

hyperthermia may be harmful to the fetus, potentially resulting in death or severe growth retardation [18, 27, 43]. Hyperthermia has been treated with cooling and acetaminophen [32, 34]. Warmed fluids and warming blankets have been utilised to treat and prevent hypothermia [6]. A temperature regulating system based on biofeedback may be used to avoid both over- and undertreatment.

29.5.5 Nutrition

Following brain death, resting energy expenditure will be reduced by up to 25% [44], and the use of indirect calorimetry may help in determining appropriate caloric goals [32]. Daily protein intake during pregnancy is approximately the normal adult intake of 0.8 g kg^{-1} day^{-1} plus a proportional increase as pregnancy develops [18, 32, 45]. Given the variability in energy requirements due to the combination of brain death and pregnancy, nutrition should be titrated against a serum indicator of protein metabolism [34] and a positive nitrogen balance maintained [18, 32, 34]. See Chap. 32 for more details regarding nutritional requirements in pregnancy.

Nutrition should be instituted early via the enteral route where possible [32, 46]. Reflux and reduced motility may prove a problem in both pregnancy and brain death, and this may limit the ability to provide enteral nutrition [18]. Where it is not possible to feed via the enteral route, total parenteral nutrition (TPN) has been successfully given [6]. However, TPN may increase the risk of maternal sepsis [27].

29.5.6 The Coagulation System

Pregnancy itself is a hypercoagulable state. In addition, prolonged immobility (given the potential duration of therapy), the neuroendocrine stress response to brain injury and cytokine release all place the pregnant brain-dead patient at high risk of developing deep vein thrombosis and pulmonary embolism. All such patients should be treated with low-molecular-weight heparin in prophylactic doses. At the same time, coagulation and platelet counts should be monitored as DIC and other secondary coagulopathies are described in brain death. As the time of delivery approaches, the risk of thromboembolic complications should be balanced against the risk of hemorrhage [47] (see also Chaps. 5 and 8).

29.5.7 Infections

Infectious complications were observed in all the brain-dead pregnant women described in the literature [32]. This is likely due to the prolonged duration of treatment, combined with immune dysfunction secondary to systemic stress and the pregnant state itself. The most common sources of infection are intravascular catheters, urinary catheters and recurrent pneumonias while ventilated [46]. Treatment may prove difficult; recurrent treatment of infections generates resistance, and fetal well-being (i.e. risk of teratogenesis) limits the choice of antibiotic.

Penicillins, cephalosporins and erythromycin are all safe in pregnancy and should be favoured where sensitivity allows [48]. Fluoroquinolones have caused fetal arthropathy in animal studies, while tetracyclines are linked to interference with bone growth. Sulphonamides and trimethoprim may cause neural tube defects, particularly in the first trimester [46]. Gentamicin may cause fetal nephrotoxicity and ototoxicity, and levels should be monitored.

Recurrent treatment and prolonged courses of antibiotics may also predispose to fungal infection. Antifungal agents carry a higher risk of fetal toxicity. The antifungal of choice is amphotericin B; there are no reports of teratogenesis attributed to this agent although it does cross the placenta [49].

29.5.8 Fetal Monitoring, Tocolytics and Timing of Delivery

Routine fetal surveillance should only be initiated once it has been established that the gestational age at the time of arrest may be associated

with potential neonatal viability (i.e. >24 weeks). At such time, testing should begin with daily heart rate monitoring and weekly assessment of growth and lung maturity [18].

Tocolytics have been successfully used to prolong pregnancy in immature fetuses in several cases. A combination of magnesium and indomethacin has been used to control uterine contraction and prolong pregnancy [50]. While beta-2 agonists and calcium channel blockers may be used in conventional preterm labour, they may exacerbate cardiovascular instability in the brain-dead pregnant patient [34].

The timing of delivery is a balance between fetal maturity and the ongoing stability of the maternal-fetal system. The decision to deliver should be determined by fetal lung maturity in ideal uncomplicated circumstances. After 32 weeks' gestation, Caesarian delivery should be undertaken as there is no further requirement to prolong the pregnancy [18]. Delivery should be preceded by glucocorticoid-induced (and confirmed) fetal lung maturation. Circumstances which may precipitate early delivery include persistent maternal hemodynamic instability, preterm labour resistant to tocolytics and intrauterine growth retardation [32].

29.6 Potential Future Developments

Extracorporeal membrane oxygenation has been used successfully in pregnant patients with organ failure secondary to influenza and other conditions and has allowed the birth of viable infants afterwards [51]. However, as of this time, it has not yet been used as part of a package of somatic support to facilitate delivery of a fetus following catastrophic maternal injury.

Recently an artificial uterus has been developed. It has been used in animal experiments to allow the birth of a transplanted fetus. The development of a human version of this process is underway and may in the future obviate the need for prolonged maternal somatic support following brain death to allow for suitable fetal maturation [52].

29.7 Conclusion

Maternal brain death is thankfully a rare event. Many ethical and emotive issues arise in the care of the brain-dead pregnant patient. Good communication between medical teams and family members is essential not only in explaining the situation but also in attempting to elicit the patient's wishes regarding continuation of the pregnancy. The decision to continue somatic support should be informed by local laws. However, it also requires a balanced view of the chances of success, the likelihood of causing harm and the best interests of both mother and fetus. This remains a difficult area and is still very much an experimental therapy. Gestational age at the time of maternal injury affects the likelihood of success, and careful consideration should be given to proceeding with support if the injury occurs in early pregnancy. Prolonged somatic support allowing the delivery of a viable neonate has been accomplished in a small number of cases. Somatic support utilises many principles and techniques utilised in caring for the organ donor; however these are modified to minimise risk to the fetus. The principle goal in organ support is to maintain perfusion to the fetal-placental unit.

References

1. Pozhitkov AE, Neme R, Domazet-Lošo T, Leroux BG, Soni S, Tautz D, Noble PA. Tracing the dynamics of gene transcripts after organismal death. Open Biol. 2017;7(1):160267.
2. DeGrazia D. The Definition of Death. *The Stanford Encyclopedia of Philosophy* (Spring 2017 Edition), Zalta EN (ed.). https://plato.stanford.edu/archives/spr2017/entries/death-definition
3. Mollaret P, Goulon M. The depassed coma (preliminary memoir) [in French]. Rev Neurol (Paris). 1959;101:3–15.
4. WHO: International guidelines for the determination of death 2012. http://www.who.int/patientsafety/montreal-forum-report.pdf last accessed 14/4/17.
5. Smith M. Physiologic changes during brain stem death—lessons for management of the organ donor. J Heart Lung Transplant. 2004;23(9 Suppl):S217–22.
6. Field DR, Gates EA, Creasy RK, Jonsen AR, Laros RK Jr. Maternal brain death during pregnancy. Medical and ethical issues. JAMA. 1988;260(6):816–22.

7. Shewmon DA. Chronic "brain death": meta-analysis and conceptual consequences. Neurology. 1998;51(6):1538–45.
8. Pallis C. ABC of brain stem death. From brain death to brain stem death. Br Med J (Clin Res Ed). 1982;285(6353):1487–90.
9. Streat S. Reversible brain death'—is it true, confounded, or 'not proven'? Crit Care Med. 2011;39(6):1601–3.
10. Wijdicks EF, Varelas PN, Gronseth GS, Greer DM. American Academy of Neurology. Evidence-based guideline update: determining brain death in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2010;74(23):1911–8.
11. Australian and New Zealand Intensive Care Society. The ANZICS statement on death and organ donation (edition 3.2). Melbourne: ANZICS; 2013. http://www.anzics.com.au/Downloads/ANZICS%20Statement%20on%20%20Death%20and%20Organ%20Donation%20Edition%203.2.pdf Last accessed 14/4/17
12. Knight M, Nair M, Tuffnell D, Kenyon S, Shakespeare J, Brocklehurst P, Kurinczuk JJ, on behalf of MBRRACE-UK, editors. Saving lives, improving mothers' care—surveillance of maternal deaths in the UK 2012–14 and lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009–14. Oxford: National Perinatal Epidemiology Unit, University of Oxford; 2016. https://www.npeu.ox.ac.uk/downloads/files/mbrrace-uk/reports/MBRRACE-UK%20Maternal%20Report%202016%20-%20website.pdf. Last accessed 14/4/17
13. Dillon WP, Lee RV, Tronolone MJ, Buckwald S, Foote RJ. Life support and maternal death during pregnancy. JAMA. 1982;248(9):1089–91.
14. Vives A, Carmona F, Zabala E, Fernández C, Cararach V, Iglesias X. Maternal brain death during pregnancy. Int J Gynaecol Obstet. 1996;52(1):67–9.
15. Lane A, Westbrook A, Grady D, O'Connor R, Counihan TJ, Marsh B, Laffey JG. Maternal brain death: medical, ethical and legal issues. Intensive Care Med. 2004;30(7):1484–6.
16. Suddaby EC, Schaeffer MJ, Brigham LE, Shaver TR. Analysis of organ donors in the peripartum period. J Transpl Coord. 1998;8(1):35–9.
17. Farragher R, Marsh B, Laffey JG. Maternal brain death—an Irish perspective. Ir J Med Sci. 2005;174(4):55–9.
18. Esmaeilzadeh M, Dictus C, Kayvanpour E, Sedaghat-Hamedani F, Eichbaum M, Hofer S, Engelmann G, Fonouni H, Golriz M, Schmidt J, Unterberg A, Mehrabi A, Ahmadi R. One life ends, another begins: management of a brain-dead pregnant mother—a systematic review. BMC Med. 2010;8:74.
19. Bernstein IM, Watson M, Simmons GM, Catalano PM, Davis G, Collins R. Maternal brain death and prolonged fetal survival. Obstet Gynecol. 1989;74(3 part 2):434–7.
20. Gardiner D, Shemie S, Manara A, Opdam H. International perspective on the diagnosis of death. Br J Anaesth. 2012;108(Suppl 1):i14–28.
21. Wijdicks EF. Brain death worldwide: accepted fact but no global consensus in diagnostic criteria. Neurology. 2002;58(1):20–5.
22. Heran MK, Heran NS, Shemie SD. A review of ancillary tests in evaluating brain death. Can J Neurol Sci. 2008;35(4):409–19.
23. Wijdicks EF. The case against confirmatory tests for determining brain death in adults. Neurology. 2010;75(1):77–83.
24. Anstötz C. Should a brain-dead pregnant woman carry her child to full term? The case of the "Erlanger baby". Bioethics. 1993;7(4):340–50.
25. Finnerty JJ, Chisholm CA, Chapple H, Login IS, Pinkerton JV. Cerebral arteriovenous malformation in pregnancy: presentation and neurologic, obstetric, and ethical significance. Am J Obstet Gynecol. 1999;181(2):296–303.
26. Liao S, Ito S. Brain death: ethical challenges to palliative care concepts of family care. J Pain Symptom Manag. 2010;40(2):309–13.
27. FIGO Committee for Ethical Aspects of Human Reproduction and Women's Health. Brain death and pregnancy. Int J Gynaecol Obstet. 2011;115(1):84–5.
28. Clouser KD, Gert B. A critique of principlism. J Med Philos. 1990;15(2):219–36.
29. Meltzer LS, Huckabay LM. Critical care nurses' perceptions of futile care and its effect on burnout. Am J Crit Care. 2004;13(3):202–8.
30. Burkle CM, Tessmer-Tuck J, Wijdicks EF. Medical, legal, and ethical challenges associated with pregnancy and catastrophic brain injury. Int J Gynaecol Obstet. 2015;129(3):276–80.
31. Dictus C, Vienenkoetter B, Esmaeilzadeh M, Unterberg A, Ahmadi R. Critical care management of potential organ donors: our current standard. Clin Transpl. 2009;23(Suppl 21):2–9.
32. Mallampalli A, Guy E. Cardiac arrest in pregnancy and somatic support after brain death. Crit Care Med. 2005;33(10 Suppl):S325–31.
33. Gordon KG, McKinlay J. Physiological changes after brain stem death and management of the heart-beating donor. Continuing Educ Anaesth Crit Care Pain. 2012;12(5):225–9.
34. Powner DJ, Bernstein IM. Extended somatic support for pregnant women after brain death. Crit Care Med. 2003;31(4):1241–9.
35. Soma-Pillay P, Nelson-Piercy C, Tolppanen H, Mebazaa A. Physiological changes in pregnancy. Cardiovasc J Afr. 2016;27(2):89–94.
36. McKeown DW, Bonser RS, Kellum JA. Management of the heartbeating brain-dead organ donor. Br J Anaesth. 2012;108(Suppl 1):i96–107.
37. Hauksson A, Akerlund M, Melin P. Uterine blood flow and myometrial activity at menstruation, and the action of vasopressin and a synthetic antagonist. Br J Obstet Gynaecol. 1988;95(9):898–904.

38. Feldman DM, Borgida AF, Rodis JF, Campbell WA. Irreversible maternal brain injury during pregnancy: a case report and review of the literature. Obstet Gynecol Surv. 2000;55(11):708–14.
39. Yeung P Jr, McManus C, Tchabo JG. Extended somatic support for a pregnant woman with brain death from metastatic malignant melanoma: a case report. J Matern Fetal Neonatal Med. 2008;21(7): 509–11.
40. Davis WB, Rennard SI, Bitterman PB, Crystal RG. Pulmonary oxygen toxicity. Early reversible changes in human alveolar structures induced by hyperoxia. N Engl J Med. 1983;309(15):878–83.
41. van Runnard Heimel PJ, Franx A, Schobben AF, Huisjes AJ, Derks JB, Bruinse HW. Corticosteroids, pregnancy, and HELLP syndrome: a review. Obstet Gynecol Surv. 2005;60(1):57–70.
42. Venkateswaran RV, Steeds RP, Quinn DW, Nightingale P, Wilson IC, Mascaro JG, Thompson RD, Townend JN, Bonser RS. The haemodynamic effects of adjunctive hormone therapy in potential heart donors: a prospective randomized double-blind factorially designed controlled trial. Eur Heart J. 2009;30(14):1771–80.
43. Miller MW, Nyborg WL, Dewey WC, Edwards MJ, Abramowicz JS, Brayman AA. Hyperthermic teratogenicity, thermal dose and diagnostic ultrasound during pregnancy: implications of new standards on tissue heating. Int J Hyperth. 2002;18(5): 361–84.
44. Dominguez-Roldan JM, Murillo-Cabezas F, Santamaria-Mifsut JL, Muñoz-Sanchez A, Villen-Nieto J, Barrera-Chacon JM. Changes in resting energy expenditure after development of brain death. Transplant Proc. 1995;27(4):2397–8.
45. Hamaoui E, Hamaoui M. Nutritional assessment and support during pregnancy. Gastroenterol Clin N Am. 2003;32(1):59–121.
46. Farragher RA, Laffey JG. Maternal brain death and somatic support. Neurocrit Care. 2005;3(2):99–106.
47. Chhabra G, Sharma S, Subramanian A, Agrawal D, Sinha S, Mukhopadhyay AK. Coagulopathy as prognostic marker in acute traumatic brain injury. J Emerg Trauma Shock. 2013;6(3):180–5.
48. Einarson A, Shuhaiber S, Koren G. Effects of antibacterials on the unborn child: what is known and how should this influence prescribing. Paediatr Drugs. 2001;3(11):803–16.
49. King CT, Rogers PD, Cleary JD, Chapman SW. Antifungal therapy during pregnancy. Clin Infect Dis. 1998;27(5):1151–60.
50. Catanzarite VA, Willms DC, Holdy KE, Gardner SE, Ludwig DM, Cousins LM. Brain death during pregnancy: tocolytic therapy and aggressive maternal support on behalf of the Fetus. Am J Perinatol. 1997;14(7):431–4.
51. Moore SA, Dietl CA, Coleman DM. Extracorporeal life support during pregnancy. J Thorac Cardiovasc Surg. 2016;151(4):1154–60.
52. Partridge EA, Davey MG, Hornick MA, McGovern PE, Mejaddam AY, Vrecenak JD, Mesas-Burgos C, Olive A, Caskey RC, Weiland TR, Han J, Schupper AJ, Connelly JT, Dysart KC, Rychik J, Hedrick HL, Peranteau WH, Flake AW. An extra-uterine system to physiologically support the extreme premature lamb. Nat Commun. 2017;8:15112.

Part VIII

The Renal System

Renal Physiology during Normal Pregnancy

30

Rachel Savine and Lui G. Forni

Bullet Points

- Significant changes occur in renal anatomy during pregnancy, with renal volume increasing by up to 30%.
- Hemodynamic alterations, including responsiveness to vasopressors, are related to both systemic cardiovascular changes and renal adaptation.
- Tubular function, renal solute handling, and acid-base balance are affected by pregnancy.
- Traditional measures of renal function may be inaccurate in pregnancy.
- Maternal renal adaptations have important consequences in terms of defining renal injury, particularly as current definitions of acute kidney injury (AKI) rely on acute changes in serum creatinine (SCr) and urine output.
- Glomerular filtration rate (GFR) rises early in pregnancy, as systemic vascular resistance (SVR) falls progressively by approximately 35–40% until the mid-second trimester while cardiac output begins to rise.
- Commonly used creatinine-based estimating formulas are best avoided in pregnant women, as all GFR formulas consistently underestimate the true GFR in pregnancy.
- Uric acid levels are mostly determined by altered renal handling; decreased uric acid clearance may be seen in volume depletion, which is a hallmark of preeclampsia.
- The primary acid-base alteration is a relative respiratory alkalosis resulting from an increase in maternal minute ventilation, compensated through increased bicarbonate excretion.
- Although relative hyponatremia is observed in normal pregnancy, any pregnant woman presenting with a serum sodium concentration below normal should be evaluated for pathological causes, as for nonpregnant individuals.

There are no conflicts of interest regarding this topic for either author.

R. Savine
Department of Intensive Care Medicine, Royal Surrey County Hospital NHS Foundation Trust, Guildford, UK

L. G. Forni (✉)
Department of Intensive Care Medicine, Royal Surrey County Hospital NHS Foundation Trust, Guildford, UK

Department of Clinical & Experimental Medicine, Faculty of Health Sciences, University of Surrey, Guildford, UK

Surrey Peri-Operative Anaesthesia and Critical Care Collaborative Research Group (SPACER), Guildford, UK
e-mail: luiforni@nhs.net

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_30

30.1 Introduction

The kidney undergoes dramatic changes during pregnancy. These changes may be noted as early as 6 weeks gestation. Adaptation to pregnancy affects all aspects of renal function, ranging from anatomical changes to the sequelae of haemodynamic alterations accompanied by changes in glomerular filtration. These changes result in modifications in renal tubular function together with differences in renal solute handling and water resorption. Maternal renal adaptations have important consequences in terms of defining renal injury, particularly, as the current definitions of acute kidney injury (AKI) rely on acute changes in serum creatinine (SCr) and urine output.

30.1.1 Anatomical Changes

The anatomical adaptations of the kidneys to pregnancy are well documented, with the observed changes persisting for up to 6 months after delivery [1]. This is readily demonstrated by measuring the interpolar length, which may increase by up to 1–1.5 cm during pregnancy. However, this 2D value underestimates the effect on total renal volume, which may increase by up to 30% [2–4]. The total number of nephrons remains unchanged. Therefore, this increase in kidney volume was initially felt to reflect a degree of hydronephrosis, an almost ubiquitous finding in pregnancy, but recent evidence points to an increase in renal vasculature and interstitial volume as the cause [5, 6].

Understanding has been enhanced by magnetic resonance imaging, which is increasingly used as an imaging technique for the maternal abdomen [3]. Although ultrasonography remains the modality of choice, this imaging tool is operator-dependent and may be limited by body habitus. Magnetic resonance provides an important alternative imaging modality, particularly where urography is necessary. The degree of hydronephrosis observed varies, but pelvicalyceal dilatation can lead to up to 200–300 mL of urine being observed in the collecting system. This subsequent urinary stasis also translates into an increased risk of pyelonephritis in pregnant women. Several mechanisms have been touted as the cause of hydronephrosis, but the most likely is mechanical compression. Hydronephrosis more commonly affects the right kidney (>80%), as the right ureter is more susceptible to extrinsic compression. This prevalence provides support for the theory that compression is the underlying mechanism [7].

30.1.2 Renal Haemodynamics

The haemodynamic changes in pregnancy include an increase in resting cardiac output, initially through increased stroke volume together with increased RV preload. This is coupled with an expanded circulatory volume and a reduction in systemic vascular resistance, the sum of which is a reduction in blood pressure (*see* Chap. 9). It is therefore of no surprise that there is an observed and well documented increase in the glomerular filtration rate (GFR). These changes begin early in pregnancy, with the systemic vascular resistance (SVR) falling progressively by approximately 35–40% until the mid-second trimester while cardiac output begins to rise. Part of the reduction in SVR may be driven by relative insensitivity to angiotensin II despite activation of the renin aldosterone axis [8, 9]. The third trimester is characterized by a peak in cardiac output derived from a rise in maternal heart rate to approximately 25% of baseline [10] (see Chap. 9 for a more detailed description of cardiovascular changes in pregnancy). Changes in red blood cell mass together with volume expansion both begin early in the first trimester. This leads to the dilutional or physiologic anaemia of pregnancy, which is most apparent at 30–34 weeks of gestation when plasma volume peaks in relation to red cell volume [11].

30.2 Changes in Glomerular Filtration Rate (GFR)

Plasma flow within the kidney increases up to 80% by 12 weeks of gestation with an increase in the GFR detectable within just 1 month of conception,

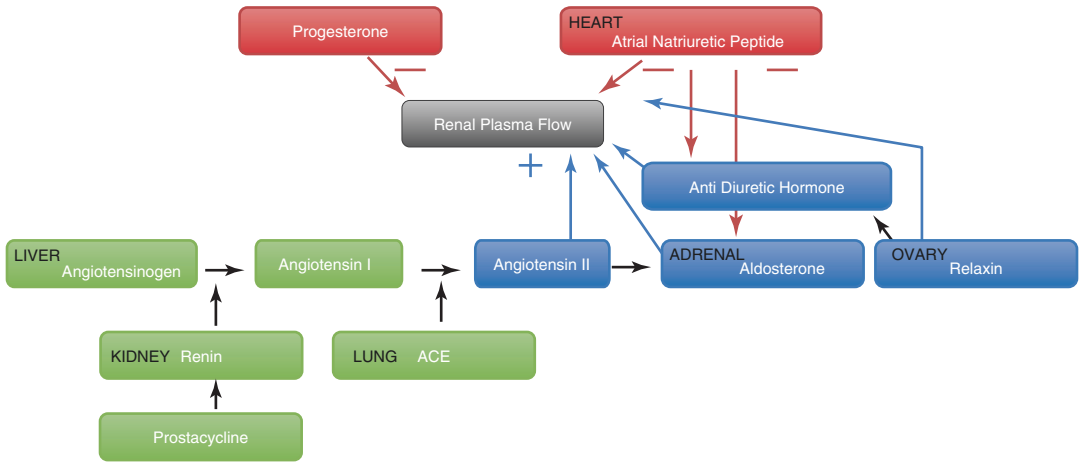


Fig. 30.1 Hormonal actions on renal plasma flow

Fig. 30.1. The GFR rises to approximately 50% above baseline by the early part of the second trimester. This process is driven by haemodynamic changes, as well as a decrease in vascular resistance and increased plasma flow. The reduction in vascular resistance reflects reduced vascular responsiveness to endogenous vasopressors mediated by changes in vascular receptor expression and an increase in nitric oxide production, which has been observed in animal models of pregnancy [12, 13]. In addition, hormonal influences dictate the renal vascular response. Relaxin, a peptide hormone belonging to the insulin family, is normally produced in the corpus luteum and plays a major role in these changes. During pregnancy, relaxin is secreted by the placenta and decidua in response to human chorionic gonadotropin (hCG). This hormone increases endothelin and nitric oxide production in the renal circulation which leads to decreased renal afferent and efferent arteriolar resistance, generalized vasodilatation, and a subsequent increase in renal blood flow and GFR [14]. Towards the latter stages of pregnancy, GFR falls slowly with plasma flow following a similar pattern, i.e., decreasing during the third trimester [15].

The GFR can be represented by the following equation:

$$\mathrm{GFR} = Kf \times \left(\Delta P - \pi GC\right)$$

where ΔP is the pressure generated across the glomerulus (the transcapillary hydraulic pressure difference), πGC is the mean glomerular intracapillary oncotic pressure (the force that opposes GFR), and Kf is the product of the surface area available for filtration and the hydraulic permeability, which is the permeability to ultrafiltration across the glomerulus [16]. Given the fall in renal plasma flow observed during late pregnancy, one may expect a more significant fall in GFR. However, GFR is maintained at this stage of pregnancy through a rise in the filtration fraction. This process is secondary both to decreasing capillary oncotic pressure, which, as noted above, opposes GFR, as well as to increased hydraulic permeability of the glomerular filtration barrier. Animal models suggest that the pressure generated across the glomerulus remains unchanged given proportional changes in the afferent and efferent arterioles, so the hyperfiltration is driven by the increase in renal plasma flow (RPF). However, in humans, the mechanism may not be entirely RPF-driven. For example, in women with underlying renal disease, pregnancy may result in deterioration of renal function. The determinants of GFR have not been examined thoroughly in pregnant women but rely on a few small studies [17–19].

30.3 Calculating the GFR in Pregnancy

Commonly used creatinine-based estimating formulas are best avoided in pregnant women, as all GFR formulae consistently underestimate the true GFR in pregnancy [20–24]. For example, the Modification of Diet in Renal Disease (MDRD) equation is potentially attractive for use in pregnancy as it is not individualized for body surface area. However, the MDRD consistently underestimates the GFR not only in patients with normal renal function but also in those with renal impairment [22].

The gold standard for measuring GFR is inulin clearance, but this is impractical in routine clinical use. The best estimate therefore remains that derived from a 24-h urine collection, although this may be prone to errors in collection. Collections should therefore be assessed for accuracy through measuring urinary creatinine excretion; 10–15 mg of creatinine/kg corresponds to a complete collection [25]. Given that skeletal muscle production remains constant throughout pregnancy, the increase in GFR contributes to the observed reduction in serum creatinine. Similar findings are seen with the serum urea as this is also freely filtered at the glomerulus.

30.4 Tubular Function

The physiological changes in renal function seen in pregnancy are not only secondary to changes in renal haemodynamics; there are also well-recognized changes in tubular function. Of perhaps the greatest importance is the renal handling of protein, given the fact that assessment of proteinuria is pivotal in monitoring coexistent renal disease as well as pregnancy-specific renal conditions, including pre-eclampsia. Twenty-four hour protein excretion in excess of 300 mg, double that of non-pregnant normal individuals, and an albumin excretion of >20 mg is considered abnormal [26].

The mechanism/s underlying this ‘protein leak’ are not well understood. Most probably these include not only a degree of hyperfiltration related to the increased GFR but also alterations in glomerular charge selectivity. This may result in impairment of proximal tubular resorptive capacity as evidenced by increased urinary excretion of renal tubular enzymes and other low molecular weight proteins rather than a non-selective loss of proteins based on molecular weight or molecular size [27]. Furthermore, circulating antiangiogenic factors, which are known to cause glomerular endothelial dysfunction and proteinuria in pre-eclampsia, increase towards term even in normal pregnancies and may contribute to late gestational proteinuria [28].

Urinary glucose excretion is minimal under normal circumstances. Glucose is freely filtered at the glomerulus and almost completely reabsorbed in the proximal tubule, and to a lesser extent in the collecting tubule, through sodium-coupled active transport. Glycosuria is only observed when the plasma concentration of glucose exceeds the maximal tubular resorptive capacity or a threshold concentration of approximately 10 mmol/L. The increased GFR and tubular flow in the pregnant state may result in physiological glycosuria, since the ability of the proximal tubule to completely reabsorb glucose may be limited. As a consequence of these physiological changes, during pregnancy, glycosuria per se does not indicate renal tubular dysfunction. Similarly there is evidence for increased urinary excretion of amino acids as well as some water-soluble vitamins [29].

The renal handling of uric acid deserves mention given the importance of uric acid levels in the diagnosis of pre-eclampsia [30]. In normal pregnancy, serum uric acid is decreased by 25–35% with lowest levels observed at 24 weeks. Clearance of circulating uric acid is primarily by renal excretion. Most is filtered by the glomerulus. Uric acid is reabsorbed as well as secreted by the proximal tubule of the kidney, with only 7–12% of the filtered load undergoing urinary excretion [31]. Therefore, during pregnancy, uric acid levels are mostly determined by the through alterations occurring in renal handling. Increased GFR and reduced proximal tubular reabsorption, either alone or

in combination, play a role in uric acid clearance, although multiple factors may also play a role in this process. Decreased uric acid clearance may be seen in volume depletion, which is a hallmark of pre-eclampsia.

30.5 Acid-Base and Electrolyte Balance

The primary acid-base alteration in pregnancy is a relative respiratory alkalosis resulting from an increase in maternal minute ventilation. This is compensated through increased bicarbonate excretion. The end result of this process is a potential decrease in buffering capacity, which is important when interpreting laboratory values and arterial blood gases during pregnancy. Unsurprisingly, the changes in maternal renal haemodynamics and solute handling also influence laboratory test results. For example, the serum sodium tends to drop by 4–5 mmol/L below non-pregnancy levels, resulting in a lower plasma osmolality of about 270 mosmol/kg [32]. This hyponatraemia is hormonally mediated and correlates closely with hCG levels which may reset the ADH threshold through the release of relaxin. Although relative hyponatraemia is observed in normal pregnancy, any pregnant individual presenting with a serum sodium concentration below normal should be evaluated for pathological causes similarly to non-pregnant individuals.

30.6 Conclusion

It is clear that renal physiology is changed significantly during pregnancy and that some of these changes may persist into the post-partum period. For example, hyperfiltration at levels 20% above prepartum have been observed at 2 weeks into the post-partum period, although these changes tend to resolve by 28 days [33, 34]. Of note is that some of these changes in the non-pregnant state may reflect underlying pathological processes but are expected in the pregnant state. These, together with the inaccuracies of conventional estimates of creatinine clearance, are potential pitfalls in the management of peripartum women, particularly where renal dysfunction is suspected.

References

1. Bailey RR, Rolleston GL. Kidney length and ureteric dilatation in the puerperium. J Obstet Gynaecol Br Commonw. 1971;78:55–61.
2. Christensen T, Klebe JG, Bertelsen V, Hansen HE. Changes in renal volume during normal pregnancy. Acta Obstet Gynecol Scand. 1989;68(6):541–3.
3. Leyendecker JR, Gorengaut V, Brown JJ. MR imaging of maternal diseases of the abdomen and pelvis during pregnancy and the immediate postpartum period. Radiographics. 2004;24:1301–16.
4. Roy C, Saussine C, Jahn C, et al. Fast imaging MR assessment of ureterohydronephrosis during pregnancy. Magn Reson Imaging. 1995;13(6):767–72.
5. Beydoun SN. Morphologic changes in the renal tract in pregnancy. Clin Obstet Gynecol. 1985;28(2):249–56.
6. Strevens H, Wide-Swensson D, Hansen A, et al. Glomerular endotheliosis in normal pregnancy and pre-eclampsia. BJOG. 2003;110(9):831–6.
7. Cheung KL, Lafayette RA. Renal physiology of pregnancy. Adv Chronic Kidney Dis. 2013;20(3):209–14.
8. Abdul-Karim R, Assalin S. Pressor response to angiotonin in pregnant and nonpregnant women. Am J Obstet Gynecol. 1961;82:246–51.
9. Schrier RW, Briner VA. Peripheral arterial vasodilation hypothesis of sodium and water retention in pregnancy: implications for pathogenesis of pre-eclampsia-eclampsia. Obstet Gynecol. 1991;77:632–9.
10. Duvekot JJ, Cheriex EC, Pieters FA, Menheere PP, Peeters LH. Early pregnancy changes in hemodynamics and volume homeostasis are consecutive adjustments triggered by a primary fall in systemic vascular tone. Am J Obstet Gynecol. 1993;169:1382–92.
11. Jansen AJ, van Rhenen DJ, Steegers EA, Duvekot JJ. Postpartum hemorrhage and transfusion of blood and blood components. Obstet Gynecol Surv. 2005;60:663–71.
12. Danielson LA, Conrad KP. Acute blockade of nitric oxide synthase inhibits renal vasodilation and hyperfiltration during pregnancy in chronically instrumented conscious rats. J Clin Invest. 1995;96:482–90.
13. Deng A, Engels K, Baylis C. Impact of nitric oxide deficiency on blood pressure and glomerular hemodynamic adaptations to pregnancy in the rat. Kidney Int. 1996;50:1132–8.
14. Conrad KP, Jeyabalan A, Danielson LA, Kerchner LJ, Novak J. Role of relaxin in maternal renal vasodilation of pregnancy. Ann N Y Acad Sci. 2005;1041:147–54.
15. Davison JM, Dunlop W. Renal hemodynamics and tubular function normal human pregnancy. Kidney Int. 1980;18:152–61.

16. Deen WM, Robertson CR, Brenner BM. A model of glomerular ultrafiltration in the rat. Am J Phys. 1972;223:1178–83.
17. Lafayette RA, Malik T, Druzin M, Derby G, Myers BD. The dynamics of glomerular filtration after Caesarean section. J Am Soc Nephrol. 1999;10:1561–5.
18. Sims EA, Krantz KE. Serial studies of renal function during pregnancy and the puerperium in normal women. J Clin Invest. 1958;37:1764–74.
19. Dunlop W. Serial changes in renal haemodynamics during normal human pregnancy. Br J Obstet Gynaecol. 1981;88:1–9.
20. Nguyen MT, Maynard SE, Kimmel PL. Misapplications of commonly used kidney equations: renal physiology in practice. Clin J Am Soc Nephrol. 2009;4:528–34.
21. Smith JD, Banner NR, Hamour IM, et al. De novo donor HLA-specific antibodies after heart transplantation are an independent predictor of poor patient survival. Am J Transplant. 2011;11:312–9.
22. Smith MC, Moran P, Ward MK, Davison JM. Assessment of glomerular filtration rate during pregnancy using the MDRD formula. BJOG. 2008;115:109–12.
23. Alper AB, Yi Y, Webber LS, et al. Estimation of glomerular filtration rate in preeclamptic patients. Am J Perinatol. 2007;24:569–74.
24. Ahmed SB, Bentley-Lewis R, Hollenberg NK, Graves SW, Seely EW. A comparison of prediction equations for estimating glomerular filtration rate in pregnancy. Hypertens Pregnancy. 2009;28:243–55.
25. Cote AM, Firoz T, Mattman A, Lam EM, von Dadelszen P, Magee LA. The 24-hour urine collection: gold standard or historical practice? Am J Obstet Gynecol. 2008;199:625 e1–6.
26. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertens Pregnancy. 2001;20:IX–XIV.
27. Bernard A, Thielemans N, Lauwerys R, van Lierde M. Selective increase in the urinary excretion of protein 1 (Clara cell protein) and other low molecular weight proteins during normal pregnancy. Scand J Clin Lab Invest. 1992;52:871–8.
28. Yoshimatsu J, Matsumoto H, Goto K, Shimano M, Narahara H, Miyakawa I. Relationship between urinary albumin and serum soluble fms-like tyrosine kinase 1 (sFlt-1) in normal pregnancy. Eur J Obstet Gynecol Reprod Biol. 2006;128:204–8.
29. Hytten FE, Cheyne GA. The aminoaciduria of pregnancy. J Obstet Gynaecol Br Commonw. 1972;79:424–32.
30. Thangaratinam S, Ismail KM, Sharp S, Coomarasamy A, Khan KS. Tests in prediction of pre-eclampsia severity review group. Accuracy of serum uric acid in predicting complications of pre-eclampsia: a systematic review. BJOG. 2006;113(4):369–78.
31. Boyle JA, Campbell S, Duncan AM, Greig WR, Buchanan WW. Serum uric acid levels in normal pregnancy with observations on the renal excretion of urate in pregnancy. J Clin Pathol. 1966;19:501–3.
32. Lindheimer MD, Barron WM, Davison JM. Osmotic and volume control of vasopressin release in pregnancy. Am J Kidney Dis. 1991;17:105–11.
33. Krutzen E, Olofsson P, Back SE, Nilsson-Ehle P. Glomerular filtration rate in pregnancy: a study in normal subjects and in patients with hypertension, preeclampsia and diabetes. Scand J Clin Lab Invest. 1992;52:387–92.
34. Hladunewich MA, Lafayette RA, Derby GC, et al. The dynamics of glomerular filtration in the puerperium. Am J Physiol Renal Physiol. 2004;286:F496–503.

31 Renal Failure and Renal Replacement Therapy During Pregnancy and the Peripartum Period

Emma Roche-Kelly and Marlies Ostermann

Bullet Points

- Renal failure during pregnancy and the peripartum period includes acute kidney injury (AKI), chronic kidney disease, and end-stage renal disease (ESRD). The incidences of each vary worldwide.
- Acute kidney injury may be due to conditions specific to pregnancy (i.e., pre-eclampsia, HELLP and acute fatty liver of pregnancy), disorders that coincide with pregnancy (i.e., major surgery), or an exacerbation of a pre-existing renal disorder.
- Management of AKI consists of prompt resuscitation of hemodynamics, correction of hypovolemia, avoidance of further nephrotoxic insults, and treatment of the disease process leading to AKI.
- In women with preeclampsia, HELLP, or acute fatty liver of pregnancy, multidisciplinary input is essential when determining the maternal and fetal indications for delivery.
- Renal replacement therapy may be necessary in women with progressive AKI or severe complications of AKI; it is essential in those with pre-existing end-stage renal failure.
- During critical illness, continuous renal replacement therapy is the preferred modality. The timing and dose should be guided by the overall aim to maintain blood urea nitrogen <16 mmol/L.
- Most women with AKI during pregnancy recover renal function; however, some will need long-term renal replacement therapy and appropriate nephrology follow-up care.
- Women with a renal transplant require multidisciplinary input throughout pregnancy including close nephrology and obstetric follow-up.

31.1 Introduction

The management of critically ill pregnant women with renal disease is challenging for obstetricians, nephrologists, anesthesiologists, and critical care clinicians. Although the type and severity of renal disease may vary, ranging from pre-existing chronic kidney disease (CKD) and end-stage renal disease (ESRD) to pregnancy-related acute

E. Roche-Kelly
Department of Intensive Care, King's College NHS Foundation Hospital, London, UK

M. Ostermann (✉)
Department of Intensive Care, King's College London, Guy's & St Thomas' NHS Foundation Hospital, London, UK
e-mail: Marlies.Ostermann@gstt.nhs.uk

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_31

kidney injury (AKI), some general principles apply to all patients. Management is often complicated by the fact that both maternal and fetal health has to be considered.

31.2 Acute Kidney Injury

31.2.1 Definition

Pregnancy-related AKI refers to AKI occurring during pregnancy, labor, and delivery or the postpartum period, defined as the 6 weeks after childbirth. The incidence and etiology of AKI vary greatly between different geographical regions.

To date, there is no widely accepted definition for AKI during pregnancy. In the general population, AKI is defined by the criteria of the Kidney Disease Improving Global Outcome (KDIGO) classification, i.e., a rise in serum creatinine, fall in urine output, or both; but these criteria are not applicable to pregnant women [1]. Indeed, due to the normal physiologic drop in serum creatinine during pregnancy, seemingly "normal" creatinine results (i.e. 0.7–0.9 mg/dL) may represent significant increases from baseline, and the diagnosis of early AKI may easily be missed. Different criteria and creatinine cut-offs have been used to define AKI in pregnancy [2–9] (Table 31.1).

Various formulas are available to estimate glomerular filtration rate (eGFR). They serve to give an estimate of renal function but rely on renal function being stable. As such, they have no role in the acute setting, including in pregnant women with AKI, since renal function may change rapidly.

Table 31.1 Criteria used to diagnose acute kidney injury (AKI) in pregnancy

Diagnostic criteria for AKI in pregnancy	References
Serum creatinine >1.1 mg/dL (97 μmol/L) or doubling of serum creatinine	American College of Obstetrics and Gynecology (ACOG), 2013 [2]
Serum creatinine >0.8 mg/dL (70 μmol/L)	Liu Y et al. 2017 [3]
Obstetric acute renal failure defined according to international classification of diseases, ninth revision, clinical modification codes for acute kidney failure after labor and delivery (code 669.3), acute renal failure (code 584), and unspecified renal failure (code 586)	Mehrabadi et al. 2016 [4]
1.5× increase of serum creatinine from baseline and/or decrease of urine output to <400 mL for ≥6 h	Gopalakrishnan N et al. 2015 [5]
Risk—Injury—Failure—Loss—End-stage (RIFLE) classification	Kamal EM et al. 2014 [6]
Modified acute kidney injury network (AKIN) criteria: serum creatinine increase ≥0.3 mg/dL (≥26.4 μmol/L) during pregnancy or within 30 days postpartum	Gurrieri C et al. 2012 [7]
Need for dialysis	Prakash J et al. 2016 [8]

31.2.1.1 Role of AKI Biomarkers

In the future, the diagnosis of AKI in pregnancy may also include novel biomarkers. For example, serum levels of neutrophil gelatinase-associated lipocalin (NGAL) and proteinuria both increase with worsening endothelial dysfunction. In hypertensive pregnant women, a rise in NGAL has been shown to correlate with increasing proteinuria and serum creatinine (correlation coefficient 0.4) [10]. However, the cut-off values of most biomarkers with diagnostic potential are only now being clarified in the general adult population; whether these values will differ in pregnant women remains unclear. Furthermore, in most biomarker studies, pregnant women were excluded. More research is necessary to evaluate the role of novel biomarkers in this population.

31.2.2 Epidemiology

The lack of consensus criteria for AKI in pregnancy, added to wide variations in demographics and standards of care among populations, have made estimation of the incidence of pregnancy-related AKI difficult. In a study of 1.9 million pregnancies over a 15-year period, 1 in 10,000 pregnancies had severe AKI and needed dialysis [4]. Risk factors included pre-pregnancy hypertension, diabetes, CKD, and systemic lupus erythematosus (SLE). Women who had a major

Table 31.2 Causes of AKI in critically ill women during pregnancy or the peripartum period

Category	Examples	Underlying pathophysiology leading to AKI	Typical time of onset
Pregnancy-specific	Pre-eclampsia Hemorrhage Ureteric obstruction Amniotic fluid embolism	• Hypertension/vasoconstriction • Volume depletion • Obstruction • Cardiovascular collapse	Third trimester or postpartum
Conditions coinciding with pregnancy	Glomerulonephritis Sepsis Major surgery	• De-novo primary renal disease • Systemic inflammation/endothelial dysfunction/hemodynamic instability	Any stage
Pre-existing renal disease	CKD Lupus nephritis Renal transplant	• Exacerbation/flare of underlying disease • Acute rejection	Any stage

Abbreviations: *AKI* acute kidney injury, *CKD* chronic kidney disease

complication of pregnancy (e.g., pre-eclampsia, thrombotic microangiopathy, heart failure, pyelonephritis, sepsis, placental abruption and postpartum hemorrhage) were nearly four times more likely to need dialysis. A retrospective study from 1995 to 1998 showed that 10% of women with severe pre-eclampsia needed dialysis in the short term but none required long-term dialysis or a kidney transplant [11]. The risk of dialysis is higher in women with pre-existing kidney problems.

A multinational cross-sectional prevalence study of all causes of AKI organized by the International Society of Nephrology revealed that pregnancy-related AKI constituted 1% of all cases of reported AKI [12]. In this study, pregnancy-related AKI was reported more frequently from samples in low-income countries compared to other geographical areas. The study identified dehydration and hypotension as risk factors across all income groups. However, in low-income countries, complicated pregnancy was one of the most important contributors to AKI in younger women. In addition, it was noted that access to dialysis was scarce in low-income countries, with variations seen in different regions of the same country or even in different areas of the same city [12].

31.2.3 Etiology of AKI

Traditionally, the causes of AKI are classified as pre-renal, renal, and post-renal. While the mechanisms suggested by this classification remain pertinent, in critically ill pregnant women, a different classification method is recommended. AKI in pregnancy may be caused by (1) diseases that are specific and unique to pregnancy, (2) acute conditions that coincide with pregnancy but are not directly related to pregnancy, or (3) an exacerbation of pre-existing renal disease. The latter includes "flares" of primary renal disorders and also acute deterioration of renal function in a kidney transplant recipient (Table 31.2). Certain types of AKI are more frequently seen at particular stages of pregnancy, but AKI in the context of critical illness may occur at any time (Fig. 31.1).

31.2.3.1 Common Pregnancy-Specific Causes of AKI

In pregnant women, AKI is a heterogeneous and often multifactorial syndrome, but some etiologies are more common and are important to recognize early.

Hypertensive Disorders of Pregnancy

Pre-eclampsia, HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, and acute fatty liver of pregnancy (ALFP) describe the wide spectrum of a continuum of pregnancy-specific disorders characterized by new-onset hypertension, proteinuria, and AKI occurring after 20 weeks' gestation (Table 31.2). The clinical features of these disorders may overlap, complicating distinction between them [13].

HELLP syndrome is the leading cause of pregnancy-associated AKI [14]. It occurs typically in the third trimester but may be diagnosed in the second trimester or in the postpartum

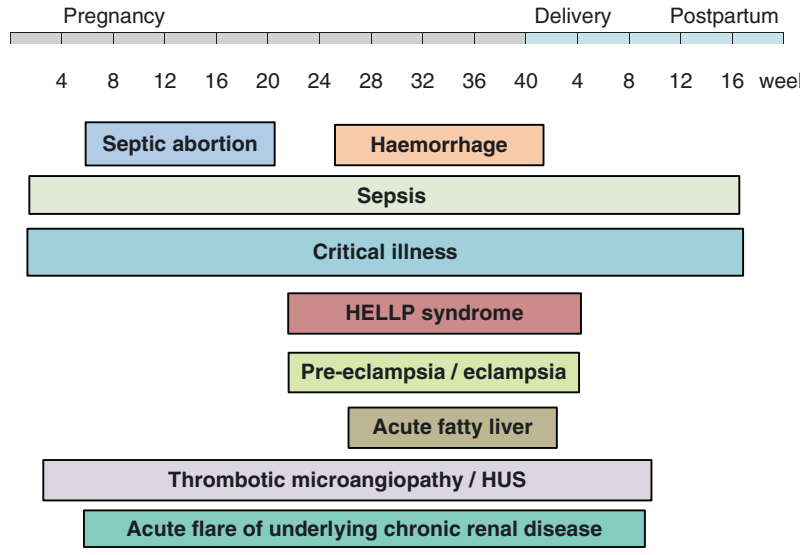


Fig. 31.1 Main causes of acute kidny injury in critically ill pregnant women and their typical time of occurrence. Abbreviations: *HUS* hemolytic-uremic syndrome

period. The clinical features of HELLP vary. The most common symptoms are epigastric/right upper quadrant pain, nausea, vomiting, and headache. However, HELLP syndrome may also manifest by its complications, such as disseminated intravascular coagulopathy, placental abruption, AKI (7–36%), pulmonary edema, hepatic capsular hematoma, and retinal detachment [15]. Severe HELLP syndrome may resemble thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), or autoimmune disorders such as SLE and antiphospholipid syndrome (APS) [14]. Differentiation between these conditions is important as their therapies vary. Delivery of the baby is the treatment of choice for pre-eclampsia-related AKI, whereas immunosuppression and plasma exchange have a role in autoimmune disorders (see Chaps. 5 and 16).

Pre-eclampsia is a pregnancy-specific disorder that typically presents with new onset of hypertension and proteinuria after 32 weeks' gestation but may occur earlier in women with pre-existing chronic renal disease. The most common maternal complications of pre-eclampsia include DIC (10–20%), HELLP syndrome (20%), pulmonary edema (2–5%), AKI (1–5%), and placental abruption (1–2%) [15]. The characteristic renal lesion of pre-eclampsia is swelling and detachment of glomerular endothelial cells with loss of endothelial fenestrae and occlusion of capillary lumens [15]. Pre-eclampsia is also associated with hemodynamic abnormalities such as decreased renal plasma flow, reduction in glomerular filtration rate by 30–40%, renal vasoconstriction, and acute tubular injury. Thus, the kidney in pre-eclamptic women is highly susceptible to ischemic injury, especially in those with pre-existing renal disease. Renal cortical necrosis has also been reported in this scenario. Patients with additional pregnancy-related complications resulting in intravascular volume depletion superimposed on pre-eclampsia are particularly at risk of developing AKI.

Acute fatty liver of pregnancy (AFLP) is characterized by rapidly progressive liver failure in late gestation. It can imitate pre-eclampsia but may also occur simultaneously with pre-eclampsia [6]. The renal dysfunction seen in ALFP is usually multifactorial, including intravascular volume depletion, co-existing pre-eclampsia, and liver failure. See Chaps. 5, 16, and 33 for more details regarding these conditions.

Volume Depletion

Uterine blood flow increases from 50 mL/min prior to pregnancy to approximately 1000 mL/min

at term. Thus, pregnancy-related bleeding can be rapid and massive, resulting in hypovolemia, renal hypoperfusion, and AKI. Common causes include induced or spontaneous abortion, ectopic pregnancy, placenta previa, placental abruption, and intra- or postpartum hemorrhage (see Chap. 6). In severe cases of hypotension and hypoperfusion, irreversible cortical necrosis can occur.

Severe or untreated cases of hyperemesis gravidarum can also lead to clinically significant intravascular volume depletion and AKI.

Infection

Sepsis from any cause can lead to AKI. Contributing factors are hemodynamic instability, endothelial dysfunction, altered renal microcirculation, tubular cell injury, and the formation of microthrombi [16]. The most common sources of sepsis in pregnancy include pyelonephritis, chorioamnionitis, and pneumonia (see Chaps. 18 and 19). Asymptomatic bacteriuria, ureteral dilation, and increased bladder wall flaccidity in particular contribute to the increased risk of pyelonephritis.

Septic abortion is uncommon in countries where abortion has been legalized but is still a significant cause of maternal mortality and morbidity worldwide, including the development of AKI. A survey of 246 units in 14 countries in Latin America revealed that septic abortion, hemolytic-uremic syndrome, community-acquired diarrhea, and leptospirosis were the etiologies most frequently associated with AKI [17]. A recent report from India showed that puerperal sepsis contributed to AKI in one-fourth of pregnant women [18].

Severe sepsis can mimic HELLP syndrome. When faced with presumed HELLP syndrome with no improvement in the inflammatory markers following delivery, sepsis should be suspected, actively sought, and managed [6].

Obstruction

Hydronephrosis and hydroureter have been described as physiological in pregnancy (seen in up to 80%) and appear to be related to direct ureteric compression by the gravid uterus at the pelvic brim [19]. Risk factors are polyhydramnios, multi-fetal gestation, and pre-existing large uterine fibroids. Resultant urinary stasis acting as a bacterial reservoir is thought to account for the increased risk of pyelonephritis. Pathological urinary obstruction may also occur secondary to renal stone disease or ureteric strictures. Even spontaneous renal rupture has been described during pregnancy but is very rare. Iatrogenic injury to the bladder or ureter has been estimated to occur in less than 1% of deliveries, often associated with emergency caesarian section, and should be considered in the differential diagnosis of new onset of AKI after emergency surgery [20].

Cardiovascular Collapse

While any type of severe cardiovascular deterioration can lead to AKI, collapse due to amniotic fluid embolism (AFE) occurs only in pregnancy (Chap. 8). Amniotic fluid embolism is a very rare complication of pregnancy but is associated with a high risk of maternal death. Due to the syndrome's associated cardiac dysfunction, disseminated intravascular coagulopathy, and intravascular volume depletion, AKI is very common in survivors [21].

It presents suddenly with fulminant respiratory failure, hypoxia, hypotension, and cardiogenic shock and is often accompanied by disseminated intravascular coagulation and multi-organ failure [22]. The precise cause of AFE is unclear, with early case series describing squamous cells and mucin of fetal origin in the maternal pulmonary vasculature [23].

31.2.3.2 Other Causes of AKI that May be Co-incident but Not Specific to Pregnancy

Thrombotic Thrombocytopenic Purpura/ Hemolytic-Uremic Syndrome

These multisystem disorders share clinical features of AKI, thrombocytopenia, hemolytic anemia, and thrombotic microangiopathy which are also seen in pre-eclampsia, HELLP syndrome, and ALFP. The relative incidence is very low, with HUS affecting 1 in 25,000 pregnancies and TTP affecting less than 1 in 100,000 pregnancies [24, 25]. They may develop at any stage of

Table 31.3 Characteristics of different hypertensive disorders during pregnancy

Characteristic	Pre-eclampsia or HELLP	Acute fatty liver of pregnancy	Thrombotic thrombocytopenic purpura	Hemolytic-uremic syndrome
Pregnancy-specific	Yes	Yes	No	No
Typical onset	Usually third trimester	Usually third trimester	Median 23 weeks	Often postpartum
Unique clinical manifestation	Hypertension and proteinuria; AKI possible	Nausea, vomiting, malaise; AKI possible	Neurologic symptoms; AKI possible	AKI and hemolysis
Fever	No	No	Yes	No
Purpura	No	No	Yes	No
Hemolysis	Mild	Mild	Severe	Severe
Platelet count	Variable (normal to low)	Variable (normal to low)	Low	Variable (normal to low)
Coagulation	Variable	Abnormal	Normal	Normal
Hypoglycemia	No	Yes	No	No
Classic histological findings	Swelling and detachment of glomerular endothelial cells and associated occlusion of capillary lumen; also acute tubular injury	Acute tubular injury	Thrombotic microangiopathy with swelling of endothelial cells, thickening of the capillary wall, fibrin thrombi within glomeruli, microvascular thromboses, and acute tubular injury	
Treatment for AKI	Delivery	Delivery	Plasmapheresis	Plasmapheresis

Abbreviations: *AKI* acute kidney injury

pregnancy or after and are not pregnancy-specific. However, they often exhibit overlapping features resulting in diagnostic and therapeutic challenges (Table 31.3). Uncommonly, a renal biopsy may need to be considered to determine the exact diagnosis and to facilitate appropriate treatment. The potential diagnostic benefit of a renal biopsy needs to be carefully weighed against the increased risk of perinephric bleeding and renal trauma, especially during critical illness and pregnancy (see diagnostic work-up for additional details). A multidisciplinary team including hematologists, nephrologists, obstetricians, radiologists, and critical care specialists should be involved when deciding whether a renal biopsy should be performed during pregnancy.

Primary Renal Diseases, Including Autoimmune Disease and Vasculitis

Differentiating between acute glomerulonephritis and pre-eclampsia can be challenging in the late second and third trimester, especially since the clinical presentation may be similar and auto-antibodies and complement levels may not be reliable during pregnancy [26, 27]. In women who are not critically ill, a renal biopsy may be necessary to differentiate between an acute glomerulonephritis and pre-eclampsia. As mentioned above, in light of the risk of perinephric bleeding and potential renal injury, the decision to proceed with a renal biopsy should be made jointly the patient as well as by all clinical teams involved. In non-pregnant critically ill patients, it has been suggested that a transjugular renal biopsy may be safer than a percutaneous or open technique, but there is little information on this procedure in pregnant women [28].

Drug Nephrotoxicity

Another common co-incident cause of AKI during pregnancy is drug nephrotoxicity. There are several mechanisms through which drugs may exert their nephrotoxic effects, including direct tubular injury (i.e., aminoglycosides), effects on glomerular hemodynamics (i.e., ACE inhibitors), alteration of microcirculation [i.e., nonsteroidal anti-inflammatory drugs (NSAIDs)], tubular obstruction (i.e., indinavir, acyclovir, or metho-

Table 31.4 Diagnostic work-up of acute kidney injury in pregnant critically ill patients

Diagnostic tests	Potential causes of acute kidney injury
Full blood count	Bleeding Hemolytic-uremic syndrome Thrombotic thrombocytopenic purpura HELLP syndrome Sepsis
Clotting profile	Disseminated intravascular coagulopathy Antiphospholipid syndrome Sepsis
Liver enzymes	Sepsis Acute fatty liver of pregnancy HELLP syndrome
Ammonia	Acute fatty liver of pregnancy
Serum glucose	Acute fatty liver of pregnancy
Serum uric acid	Pre-eclampsia/eclampsia
Lactate dehydrogenase (LDH) Haptoglobin Reticulocytes Fragmentocytes	HELLP syndrome Pre-eclampsia/eclampsia Thrombotic thrombocytopenic purpura hemolytic-uremic syndrome
Auto-antibody screen, including ANA titer Anti-ds-DNA titer Complement C3 and C4	Primary glomerulonephritis Systemic lupus erythematosus Vasculitis
C-reactive protein (CRP)	Sepsis
Antiphospholipid antibodies, including Anticardiolipin antibodies Lupus anticoagulant	Antiphospholipid syndrome
ADAMTS-13 activity	Thrombotic thrombocytopenic purpura
Sepsis screen, including Blood cultures Mid-stream urine culture Sputum culture Wound swabs	Sepsis
Urinalysis	Sepsis Primary glomerular disease Pre-eclampsia/eclampsia HELLP syndrome
Renal ultrasound	Obstruction Pre-existing chronic kidney disease
Renal biopsy	Primary glomerular disease Vasculitis Interstitial nephritis Rejection of renal transplant

Abbreviations: *ADAMTS-13* a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, *HELLP* hemolysis, elevated liver enzymes, low platelets, *ANA* anti-nuclear antibody, *Anti-ds-DNA* anti-double-stranded DNA

trexate), and in the form of idiosyncratic reactions (i.e., antibiotic-induced interstitial nephritis). In general, potentially nephrotoxic drugs should always be avoided. However, the benefits of starting or continuing a nephrotoxic medication may outweigh the risks; therefore, a personalized approach is always necessary, independent of pregnancy.

31.2.4 Diagnostic Work-Up

To determine the etiology of AKI, baseline tests are recommended for all patients. In order to confirm or rule out specific causes of AKI, a proportion of patients may need additional tests as directed by clinical presentation and potential differential diagnoses [27] (Table 31.4).

Of note, complement levels and serological markers of SLE activity (i.e., anti-ds-DNA) can be affected by pregnancy and may be difficult to interpret [28].

Occasionally, a renal biopsy may need to be considered, especially if AKI occurs before 24 weeks' gestation and there is concern about a potentially treatable primary renal disease. General complications include bleeding ranging from asymptomatic macroscopic hematuria to events requiring interventional radiological embolization or surgical nephrectomy. A systematic review concluded that a renal biopsy in gestation up to 22 weeks was not associated with any additional risks; however, biopsy in later pregnancy was associated with bleeding complications requiring transfusion or interventional procedure and worse obstetric outcome including preterm labor [29].

The indication for an ultrasound-guided or transjugular renal biopsy should always be discussed and agreed on by the nephrology and obstetric team.

31.2.5 Treatment

31.2.5.1 General Measures

The key therapeutic strategies of AKI are similar in pregnant/postpartum women and in nonpregnant patients. These consist of optimization of hemodynamic status, correction of hypovolemia, and prevention of further nephrotoxic insults, combined with management of the underlying disease leading to AKI. There are no specific drug therapies for AKI. Renal replacement therapy (RRT) should be considered in those with progressive AKI and complications of AKI.

In general, maternal health takes priority; however, the condition of the fetus should be optimized whenever possible. Fetal well-being and neonatal outcomes are closely linked to maternal status. Adequate blood flow to the uterus and placenta is essential to prevent fetal compromise; as such, intravascular volume depletion and hypotension should be corrected as a matter of urgency, aiming for a mean arterial blood pressure >65 mmHg. Fluid resuscitation should be conducted according to current recommendations (see Chap. 7). There are no specific recommendations for pregnant women with AKI, and there is no specific measure to assess fluid status of the kidneys [30].

31.2.5.2 Treatment of Specific Causes of AKI

Control of Hypertensive Disorders of Pregnancy

The only effective cure for pre-eclampsia, HELLP, and acute fatty liver of pregnancy is delivery of the fetus and placenta (Chaps. 16 and 33). However, selected cases of pre-eclampsia without evidence of end-organ involvement (neurologic symptoms, hepatic or renal dysfunction, or low platelets) may be managed medically, with blood pressure control and intravenous magnesium. In the USA, the National High Blood Pressure Education Program (NHBPEP) recommends to aim for systolic blood pressure ≤140 mmHg and diastolic blood pressure of ≤90 mmHg during pregnancy [31].

For emergency treatment of hypertension in pre-eclampsia, intravenous hydralazine, labetalol, and oral nifedipine can be used. Methyldopa and labetalol are also appropriate first-line agents, but angiotensin-converting enzyme inhibitors should not be used.

Magnesium levels should be monitored in case of renal impairment to avoid toxicity as levels may rise due to reduced renal excretion.

Relief of Obstruction

Delivery may be considered based on gestational age and is often the definitive treatment. Retrograde ureteral stent placement using cystoscopy and percutaneous nephrostomy are alternatives to relieve or bypass the ureteral obstruction [32]. Ureteroscopy has also been applied in this setting [33].

Management of Amniotic Fluid Embolism

Rapid resuscitation, cardiopulmonary support, and correction of coagulopathy are the mainstays of treatment [34].

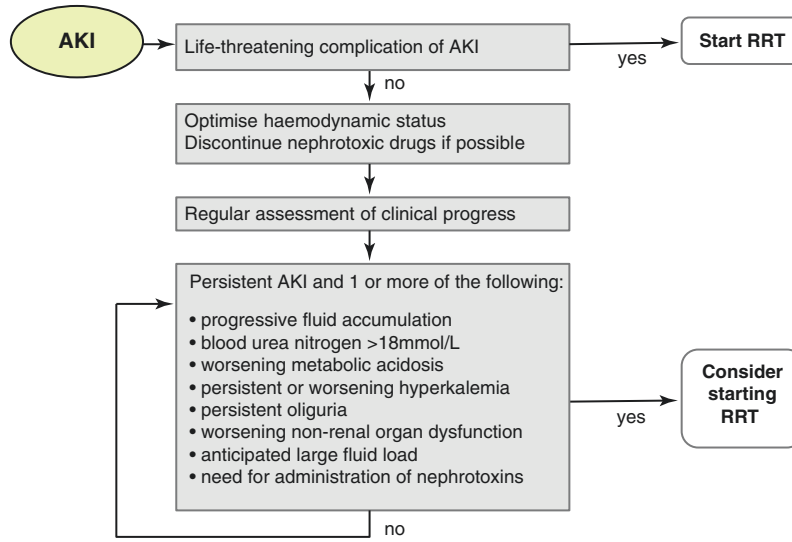


Fig. 31.2 Algorithm to guide timing of renal replacement therapy (RRT) in pregnancy-related acute kidney injury (AKI)

31.2.5.3 Renal Replacement Therapy

In patients with severe AKI at risk of life-threatening complications, RRT may be necessary to remove excess fluid and waste products.

Timing of RRT

In nonpregnant critically ill patients with AKI, there is no uniform agreement or consensus on the optimal timing of RRT initiation, the practice of discontinuing RRT, or the optimal modality [12]. This also applies to pregnant women with AKI. The only exception is that acute peritoneal dialysis is usually not an option. The decision to start RRT will be determined by the maternal clinical presentation; there are no fetal indications for RRT. Absolute indications for RRT include maternal hyperkalemia with ECG changes, refractory metabolic acidosis with serum pH ≤7.20, symptoms or complications of uremia (e.g., pericarditis or encephalopathy), and refractory fluid overload including pulmonary edema. These indications represent a medical emergency, and the pregnant woman should be urgently transferred to a setting where RRT can be provided.

In patients with AKI not complicated by emergent indications, the optimal time to initiate or withhold RRT is unknown [35, 36]. In nonpregnant patients, there is general consensus that the decision to commence RRT should not be based solely on the degree of renal function or stage of AKI but be individualized based on the clinical context [36]. The severity of metabolic derangements and fluid accumulation, their trajectories, and the impact on other organs are key factors that need to be considered when deciding whether to start or withhold RRT (Fig. 31.2).

In chronic dialysis patients, it is recommended to keep blood urea nitrogen (BUN) concentration <16–18 mmol/L during pregnancy and to minimize fluid shifts in order to promote fetal well-being [37]. Although not specifically tested, it makes sense to apply these cut-offs to the critical care setting and to initiate acute RRT in critically ill pregnant patients before BUN >18 mmol/L.

Modality of RRT

In critically ill pregnant women with AKI, the choice is between intermittent RRT, continuous RRT (CRRT), and hybrid techniques. Acute peritoneal dialysis is not an option. Despite differences in characteristics, all extracorporeal modalities are capable of achieving adequate metabolic control and fluid removal (Table 31.5).

In critically ill nonpregnant adults with AKI, repeated meta-analyses of existing published evidence have not demonstrated a definite advantage in short-term patient survival for any modality [35–37]. The final choice of modality depends on the degree of hemodynamic stability, severity of

Table 31.5 Characteristics of different renal replacement therapy modalities used for acute kidney injury during pregnancy

Parameter	Intermittent RRT	Hybrid RRT SLED/ EDD/PIRRT	Continuous RRT
Duration (h)	4–6	6–16	24
Frequency	Daily/alternate days	Daily/alternate days	Daily
Mode of solute transport	Diffusion	Diffusion or convection or both	Diffusion or convection or both
Blood flow (mL/min)	200–350	100–300	100–250
Dialysate flow (mL/min)	300–800	200–300	0–50
Urea clearance (mL/min)	150–180	90–140	20–45
Need for anticoagulation	Usually but not absolutely necessary	Usually but not absolutely necessary	Yes
Fluctuations of osmotically active metabolites	++	+	Less; fluctuations may occur in case of treatment interruptions
Fluid shifts	++	+	Less; shifts may occur in case of treatment interruptions
Effect on ICP in patients with acute brain injury	Increase	Potential increase	Usually no change
Effect on serum concentrations of renally cleared drugs	Major fluctuations	Some fluctuations	Less fluctuations
Loss of nutrients into dialysate/filtrate	Yes	Yes	Yes

Abbreviations: *ICP* intracerebral pressure, *RRT* renal replacement therapy, *SLED* slow extended dialysis, *EDD* extended daily dialysis, *PIRRT* prolonged intermittent renal replacement therapy

fluid overload, and ability to tolerate shifts in fluid status and metabolic fluctuations.

In pregnancy, hemodynamic instability during RRT has been associated with changes in amniotic fluid volume, fetal tachycardia, and transient uterine contractions [38]. Therefore, if the pregnant woman is hemodynamically unstable (for instance, due to sepsis), CRRT is generally the preferred modality as it allows gentler fluid removal and prevents metabolic fluctuations. Hybrid therapies such as "sustained low efficiency dialysis" (SLED), "extended daily dialysis" (EDD), and "prolonged intermittent renal replacement therapy" (PIRRT) combine the hemodynamic stability of CRRT with the advantages of intermittent techniques (mobilization, reduced need for anticoagulation) but have not been specifically studied in pregnant women.

Both hemodialysis (using diffusion) and hemofiltration (using convection) can be provided intermittently or continuously. They are equally efficient in the removal of small molecular weight solutes, including urea and creatinine. There are no data suggesting that either hemodialysis or hemofiltration are preferable in pregnancy-related AKI.

Dose of RRT

There is no data to date to inform the recommended dose of RRT for the mother during pregnancy. However, the delivered dose should be sufficient to ensure that BUN levels are maintained <16 mmol/L and metabolic fluctuations are minimized at all times. Regarding the fetus, a trend towards better pregnancy outcomes with more frequent and longer dialysis sessions was observed [39].

Anticoagulation

Regardless of the chosen method of RRT, clotting of the blood flowing through the circuit filter must be prevented. Current options include systemic anticoagulation with heparin or epoprostenol, the addition of heparin into the circuit, or regional anticoagulation with citrate. Rising pressures within the circuit should be regarded as signs of impending filter clotting.

There are no specific recommendations regarding the preferred method to maintain

patency of the circuit in pregnant patients undergoing RRT. However, in those with an increased bleeding risk, regional anticoagulation with citrate, or complete avoidance of any anticoagulants should be considered. Citrate acts by chelating calcium, thereby inhibiting the clotting cascade at several levels. It is infused into the circuit prior to the filter to achieve an ionized Ca concentration <0.35 mmol/L in blood passing through the filter. Calcium is replaced post-filter to correct the calcium deficit in the blood returning to the patient. As a result, the extracorporeal circuit is fully anticoagulated, while the patient is not [40].

31.2.5.4 Perioperative Management of AKI

During preoperative surgical and anesthetic assessment of pregnant patients with AKI, special attention to electrolytic, metabolic, and hemodynamic status is required. Any life-threatening complication of AKI should be corrected prior to the procedure, including medical management of hyperkalemia and fluid overload and RRT, if necessary. However, if surgery cannot be delayed, medical management and RRT should continue during the intraoperative provided.

Intraoperatively, there are no particular strategies for pregnant women with AKI apart from a general recommendation to avoid fluid overload, not to administer any anesthetic agents associated with hyperkalemia and to maintain mean arterial blood pressure ≥65 mmHg. Postoperatively, RRT should be restarted as soon as possible, with the decision for anticoagulation to be determined by the relative risk of post-procedural bleeding.

31.2.6 Long-Term Prognosis

Once the underlying cause is identified and treated, most cases of pregnancy-related AKI recover. Whether AKI during pregnancy increases the risk of long-term CKD remains inconclusive. A case-control study from Gul et al. showed no significant difference in kidney outcome between pregnant women with and without AKI [40]. In a retrospective study conducted in women with AKI treated with RRT during pregnancy over a 15-year period in Canada, Hildebrand and colleagues observed that 3.9% of patients remained dialysis-dependent 4 months after delivery [9]. In a different study, 2.4% of women with AKI during pregnancy progressed to end-stage renal disease requiring long-term dialysis [3]. Due to small sample sizes with limited follow-up time and lack of a control group, the impact of pregnancy-associated AKI on long-term renal function is unknown. However, women with incomplete renal recovery should be considered for follow-up by a nephrology team.

31.2.7 End-Stage Renal Disease

The reported rate of pregnancies in chronic dialysis patients ranges between 0.3 and 1.5% per year but is increasing [41]. Women with ESRD requiring dialysis are at increased risk of severe hypertension (18–70%) and pre-eclampsia (5–67%), in addition to increased risks of obstetric and fetal complications of pregnancy [41, 42].

When admitted to the ICU for co-incident medical problems, these patients will inevitably require ongoing RRT [42]. The modality and timing of RRT should be determined by the degree of hemodynamic and metabolic derangement, as CRRT may be preferred.

31.2.8 Renal Transplant Recipients

The recipients of renal transplants will require multidisciplinary input from nephrologists and obstetricians throughout pregnancy, especially during a stay in the critical care unit. The principles of management of the kidney graft function are equivalent to that of a woman with native kidney function, including avoidance of nephrotoxic drugs, targeted blood pressure control, and adequate fluid resuscitation if required.

Pregnant transplant patients develop AKI for all the usual reasons, but the differential diagnosis is wider and includes specific problems like obstruction of a single functioning kidney, vessel

thrombosis, rejection, calcineurin toxicity, and calcineurin-induced thrombotic microangiopathy. Septic AKI is common, but again, the differential diagnosis of sepsis is wider.

31.2.8.1 Immune Suppression and Rejection

In critical illness, immune suppression and risk of graft rejection must be balanced against maternal risk of sepsis. There are many different combinations of immunosuppressants following a transplant, depending on the risk of rejection of the individual patient, time course following transplantation, previous adverse effects of immunosuppressants, and local policy. The risk of rejection should always be balanced with the risk of life-threatening complications. In most cases of severe sepsis, the benefits of reducing/discontinuing immunosuppressive drugs outweigh any benefits of continuing. Conversely, long-term steroids should not be stopped but increased to compensate for potential adrenal insufficiency.

When deciding which immunosuppressant to reduce or stop, a discussion with the nephrology team is advisable. Similarly, the decision when to re-introduce immunosuppressive drugs depends on the progress of the patient, existing acute and chronic comorbidities, and the patient's overall ability to tolerate immunosuppression. The decision is usually jointly made by the treating acute medical team and transplant team.

References

1. Machado S, Figueiredo N, Borges A, et al. Acute kidney injury in pregnancy: a clinical challenge. J Nephrol. 2012;25:19–30.
2. American College of Obstetricians and Gynecologists. Task force on hypertension in pregnancy; 2013. https://www.acog.org/~/media/Task%20Force%20and%20Work%20Group%20Reports/public/HypertensioninPregnancy.pdf. Last Accessed 25 Feb 2018.
3. Liu Y, Ma X, Zheng J, Liu X, Yan T. Pregnancy outcomes in patients with acute kidney injury during pregnancy: a systematic review and meta-analysis. BMC Pregnancy Childbirth. 2017;17(1):235.
4. Mehrabadi A, Dahhou M, Joseph KS, Kramer MS. Investigation of a rise in obstetric acute renal failure in the United States, 1999–2011. Obstet Gynecol. 2016;127(5):899–906.
5. Gopalakrishnan N, Dhanapriya J, Muthukumar P, et al. Acute kidney injury in pregnancy–a single center experience. Ren Fail. 2015;37:1476–80.
6. Kamal EM, Behery MM, Sayed GA, Abdulatif HK. RIFLE classification and mortality in obstetric patients admitted to the intensive care unit with acute kidney injury: a 3-year prospective study. Reprod Sci. 2014;21:1281–7.
7. Gurrieri C, Garovic VD, Gullo A, et al. Kidney injury during pregnancy: associated comorbid conditions and outcomes. Arch Gynecol Obstet. 2012;286:567–73.
8. Prakash J, Pant P, Prakash S, et al. Changing picture of acute kidney injury in pregnancy: study of 259 cases over a period of 33 years. Indian J Nephrol. 2016;26(4):262–7.
9. Hildebrand AM, Liu K, Shariff SZ, et al. Characteristics and outcomes of AKI treated with dialysis during pregnancy and the postpartum period. J Am Soc Nephrol. 2015;26(12):3085–91.
10. Patel M, Sachan R, Gangwar R, Sachan P, Natu S. Correlation of serum neutrophil gelatinase-associated lipocalin with acute kidney injury in hypertensive disorders of pregnancy. Int J Nephrol Renovasc Dis. 2013;6:181–6.
11. Drakeley AJ, Le Roux PA, Anthony J, Penny J. Acute renal failure complicating severe preeclampsia requiring admission to an obstetric intensive care unit. Am J Obstet Gynecol. 2002;186(2):253–6.
12. Mehta RL, Burdmann EA, Cerda J, et al. Recognition and management of acute kidney injury in the International Society of Nephrology 0by25 Global Snapshot: a multinational cross-sectional study. Lancet. 2016;387(10032):2017–25.
13. Pourrat O, Coudroy R, Pierre F. Differentiation between severe HELLP syndrome and thrombotic microangiopathy, thrombotic thrombocytopenic purpura and other imitators. Eur J Obstet Gynecol Reprod Biol. 2015;189:68–72.
14. Fakhouri F, Vercel C, Fremeaux-Bacchi V. Obstetric nephrology: AKI and thrombotic microangiopathies in pregnancy. Clin J Am Soc Nephrol. 2012;7:2100–6.
15. Prakash J, Ganiger VC. Acute kidney injury in pregnancy—specific disorders. Indian J Nephrol. 2017;27(4):258–70.
16. Ostermann M, Liu K. Pathophysiology of AKI. Best Pract Res Clin Anaesthesiol. 2017;31(3):305–14.
17. Lombardi R, Rosa-Diez G, Ferreiro A, et al. Acute kidney injury in Latin America: a view on renal replacement therapy resources. Nephrol Dial Transplant. 2014;29(7):1369–76.
18. Prakash J, Ganiger VC, Prakash S, et al. Acute kidney injury in pregnancy with special reference to pregnancy-specific disorders: a hospital based study (2014–2016). J Nephrol. 2018;31(1):79–85.
19. Rasmussen PE, Nielsen FR. Hydronephrosis during pregnancy: a literature survey. Eur J Obstet Gynecol Reprod Biol. 1988;27(3):249–59.

20. Rajasekar D, Hall M. Urinary tract injuries during obstetric intervention. Br J Obstet Gynaecol. 1997;104(6):731–4.
21. Gammill HS, Jeyabalan A. Acute renal failure in pregnancy. Crit Care Med. 2005;33(10 Suppl):S372–84.
22. Clark SL, Hankins GD, Dudley DA, et al. Amniotic fluid embolism: analysis of national registry. Am J Obstet Gynecol. 1995;172:1158–69.
23. Clark SL, Pavlova Z, Greenspoon J, Horenstein J, Phelan JP. Squamous cells in the maternal pulmonary circulation. Am J Obstet Gynecol. 1986;154(1):104–6.
24. Saad AF, Roman J, Wyble A, Pacheco LD. Pregnancy-associated atypical hemolytic-uremic syndrome. AJP Rep. 2016;6(1):e125–8.
25. Delmas Y, Helou S, Chabanier P, et al. Incidence of obstetrical thrombotic thrombocytopenic purpura in a retrospective study within thrombocytopenic pregnant women. A difficult diagnosis and a treatable disease. BMC Pregnancy Childbirth. 2015;15:137.
26. Kiuttu J, Hartikainen-Sorri AL, Mäkitalo R. Occurrence of antinuclear antibodies in an unselected pregnancy population. Gynecol Obstet Investig. 1992;33(1):21–5.
27. Darmon M, Ostermann M, Cerda J, et al. Diagnostic work-up and specific causes of acute kidney injury. Intensive Care Med. 2017;43(6):829–40.
28. Clowse ME, Magder LS, Petri M. The clinical utility of measuring complement and anti-dsDNA antibodies during pregnancy in patients with systemic lupus erythematosus. J Rheumatol. 2011;38(6):1012–6.
29. Piccoli GB, Daidola G, Attini R, et al. Kidney biopsy in pregnancy: evidence for counselling? A systematic narrative review. BJOG. 2013;120(4):412–27.
30. Joannidis M, Druml W, Forni LG, et al. Prevention of acute kidney injury and protection of renal function in the intensive care unit: update 2017: expert opinion of the working group on prevention, AKI section, European Society of Intensive Care Medicine. Intensive Care Med. 2017;43(6):730–49.
31. Brown CM, Garovic VD. Drug treatment of hypertension in pregnancy. Drugs. 2014;74(3):283–98.
32. Semins MJ, Trock BJ, Matlaga BR. The safety of ureteroscopy during pregnancy: a systematic review and meta-analysis. J Urol. 2009;181(1):139–43.
33. Semins MJ, Matlaga BR. Ureteroscopy during pregnancy. Indian J Urol. 2009;25(3):291–5.
34. Society for Maternal-Fetal Medicine (SMFM), Pacheco LD, Saade G, Hankins GD, Clark SL. Amniotic fluid embolism: diagnosis and management. Am J Obstet Gynecol. 2016;215(2):B16–24.
35. Bagshaw SM, Darmon M, Ostermann M, et al. Current state of the art for renal replacement therapy in critically ill patients with acute kidney injury. Intensive Care Med. 2017;43(6):841–54.
36. Ostermann M, Wald R, Bagshaw SM. Timing of renal replacement therapy in acute kidney injury. Contrib Nephrol. 2016;187:106–20.
37. Nash DM, Prech S, Wald R, O'Reilly D. Systematic review and meta-analysis of renal replacement therapy modalities for acute kidney injury in the intensive care unit. J Crit Care. 2017;41:138–44.
38. Manisco G, Poti M, Maggiulli G, et al. Pregnancy in end-stage renal disease patients on dialysis: how to achieve a successful delivery. Clin Kidney J. 2015;8(3):293–9.
39. Piccoli GB, Minelli F, Versino E, et al. Pregnancy in dialysis patients in the new millennium: a systematic review and meta-regression analysis correlating dialysis schedules and pregnancy outcomes. Nephrol Dial Transplant. 2016;31(11):1915–34.
40. Morabito S, Pistolesi V, Tritapepe L, et al. Regional citrate anticoagulation for RRTs in critically ill patients with AKI. Clin J Am Soc Nephrol. 2014;9(12):2173–88.
41. Gul A, Aslan H, Cebeci A, et al. Maternal and fetal outcomes in HELLP syndrome complicated with acute renal failure. Ren Fail. 2004;35:557–62.
42. Hladunewich M, Schatell D. Intensive dialysis and pregnancy. Hemodial Int. 2016;20(3):339–48.

Part IX

The Endocrine and Metabolic Systems

Nutrition in Critical Illness During Pregnancy

32

Itai Bendavid and Pierre Singer

Bullet Points

- The area of nutrition therapy during critical illness in pregnant or postpartum patients is highly controversial, not the least owing to paucity of evidence.
- Indirect calorimetry is the gold standard for assessing the energetic requirements of these complicated patients and should be used when available.
- In the absence of indirect calorimetry, predictive formulas may be used but are of low accuracy.
- As a rule of thumb, 25 kcal/kg/day may be administered to most patients, with adaptations in obese or undernourished cases.
- Lipids must be prescribed as they are essential for the mother as well as for normal fetal development. However, the choice between different lipids remains highly controversial.
- Immune-modulating diets have not shown higher efficacy in most states of critical illness. Proteins should be aimed to a minimum of 1.3 g/kg/day.
- Routine doses of trace elements and vitamins must be ensured.
- The oral route is preferred, followed by the use of a gastric tube.
- In the case of gastric intolerance, prokinetics may be tried. If these fail, either an enteral tube or supplemental parenteral nutrition may be used.
- If nutrition therapy is not achieved using these routes, parenteral nutrition may be prescribed.

32.1 Introduction

The metabolic response to stress is a complex process. It involves hormones, cytokines, prostaglandins, neural mediators, and various cellular tissues, including immune cells, adipose tissue, and the gastrointestinal tract. The severity of the response may range from mild to very severe, depending on the type and degree of insult as well as on host-dependent factors (e.g., the general medical condition of the patient). This response is further complicated when the critically ill patient is pregnant, as the response to stress may be affected by the physiological changes of pregnancy. Nutritional priorities are expected to be modified. However, since studies

I. Bendavid · P. Singer (✉)
Department of General Intensive Care and Institute for Nutrition Research, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel

Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
e-mail: Itaibd@clalit.org.il; psinger@clalit.org.il

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_32

are rare in this population, support should be carefully guided using select monitoring tools. This chapter will discuss the metabolic changes which occur during pregnancy and during critical illness, followed by recommendations on nutritional assessment, support, and monitoring in the pregnant critically ill patient.

32.2 Metabolic Changes During Pregnancy

Metabolism changes substantially during and following pregnancy. The maternal metabolism is generally considered an anabolic process [1]. The most prominent change is in the body water and blood composition. As mentioned elsewhere in this book, the plasma volume increases by 45%, while the cellular component increases by only 33% [2], resulting in hemodilution with lower hematocrit levels (Chaps. 5 and 7). In states of pre-eclampsia there is significant hemoconcentration, and the hematocrit levels rises [3]. Additional metabolic changes, mainly in carbohydrate and lipid metabolism, occur during normal and complicated pregnancy change. These are addressed in detail in this chapter.

32.3 Nutritional Assessment During Normal Pregnancy

Nutritional assessment during pregnancy relies on anthropometric tables [4]. There is a strong relationship between anthropometric measurements and nutritional intake of energy and substrates [5]. These measurements may later be related to physiologic birth outcomes [6–8].

Laboratory analysis for healthy pregnant woman includes screening for diabetes and anemia. The former is intended to diagnose gestational diabetes and non-gestational diabetes which manifests during pregnancy as both carry implications in terms of morbidity for the mother and the fetus. The latter, anemia, is not a disease state but has been associated with poor pregnancy outcomes [9] and is a marker of poor nutrition and possible maternal neglect [10]. Nutrient deficiencies are not generally sought after unless a specific indication exists [11]. However, some studies suggest that deficiencies of nutrients such as iron, B12, zinc, and folic acid are very common during pregnancy [12], while others suggest the levels of most of these nutrients are usually normal [13]. This variability may stem from differences in laboratory methods and different woman populations. Additional controversy exists regarding the range of normal levels, and much of this controversy is due to the aforementioned changes in blood plasma and cell volume [11].

32.4 Nutritional Assessment in the Intensive Care Unit

Nutritional risk increases with age, severity of illness, and length of intensive care unit (ICU) hospitalization [14]. It is widely accepted that nutrition should be assessed throughout ICU admission. These may be performed using anthropometric measurements such as the body mass index (BMI), triceps fold thickness, mid-arm circumference, and calf circumference; laboratory measurements such as the serum albumin levels or cholesterol; or multivariate tools such as the subjective global assessment [15]. However, no consensus exists as to which tool or tools should be used across different patient populations.

Critical illness takes its toll on different organ systems. One of the changes that occur in critically ill patients is loss of muscle/lean body mass. This translates into poorer muscle function and worse overall prognosis, including mortality [16]. The etiology of these changes is multifactorial. Causes include both disease-related parameters such as inflammatory mediators and treatment-related factors such as inadequate nutrition, immobilization, and sedation [17]. The severity of nutritional risk must therefore be actively sought and addressed in all critically ill patients. However, the assessment of nutritional risk is generally difficult in critically ill patients for a variety of reasons [18]: The nutritional history can only be obtained in a minority of patients [19], actual height and weight are hard to mea-

Table 32.1 Commonly used predictive equations for energetic requirements

	The calculation
ACCP	
BMI < 25	25 × ABW
BMI ≥ 25	25 × IBW
Harris-Benedict	
Males	66.47 + (13.75 × ABW) + (5 × Ht) − (6.76 × age)
Females	655.1 + 66.47 + (9.56 × ABW) + (1.85 × Ht) − (4.68 × age)
Ireton-Jones	
Males	606 + (9 × ABW) − (12 × age) + 400 (if ventilated) + 1400
Females	ABW − (12 × age) + 400 (if ventilated) + 1444
Faisy-Fagon	(8 × ABW) + (14 × Ht) + (32 × Ve) + (94 × Temp) − 4834
Mifflin	
Males	(10 × ABW) + (6.25 × Ht) − (5 × age) + 5
Females	(10 × ABW) + (6.25 × Ht) − (5 × age) − 161

ACCP American college of chest physicians, *ABW* actual body weight measured in kilograms on admission, *IBW* ideal body weight in kilograms = 50 + 0.9 × height in centimeters—88 (males); 0.9 × height in centimeters—92 (females), *Ht* height in centimeters, *Ve* minute ventilation in liters per minute, *Temp* temperature in Celsius degrees

sure, and assessment of weight loss is confounded by water retention and edema [20]. Traditional nutrition risk assessment tools categorize more than 80% of ICU patients as malnourished or at risk [18]. Therefore controversy has arisen over the appropriate tool for nutrition risk assessment in the ICU setting [21].

In order to determine the amount of calories administered to a critically ill patient, the clinician may measure energy expenditure, assess it using predictive equations, or opt for a "rule of thumb" estimation of caloric needs. Indirect calorimetry is considered the gold standard for assessing the energy expenditure [22]. By measuring inspired and expired oxygen and carbon dioxide levels along with the minute ventilation, the amount of carbohydrates and fat used for energy production can be calculated. Protein metabolism is omitted as its effect is negligible. Indirect calorimetry is the most accurate way to measure energy expenditure in patients [23], and its use is recommended in critically ill patients [24]. However, indirect calorimetry is expensive and requires a dedicated team with experience in the use of this measurement technique. Furthermore, it may not be reliable in certain physiological conditions such as severe hypoxemia [25].

Various formulas are available for estimating energy expenditure (Table 32.1). All have been validated and correlated significantly with indirect calorimetry. These equations, such as the Harris-Benedict, Faisy-Fagon, or Ireton-Jones, are widely used. However, their use is limited by gross inaccuracy and lack of precision [26]. Moreover, because of their complexity, many clinicians prefer to use "rule of thumb" guidelines. These include simplistic weight-based calculations [24], generally 25–30 kcal/kg/day, with some alterations according to weight groups and certain critical illness states.

32.5 Nutritional Concerns During Critical Illness and Pregnancy

During pregnancy the nutritional requirements are higher. Energy is deposited in both fetal and maternal tissues with changes in both the basal and the exertional metabolic rates [27]. Measurements of resting energy expenditure (REE) using respiration calorimetry over 24 h periods in mostly sedentary pregnant women revealed a mean increase in the daily energy requirement of 11.3 ± 6.3 kcal for each gestational week. Of note, energy requirements differ widely among women from different populations with different lifestyles and diets. Activity energy

expenditure (AEE) tends to fall during pregnancy. However, as a pregnant woman becomes critically ill, a rise in resting energy expenditure is expected, as noted in states of sepsis [28, 29]. The body temperature rises and stress mediators accelerate an already hyper-dynamic state. These effects may be countered, at least partially, by pharmacologically induced sedation and immobility [30]. Addition of neuromuscular blockers may reduce energy expenditure further [31, 32].

Excessive gestational weight gain is known to have undesirable effects [33]. Excess weight gain generally results in fat mass and not lean mass accumulation. In turn, these lead to higher rates of maternal (glucose intolerance, hypertension, venous thromboembolism) and fetal (macrosomia, fetal malformations, and later obesity) pathologies [33]. Some of these maternal complications (e.g., hypertensive disorders) may expose the pregnant woman to life-threatening conditions requiring ICU admission. However, this increased risk should be balanced with what is known as the obesity paradox [34, 35]. Overweight (BMI = 25–30 kg/m^2) and obese (BMI = 30–40 kg/m^2) ICU patients generally fare better in terms of mortality risk than do normal weight and underweight (BMI < 18.5 kg/m^2) ICU patients.

Humans are genetically programmed to starve and remain inert during critical illness (from different causes), while the body tries to heal itself. This response evolved before modern medical and intensive care were introduced. The stress induced by critical illness changes metabolism and immunity (Fig. 32.1). Together with the treatments provided in the course of intensive care, these systemic changes may become deleterious. As mentioned earlier, the body enters a catabolic state due to various mechanisms such as the effects of prostaglandins [36] and the ubiquitin-proteasome pathway [37]. Patients in the ICU have negative protein and calorie balances (i.e., the amount given minus the expenditure) due to reduced intake and increased catabolism [38, 39]. Such negative balances have been associated with higher mortality as well as many serious complications such as infections [38], pressure sores, renal failure, and impaired wound healing [40]. Long-term effects on mortality and overall quality of life have been observed as well [41]. However, even with provision of nutrition according to energy expenditure measurements, muscle wasting is practically omnipresent [42]. Overfeeding (i.e., providing a caloric intake above the estimated caloric needs) does not prevent muscle loss but rather increases fat tissue mass [43] and causes muscle fatty infiltration [44] which translates into worse outcomes.

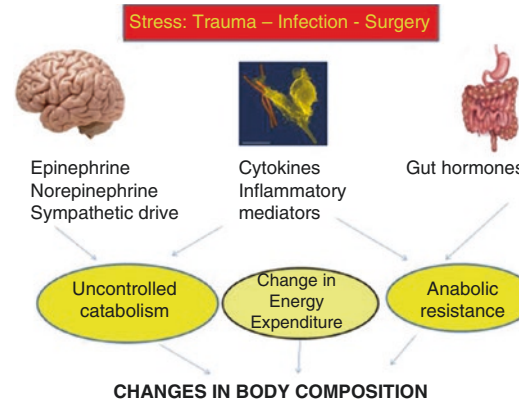


Fig. 32.1 The major metabolic alterations during stress and critical illness

Large controversies exist regarding basic topics in nutrition during critical illness. Existing conundrums include the correct timing to initiate nutrition, the route to use, the optimal amount of calories, and the optimal amount of nutrients and macronutrients. The clinician is not only faced with guidelines that do not address the needs of the specific patient, but is also often challenged by obstacles to provision of nutrition. These include, among others, lack of enteral access, airway manipulations, nausea and vomiting, gastrointestinal bleeding, high gastric residual volumes, and recurring patient transfers and surgery [44]. Failure to provide adequate nutrition is more common in patients with greater disease severity [45].

32.6 Carbohydrate and Insulin Metabolism

Glucose, along with lactate, is the primary nutrient utilized by the fetus and placenta [46]. The placenta consumes much more energy than its weight would indicate, and studies indicate glucose diffusion into the placenta is facilitated [47]. Glucose is also a vital substrate for lactose synthesis in the mammary glands. Glucose oxidative requirements therefore increase in the second trimester [48], and this state continues well into the period of lactation.

The increased glucose requirements of the uterine and mammary glands necessitate adjustment of the metabolism of the liver, adipose tissue, and skeletal muscle, among other organs. During pregnancy, insulin levels rise higher and more rapidly, while glucose levels do not correlate with this rise, thus indicating peripheral resistance to the actions of insulin [46]. This rise in insulin secretion is even more pronounced in obese women suffering from gestational diabetes. Hepatic glucose production is less suppressed while insulin levels are high [49]. These metabolic responses are the hallmarks of type 2 diabetes mellitus, and unsurprisingly these women are at increased risk for development of type 2 diabetes later in life [50].

Glucose is the main source for energy (ATP production) during critical illness. Physiologic stress leads to a metabolic response involving multiple systems [51]. The sympathetic nervous system is the first to respond (within seconds), followed by the hypothalamic-pituitary axis, and later inflammatory and immune changes occur. The effects of hormones secreted from adipose tissue (leptin, resistin, adiponectin) and the gastrointestinal tract (ghrelin) are increasingly being investigated as they too contribute to the metabolic reaction to stress.

The mechanism of stress-induced hyperglycemia is different from that of gestational or type 2 diabetes mellitus even though insulin resistance is a key feature in all of these states. During critical illness a complex interplay of catecholamines, cytokines, and counter-regulatory hormones results in excessive hepatic glucose production and insulin resistance. Contrary to pregnancy, which is an anabolic process, critical illness and stress lead to an overall catabolic response. In this situation the response to anabolic signals such as insulin is diminished. This insulin resistance plays a role in ensuring that nutritional substrates are delivered to vital organs at the expense of more insulin-dependent tissues (e.g., adipose, muscle). Stress-induced hyperglycemia is associated with increased mortality independent of illness severity [52]. This association is particularly pronounced with certain admission diagnoses such as acute myocardial infarction and pulmonary embolism.

Hypoglycemia, even mild (defined as blood glucose levels lower than 70 mg/dL), is associated with even higher mortality rates [53, 54]. Individual glucose variability (the standard deviation of the mean glucose level) has also been strongly correlated with mortality in critically ill patients [55]. Whether these abnormal glycemic patterns are simply markers of more severe illness or play a causal role in the pathologic process remain unclear. The effects of hypoglycemia are negative independent of previous diabetes status, but diabetic patients are more prone to the negative effects of stress hyperglycemia [56]. During pregnancy, hypoglycemia may carry additional risks for both the mother and fetus [57, 58]. Maternal glucose deficiency may lead to ketosis which could carry devastating consequences to both the mother and fetus. Examples of such consequences are toxemia [46] and lactation acidosis [59]. These risks must be added to the balance of considerations when attempting to control glucose levels in the critically ill pregnant patient.

32.7 Fat Metabolism

Along with the change in body water composition, the second most prominent change during pregnancy is fat gain [60]. This gain is highly variable and is related to maternal baseline weight. Normal or overweight women gain about

3.5 kg of fat (with large variations across populations). Underweight women gain an average of 6 kg of fat, and obese women do not gain any fat mass. Fat gain is mostly subcutaneous in early pregnancy [61], but peritoneal fat gain is more prominent during the third trimester [62]. Maternal weight is highly associated not only with immediate pregnancy outcomes but also with long-term outcomes. The offspring of both obese and thin mothers (as defined by fat layer measurement) have a higher likelihood of developing cardiovascular disease in later life [63].

Lipids constitute the key component of cell membranes (mainly in the form of phospholipids and cholesterol). Changes in lipid composition affect various tissues and organ systems by altering enzymatic function, carrier-mediated transport, receptor function, phagocytosis, prostaglandin production, immune processes, and cell growth [64]. These changes may stem from physiologic or pathological processes. During normal pregnancy polyunsaturated fatty acids (PUFA) are mobilized from maternal to fetal tissue to ensure brain and other vital organ development. Compared to nonpregnant females, pregnant women are deficient in both omega-3 (n–3) and omega-6 (n–6) fatty acids at 36 weeks, at labor, and 6 weeks postpartum [65]. Preeclampsia [66] is characterized by prominent lipid peroxidation, and it has been postulated that many of the features of this disorder could be explained by an increase in lipid peroxides [67]. Lipid composition may also be modified by external interventions, i.e., lipid supplementation. The effect of lipid supplementation has been tested in various trials, mostly of low or moderate quality, with conflicting results [68]. The recommended intake of fish for adults in the United Kingdom, for example, is two portions per week [69]. This provides a varying but mostly sufficient amount of n–3 oils, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) according to the type of fish consumed. Women who do not consume enough fish during pregnancy may safely receive supplementation to increase the levels of n–3 in both maternal and fetal blood [70]. However, supplementation of EPA and DHA in pregnant women at risk for hypertensive complications has not been shown to provide any protection from their development [70] (Fig. 32.2).

Lipid metabolism requires functioning mitochondria and large amounts of oxygen lipids. This makes them a less immediate source of energy compared to carbohydrates [71]. During the initial phases of critical illness, lipids, as well as proteins, do not play a major part in energy production. Triglycerides are hydrolyzed into free fatty acids and glycerol, regardless of exogenous lipid or carbohydrate administration; thus, fatty acid levels are high during the first days of acute severe illness [51]. These lipid breakdown products have been described as contributors to end-organ damage [51]. Later in the course of critical illness, lipids become more central in energy production. In this later stage, fatty acids are converted into ketone bodies in the liver, and fatty acid metabolism increases in peripheral tissues.

During critical illness the immune system is dysregulated, with different components of the immune system both enhanced and suppressed [72] (see Chap. 15). This evolutionary adaptive reaction may be deleterious in critical care settings when aggressive monitoring and treatment are employed. Lipids play important roles in the mediation of these adaptive (or maladaptive) responses [73]. The membrane of cells integral to the inflammatory process, such as macrophages, is composed primarily of saturated lipids. Of the remaining 40%, about 30% are polyunsaturated fatty acids (PUFAs). These are in turn further divided into n–3 (about a third) and n–6 (two-thirds). Phospholipase A_2 acts on membrane n–6 phospholipids to produce arachidonic acid (AA) and platelet-activating factor (PAF), a reaction enhanced by systemic inflammation. Metabolism of arachidonic acid by the cyclooxygenase, 5′ lipoxygenase, and cytochrome P-450 pathways leads to the production of prostaglandins, thromboxanes, and leukotrienes which play parts in the amplification of inflammatory cascades.

In the past, n–6 rich oils (e.g., soybean oil) comprised the standard lipid emulsions used in the ICU. More recently, n–3 rich oils derived from certain saltwater fish are being increasingly

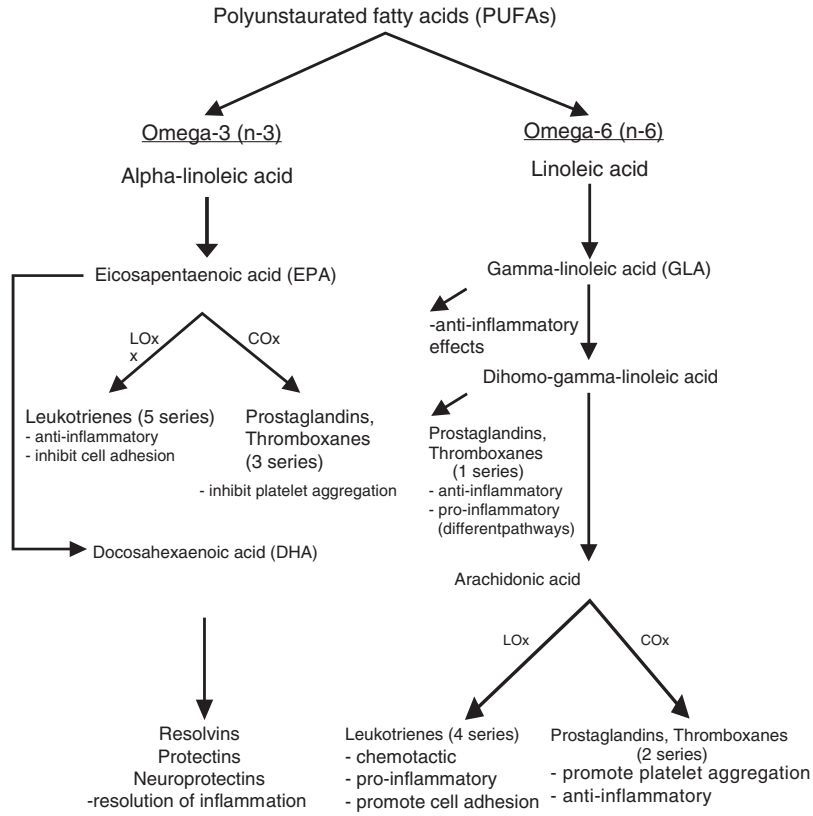


Fig. 32.2 Polyunsaturated fatty acids (n–3 and n–6): main pathways and major effects. *COx* cyclo-oxygenase, *LOx* lipo-oxygenase

used in critical care settings because of their potential to reduce the formation of pro-inflammatory lipid mediators. The term "immunonutrition" implies nutritional administration of substrates with potential anti-inflammatory characteristics (e.g., n–3 PUFAs, arginine, glutamine). Among other nutritional strategies, it has been put forward that altering cell membrane composition to increase the ratio of n–3 to n–6 will reduce arachidonic acid levels, thereby favoring the production of n–3-derived products that are less pro-inflammatory. To this end both enteral and intravenous supplementation of fish oil rich in n–3 PUFAs (EPA and DHA) have been studied in various critical illness settings [74, 75].

Whether immunonutrition conveys any advantage has been debated in the last decades. There were data pointing to a reduction in infectious complications, mainly in surgical and cancer patients [76, 77]. However, in general ICU populations, these interventions have been less successful [78]. Most studies are small and of low quality. One meta-analysis did show a trend towards lower infection rates in critically ill patients receiving intravenous n–3 rich lipid emulsions [75], and some data even point towards a reduction in mortality [79]. Conversely enteral supplementation of n–3 in critical illness following severe traumatic injury [80] or with adult respiratory distress syndrome [81] failed to show improvement and may even be deleterious if administered as a bolus. Further research is required in this field.

32.8 Proteins

Adequate protein intake during pregnancy is necessary for both fetal development and maternal organ function [82]. Adequate intake means higher protein requirements than in the nonpregnant state. Early studies assessing nitrogen balance [83] and the estimated average requirements (EAR) set the required protein intake during

pregnancy at 0.88 g/kg/day [84]. However, Stephens et al. [85] performed a clinical study looking at protein requirements in early and late pregnancy and found the actual average requirements to be much higher than first estimated, with an EAR of 1.22 g/kg/day during early and 1.52 g/kg/day in late pregnancy. The importance of protein-energy balance to fetal outcome was demonstrated in a meta-analysis by Imdad et al. [86], who pooled results from five studies and showed significant reductions in the rates of small-for-gestational-age births, low-birth weight, and stillbirth. Studies looking into protein composition are scarce. However, 20-year follow-up on the children of 965 Danish women [87] showed that the offspring of mothers that consumed large amounts of protein from animal origin during pregnancy had a greater tendency to be overweight, particularly if they were female. On the other hand, male offspring to mothers that consumed large amounts of fat from vegetable sources had lower levels of low-density lipoprotein later in life.

While pregnancy is an anabolic process, requiring higher amounts of protein for fetal development and maternal organ adaptations, critical illness is a catabolic state. As mentioned earlier, in the early phases of critical illness, energy is derived mainly from carbohydrates [51]. Muscle tissue is catabolized due to the action of the ubiquitin-proteasome cascade, among other mechanisms. This process provides accessible energy through gluconeogenesis and mobilizes the components required for synthesis of acute phase proteins and for immune and antioxidant defenses [88]. However, since at the same time the patient is usually immobilized, it also promotes early disuse muscle atrophy [89]. In the later stages of critical illness, more energy is derived from protein catabolism, and in the recovery phase, protein requirements may be even higher as the body rebuilds lean muscle tissue. During critical illness, the recommended protein daily intake is much higher than in health. A method for providing an accurate assessment of protein requirements is still unavailable, and nitrogen balance is of very limited value to this end [88]. It is therefore best to adhere to general recommendations. The amount of protein currently recommended during critical illness is 1.2–2 g/kg/day, and it may be higher in multiple trauma or burn patients [90]. However, these amounts are often hard to reach. Most available formulas have high non-protein to protein ratios. Such ratios make it difficult to provide adequate protein intake without caloric overfeeding, which is deleterious [91].

The optimal composition of proteins to be provided is yet harder to assess [88]. Baseline protein composition as well as its dynamics during illness varies widely across patient populations and disease states. Most studies use formulas with a standard composition. Therefore there is a paucity of data addressing this issue. Heyland et al. [24] examined the effect of glutamine and antioxidants in critically ill patients and found a trend towards higher mortality in the glutamine treatment arm. Citrulline has been shown to improve microcirculation and mitigate muscle damage, and taurine has been shown to protect against ischemic-reperfusion cardiac and neurologic injuries [92], but evidence for their clinical utility is still pending. Currently, supplementation with specific amino acids (arginine and glutamine) as part of immunonutrition is recommended only in patients with severe trauma [90].

32.9 Micronutrients

Micronutrients are nutrients required by the organism in minute amounts. They consist of trace elements (minerals) and vitamins. The micronutrient deficiencies commonly seen during pregnancy are those of iron, folic acid, zinc, iodine, and magnesium [93]. Iron requirements are greater during pregnancy [94] despite cessation of menstruation. This is due to both an increase in red blood cell mass and transfer of iron to fetal and placental tissue. Assessment of iron status in pregnancy is difficult and relies on transferrin saturation and plasma ferritin levels. As folic acid deficiency may result in fetal neural tube defects, nutritional supplementation with iron and folic acid is strongly recommended by the World Health Organization (WHO) for all

pregnant women [95]. Other trace elements and vitamin deficiencies have been associated with various fetal and maternal disorders. Examples include zinc deficiency, related to pre-eclampsia and congenital abnormalities, iodine deficiency and thyroid abnormalities in both mother and offspring, and fetal wastage in vitamin A deficiency [93]. In general, supplementation is indicated in areas where deficiencies are prevalent, although often studies are lacking to support this approach. Antioxidants such as vitamin C or E have been postulated to protect from pre-eclampsia [96]. However, such a protective effect has not actually been demonstrated, and supplementation has been, in fact, associated with lower offspring birth weights [97]. Care must be taken when providing high-dose supplementation of some micronutrients. While some vitamins (e.g., folic acid) are readily excreted, others (e.g., vitamin A) may accumulate and become toxic. In low-income countries, where malnutrition is prevalent during pregnancy, there is some evidence that supplementation of multiple micronutrients is associated with lower rates of low birth-weight babies compared to iron-folate replacement alone [98].

Micronutrients with antioxidant properties have received much attention as potential tools to address tissue and organ damage in critical illness. The administration of antioxidants, either trace elements (selenium, zinc, copper, iron and manganese) or vitamins (E, C, beta-carotene) in pharmacological doses was hypothesized to reduce oxidative stress and improve patient outcomes. The results of studies on this issue have been contradictory [99]. Manzanares et al. [100] conducted a systematic review and meta-analysis of 21 randomized controlled trials and found that high-dose supplementation of vitamins and trace elements in critically ill patients was associated with better outcomes including mortality, mainly in the higher risk group. However, in an adequately powered, high-quality, randomized controlled trial, the administration of intravenous selenium with enteral selenium, zinc, beta-carotene, and vitamins C and E was not associated with any outcome benefit [24]. Nonetheless, under certain conditions, such as severe burns or continuous renal replacement therapy, trace elements and vitamins are lost at a higher rate. Therefore based on physiological reasoning rather than clinical evidence, current guidelines recommend considering high-dose supplementation of these micronutrients in patients with these conditions [101].

32.10 Feeding the Critically Ill Mother

Anorexia is a part of the adaptive response to acute illness. As a result a negative calorie and protein balance may develop, and the integrity of the gut mucosa may be placed at risk. Gut mucosal atrophy may develop even following a short period of fasting. Typically there is a decrease in villous height and crypt depth as well as abnormal gut permeability [102]. This phenomenon is at least partially explained by changes in gut microbiota. A reduction in the amount of short-chain fatty acids (acetate and mainly butyrate) produced by gut bacteria can lead to atrophic colitis of the colon [103]. The adverse systemic effects potentially associated with these changes include an increased prevalence of sepsis and multiple organ dysfunction syndrome [104].

The sick mother may be fed by the oral, enteral, or parenteral (intravenous) routes. Given to clinician discretion, the patient able to eat should be encouraged to do so, even shortly following surgery [105]. This is especially important for the malnourished patient. As the pregnant mother is potentially at a greater risk for the development of maternal and fetal malnourishment, oral feeding should be encouraged whenever possible. When the patient is unable to maintain volitional oral intake, the enteral route is preferred over the parenteral. Current recommendations advocate initiating enteral nutrition for critically ill patients unable to eat within 48 h [101]. However, if a patient is hemodynamically unstable, enteral nutrition should be delayed until stability is achieved.

The caloric intake target should be based on measurements (i.e., indirect calorimetry) when possible. When indirect calorimetry is unavailable, estimations using either elaborate or sim-

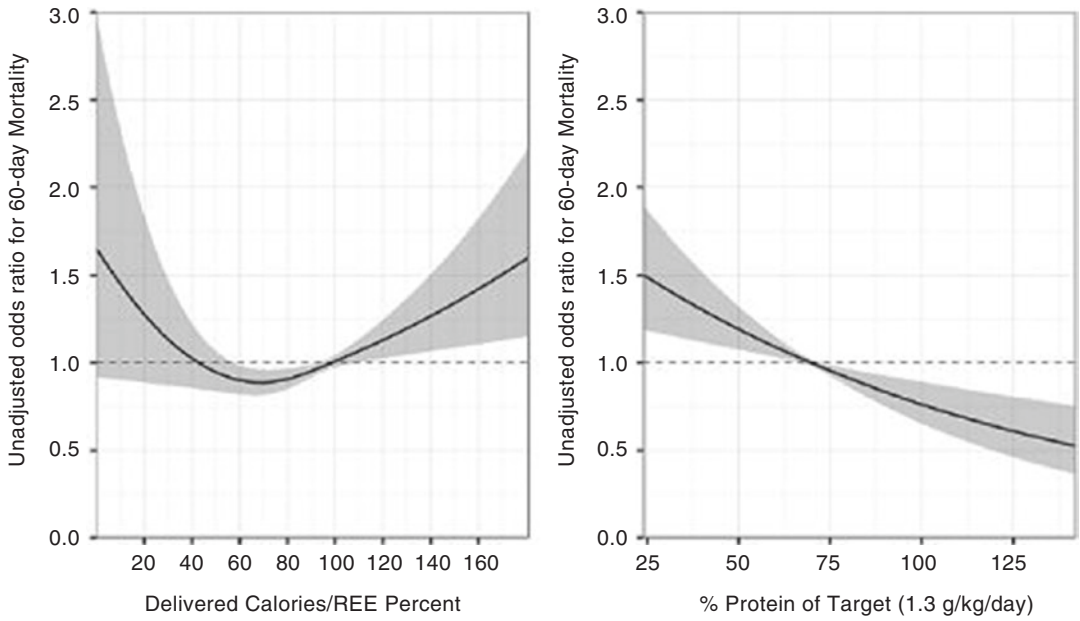


Fig. 32.3 Association of administered calories/resting energy expenditure (Administered kcal/REE) percent with 60 day mortality (left) and protein intake by daily requirement (1.3 g/kg/day) with 60 day mortality (right) by odds ratio. *REE* resting energy expenditure

plistic equations may be used. For most patients, the caloric target should be 20–25 kcal/kg-IBW/day with a protein target of 1.3 g/kg-IBW/day. In obese patients, the caloric target should be lowered to 65–70% of energy expenditure as measured by calorimetry or 11–14 kcal/kg/day while maintaining a high (2 g/kg/day) diet. The risk of overfeeding may in fact be greater than that of underfeeding in critically ill patients (Fig. 32.3). Since very few studies have been performed in pregnant critically ill patients, it is recommended that specifically in these patients calorie administration be directed by measured energy expenditure. Formulas containing Arginine and fish oil should be used in postoperative patients. There is no indication for adding glutamine to enteral nutrition.

Although enteral nutrition should be initiated within 2 days, it remains unclear whether an attempt should be made to reach the caloric target during the first 3 days after admission or only after a week. Current European Society of Parenteral and Enteral Nutrition guidelines [101] recommend hypocaloric feeding, i.e., less than 70% of the estimated caloric needs, during the first week, when indirect calorimetry is not used. Neither approach can currently be recommended. However, in a cohort of almost 10,000 critically ill patients [106], 25% were still not receiving any nutrition after 4 days. This could potentially be hazardous, especially in pregnancy.

The preferred route for administering enteral nutrition in most ICU patients is a gastric feeding tube. An enteral (post-pyloric) feeding tube is more expensive, its insertion requires more expertise, and there are higher insertion failure rates, although its use has been associated with lower rates of pneumonia [107]. Nowadays the indications for use of a feeding tube are few as specific disease conditions (e.g., pancreatitis) are no longer considered a contraindication to pre-pyloric feeding [108]. Failure to provide adequate enteral nutrition is common when a gastric feeding tube is used. The main reasons for this are high gastric residual volumes (GRV), surgical requirements, and lack of feeding during patient transfer and stay in areas outside of the ICU (mainly the operating theater) [109]. Routine repeat measurement of GRV is no longer recommended [101]. When GRV is measured, feeding

should continue as long as it is lower than 500 mL [90, 101]. In case of intolerance to enteral nutrition (GRV > 500 mL, vomiting), treatment with prokinetics such as metoclopramide or erythromycin should be tried. At the same time efforts should be made to reduce the presence of factor precipitation gastric dysmotility such as opioids and immobilization. If enteral nutrition via a gastric tube fails despite these measures, a feeding tube may be inserted, or, alternatively, nutrition may be supplemented parenterally (although the efficacy of combined enteral and parenteral nutrition remains controversial).

Parenteral nutrition should be prescribed when enteral nutrition cannot be delivered. Current guidelines advocate initiation of parenteral nutrition only after a week without nutrition; higher complication rates have been shown when parenteral nutrition is initiated earlier [110]. However, in malnourished (and perhaps pregnant) patients, parenteral nutrition can be started earlier. The aim is to slowly, i.e., within a week, reach 80–100% of the caloric target and at least 1.3 g/kg/day of protein [90, 101]. The use of parenteral nutrition in pregnant women has been shown to be safe and effective [111]. The authors have fed women parenterally (with lipid emulsions) as outpatients throughout their pregnancy. Such practice may be conducted safely with good outcomes for both the mothers and babies. As in other patients, the use of intravenous immunonutrition (antioxidants, n–3 PUFAs, arginine and glutamine) during pregnancy is not recommended as the benefit of this approach is largely unproven.

Glucose levels should be monitored closely for the development of hypo- and hyperglycemic states. This statement holds true for critically ill pregnant and postpartum women as well. In most critically ill patients, glucose levels within the range of 140–180 mg/dL are considered optimal. In some populations such as cardiothoracic surgical patients, the target may be lower, but caution must be practiced as hypoglycemia carries risk for both the mother and fetus. Insulin should be given intravenously in parallel to continuous administration of glucose through enteral or parenteral nutrition. A recent meta-analysis [112] showed that no targeted glycemic level led to any outcome advantage in terms of mortality or infection rate. Higher glycemic levels were related to less events of hypoglycemia. Hopefully, in the future, we will be able to better stratify patients that will benefit from tighter or looser glycemic regimes. Until then, each center should adopt its own protocol.

32.11 Conclusions

Providing adequate nutrition to the pregnant critically ill patient is challenging. Only few studies exist in the field of critical care that include pregnant patients. The metabolic requirements of both the mother fetus are difficult to determine, and changes in weight may not correlate with changes in energy requirements. Optimally, calorie administration should be guided by measurements of energy expenditure obtained by indirect calorimetry. Predictive equations are often inaccurate and should be used only if indirect calorimetry is not available. Carbohydrates should be administered with care so as not to induce severe hyperglycemia. As insulin is commonly used to control glucose levels, glucose levels should be monitored frequently to prevent both hyper- and hypoglycemia. Lipids are an important component of the nutritional regimen and should be administered to ensure normal development of the fetal brain. The amount of protein administered should be greater than 1.3 g/kg/day. Attention should be given to provision of adequate doses of minerals and vitamins in order to prevent occurrence of maternal and fetal nutritional deficiencies.

References

1. Lain KY, Catalano PM. Metabolic changes in pregnancy. Clin Obstet Gynecol. 2007;50(4):938–348.
2. Stosur S, Liu N, Rodrigues S, et al. Serum water analysis in normal pregnancy and preeclampsia. Clin Lab Sci. 2011;24(2):99–104.
3. Dechend R, Lamarca B, Taylor RN. Chapter 15: the renin-angiotensin system, its autoantibodies, and body fluid volume in preeclampsia. In: Taylor RN, editor. Chelsley's hypertensive disorders in

pregnancy. 4th ed. Amsterdam: Elsevier; 2015. p. 315–34.
4. Gueri M, Jutsum P, Sorhaindo B. Anthropometric assessment of nutritional status in pregnant women: a reference table of weight-for-height by week of pregnancy. Am J Clin Nutr. 1982;35(3):609–16.
5. Hronek M, Doubkova P, Tosner J, et al. Prediction of nutritive intake energy and substrates of Czech pregnant women. Nutrition. 2011;27(11–12):1118–24.
6. Hillesund ER, Bere E, Sagedal LR, et al. Pre-pregnancy and early pregnancy dietary behavior in relation to maternal and newborn health in the Norwegian Fit for Delivery study—a post hoc observational analysis. Food Nutr Res. 2018;62. https://doi.org/10.29219/fnr.v62.1273. eCollection 2018.
7. Goldstein RF, Abell SK, Ranasinha S, et al. Gestational weight gain across continents and ethnicity: systematic review and meta-analysis of maternal and infant outcomes in more than one million women. BMC Med. 2018;16(1):153.
8. Goldstein RF, Abell SK, Ranasinha S, et al. Association of gestational weight gain with maternal and infant outcomes: a systematic review and meta-analysis. JAMA. 2017;317(21):2207–25.
9. Nair M, Choudhury MK, Choudhury SS, et al. Association between maternal anaemia and pregnancy outcomes: a cohort study in Assam, India. BMJ Glob Health. 2016;1(1):e000026.
10. Einav S, Weiniger CF. Maternal anaemia—the story behind the number. Eur J Anaesthesiol. 2018;35(4):315–6.
11. National collaborating centre for women's and children's health (UK). Antenatal care: routine care for the healthy pregnant woman. NICE clinical guidelines, No. 62. London: RCOG Press; 2008.
12. Açkurt F, Wetherilt H, Löker M, et al. Biochemical assessment of nutritional status in pre- and postnatal Turkish women and outcome of pregnancy. Eur J Clin. 1995;49(8):613–22.
13. Butte NF, Calloway DH, Van Duzen JL. Nutritional assessment of pregnant and lactating Navajo women. Am J Clin Nutr. 1981;34(10):2216–28.
14. Hiesmayr M. Nutrition risk assessment in the ICU. Curr Opin Clin Nutr Metab Care. 2012;15:174–80.
15. Fontes D, Generoso Sde V, Toulson Davisson Correia MI. Subjective global assessment: a reliable nutritional assessment tool to predict outcomes in critically ill patients. Clin Nutr. 2014;33(2):291–5.
16. Ali NA, O'Brien JMJR, Hoffman SP, et al. Acquired weakness, handgrip strength, and mortality in critically ill patients. Am J Respir Crit Care Med. 2008;178:261–8.
17. Biolo G, Agostini F, Simunic B, et al. Positive energy balance is associated with accelerated muscle atrophy and increased erythrocyte glutathione turnover during 5wk of bed rest. Am J Clin Nutr. 2008;88:950–8.
18. Rahman A, Hasan MH, Agarwala R, et al. Identifying critically-ill patients who will benefit most from nutritional therapy: further validation of the "modified NUTRIC" nutritional risk assessment tool. Clin Nutr. 2017;35(1):158–62.
19. Heyland DK, Dhaliwal R, Jiang X, et al. Identifying critically ill patients who benefit most from nutrition therapy: the development and initial validation of a novel risk assessment tool. Crit Care. 2011;15:R268.
20. Danziger J, Chen K, Cavender S, et al. Admission peripheral edema, central venous pressure and survival in critically ill patients. Ann Am Thorac Soc. 2016;13(5):705–11.
21. Ravasco P, Camilo ME, Gouveia-Oliviera A, et al. A critical approach to nutritional assessment in critically ill patients. Clin Nutr. 2002;28(3):267–70.
22. McClave SA, Snider HL. Use of indirect calorimetry in clinical nutrition. Nutr Clin Pract. 1992;7(5):207–21.
23. Malone AM. Methods of assessing energy expenditure in the intensive care unit. Nutr Clin Pract. 2002;17(1):21–8.
24. Heyland D, Muscedere J, Wischmeyer PE, Canadian Critical Care Trials Group, et al. A randomized trial of glutamine and antioxidants in critically ill patients. N Engl J Med. 2013;368(16):1489–97.
25. Lev S, Cohen J, Singer P. Indirect calorimetry measurements in the ventilated critically ill patient: facts and controversies--the heat is on. Crit Care Clin. 2010;26(4):e1–9.
26. Amato P, Keating KP, Quercia RA, et al. Formulaic methods of estimating calorie requirements in mechanically ventilated obese patients: a reappraisal. Nutr Clin Pract. 1995;10(6):229–32.
27. Butte NF, Wong WW, Treuth MS, et al. Energy requirements during pregnancy based on total energy expenditure and energy deposition. Am J Clin Nutr. 2004;79:1078–87.
28. Frankenfield DC, Wiles CE 3rd, Bagley S, et al. Relationships between resting and total energy expenditure in injured and septic patients. Crit Care Med. 1994;22(11):1796–804.
29. Gariballa S, Forster S. Energy expenditure of acutely ill hospitalised patients. Nutr J. 2006;5:9.
30. Bruder N, Raynal M, Pellisier D, et al. Influence of body temperature, with or without sedation, on energy expenditure in severe head-injured patients. Crit Care Med. 1998;26(33):568–72.
31. Yüksel E, Çankayalı İ, Demirağ K, et al. The effect of neuromuscular blockade on oxygen consumption and energy expenditure in mechanically ventilated acute respiratory insufficiency patients. J Turkish Soc Intensive Care. 2012;10:8–12.
32. Vernon DD, Witte MK. Effect of neuromuscular blockade on oxygen consumption and energy expenditure in sedated, mechanically ventilated children. Crit Care Med. 2000;28(5):1569–71.
33. Yu CKH, Teoh TG, Robinson S. Obesity in pregnancy. BJOG. 2006;113:1117–25.
34. Pickkers P, De Keizer N, Dusseljee J, et al. Body mass index is associated with hospital mortality in critically ill patients: an observational cohort study. Crit Care Med. 2013;41(8):1878–83.

35. Hutagalung R, Marques J, Kobylka K. The obesity paradox in surgical intensive care unit patients. Intensive Care Med. 2011;37(11):1793–9.
36. Baracos V, Rodemann HP, Dinarello CA, et al. Stimulation of muscle protein degradation and prostaglandin E_2 release by leukocytic pyrogen (interleukin-I). N Engl J Med. 1983;308:553–8.
37. Mitch WE, Goldberg AL. Mechanisms of muscle wasting- the role of the ubiquitin-proteasome pathway. N Engl J Med. 1996;335:1897–905.
38. Villet S, Chilero RL, Bollmann MD, et al. Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. Clin Nutr. 2005;24(4):502–9.
39. Faisy C, Lerolle N, Dachraoui F, et al. Impact of energy deficit calculated by a predictive method on outcome in medical patients requiring prolonged acute mechanical ventilation. Br J Nutr. 2009;101(7):1079–87.
40. Dvir D, Cohen J, Singer P. Computerized energy balance and complications in critically ill patients: an observational study. Clin Nutr. 2006;25(1):37–44.
41. Wei X, Day AG, Oullette-Kuntz H, et al. The association between nutritional adeqacuy and long-term outcomes in critically ill patients requiring prolonged mechanical ventilation: a multicenter cohort study. Crit Care Med. 2015;43(8):1569–79.
42. Reid CL, Campbell IT, Little RA. Muscle wasting and energy balance in critical illness. Clin Nutr. 2004;23(2):273–80.
43. Looijaard WG, Dekker IM, Stapel SN, et al. Skeletal muscle quality as assessed by CT-derived skeletal muscle density is associated with 6-month mortality in mechanically ventilated critically ill patients. Crit Care. 2016;20(1):386.
44. Reid C. Frequency of under- and overfeeding in mechanically ventilated ICU patients: causes and possible consequences. J Hum Nutr Diet. 2006;19:13–22.
45. Ribeiro LM, Oliviera Filho RS, Caruso L, et al. Adequacy of energy and protein balance of enteral nutrition in intensive care: what are the limiting factors? Rev Bras Ter Intensiva. 2014;26(2):155–62.
46. Kühl C. Glucose metabolism during and after pregnancy in normal and gestational diabetic women. Acta Endocrinol. 1975;79(4):709–19.
47. Simmons MA, Battaglia FC, Meschia G. Placental transfer of glucose. J Dev Physiol. 1979;118:23–8.
48. Bell AW, Bauman DE. Adaptations of glucose metabolism during pregnancy and lactation. J Mammary Gland Biol Neoplasia. 1997;2(3):265–78.
49. Catalano PM, Hustob L, Amini SB, et al. Longitudinal changes in glucose metabolism during pregnancy in obese women with normal glucose tolerance and gestational diabetes mellitus. Am J Obstet Gynecol. 1999;180(4):903–16.
50. Bellamy L, Casas JP, Hingorani AD, et al. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet. 2009;373(9677):1773–9.
51. Preiser JC, Ichai C, Orban JC, et al. Metabolic response to critical illness. Br J Anaesth. 2014;113(6):945–54.
52. Falciglia M, Freyberg RW, Almenoff PL, et al. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. Crit Care Med. 2009;37(12):3001–9.
53. Vriesendorp TM, DeVries JH, Van Santen S, et al. Evaluation of short-term consequences of hypoglycemia in an intensive care unit. Crit Care Med. 2006;34(11):2714–8.
54. NICE-SUGER Investigators. Hypoglycemia and the risk of death in critically ill patients. N Engl J Med. 2012;367(12):1108–18.
55. Krinsley JS. Glycemic variability: a strong independent predictor of mortality in critically ill patients. Crit Care Med. 2008;36(11):3008–13.
56. Krinsley JS, Egi M, Kiss A, et al. Diabetic status and the relation of the three domains of glycemic control to mortality in critically ill patients: an international multicenter cohort study. Crit Care. 2013;17(2):R37.
57. Rosenn BM, Miodovnik M, Holcverg G, et al. Hypoglycemia: the price of intensive insulin therapy for pregnant women with insulin-dependent diabetes mellitus. Obstet Gynecol. 1995;85(3):417–22.
58. Ter Braak EW, Evers IM, Willem Erkelens D, et al. Maternal hypoglycemia during pregnancy in type 1 diabetes: maternal and fetal consequences. Diabetes Metab Res Rev. 2002;18(2):96–105.
59. Gleeson S, Mulroy E, Clarke DE. Lactation ketoacidosis: an unusual entity and a review of the literature. Perm J. 2016;20(2):71–3.
60. Lederman SA, Paxton A, Heymsfield SB, et al. Body fat and water changes during pregnancy in women with different body weight and weight gain. Obstet Gynecol. 1997;90(4 pt 1):483–8.
61. Sidebottom AC, Brown JE, Jacobs DR Jr. Pregnancy-related changes in body fat. Eur J Obstet Gynecol Reprod Biol. 2001;94(2):216–23.
62. Kinoshita T, Itoh M. Longitudinal variance of fat mass deposition during pregnancy evaluated by ultrasonography: the ration of visceral fat to subcutaneous fat in the abdomen. Gynecol Obstet Investig. 2006;61:115–8.
63. Godfrey KM, Barker DJP. Fetal nutrition and adult disease. Am J Clin Nutr. 2000;71(5 suppl):1344S–52S.
64. Spector AA, Yorek MA. Membrane lipid composition and cellular function. J Lipid Res. 1985;26(9):1015–35.
65. Hubel CA, Roberts JM, Taylor RN, et al. Lipid peroxidation in pregnancy: new perspectives on preeclampsia. Am J Obstet Gynecol. 1989;161(4):1025–34.
66. Walsh SW. Lipid peroxidation in pregnancy. Hypertens Pregnancy. 1994;13(1):1–32.
67. Holman RT, Johnson SB, Ogburn PL. Deficiency of essential fatty acids and membrane fluidity during pregnancy and lactation. Proc Natl Acad Sci U S A. 1991;88:4835–9.

68. Larqué E, Gil-Sánchez A, Prieto-Sánchez MT, et al. Omega 3 fatty acids, gestation and pregnancy outcomes. Br J Nutr. 2012;107(Suppl 2):S77–84.
69. Scientific Advisory Committee on Nutrition & Committee on Toxicity. Advice on fish comsumption: benefits and risks. London: United Kingdom: The Stationary Office; 2004.
70. Miles EA, Noakes PS, Kremmyda LS, et al. The salmon in pregnancy study: study design, subject characteristics, maternal fish and marine n-3 fatty acid intake, and marine n-3 fatty acids status in maternal and umbilical cord blood. Am J Clin Nutr. 2011;94(Suppl 6):1986S–92S.
71. Onwude JL, Lilford RJ, Hjartardottir H, et al. A randomized double blind placebo controlled trial of fish oil in high risk pregnancy. Br J Obstet Gynaecol. 1995;102(2):95–100.
72. Pinsky MR. Dysregulation of the immune response in severe sepsis. Am J Med Sci. 2004;328(4):220–9.
73. Bulger EM, Maier RV. Lipid mediators in the pathophysiology of critical illness. Crit Care Med. 2000;28(4):N27–36.
74. Mayer K, Seeger W. Fish oil in critical illness. Curr Opin Clin Nutr Metab Care. 2008;11(2):121–7.
75. Manzanares W, Langlois PL, Dhaliwal R, et al. Intravenous fish oil lipid emulsions in critically ill patients: an updated systematic review and meta-analysis. Crit Care. 2015;19:167.
76. Heyland DK, Novak F, Drover JW, et al. Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. JAMA. 2001;286(8):944–53.
77. Heys SD, Walker LG, Smith I, et al. Enteral nutritional supplementation with key nutrients in patients with critical illness and cancer: a meta-analysis of randomized controlled clinical trials. Ann Surg. 1999;229(4):467–77.
78. Kieft H, Roos AN, Van Drunen JD, et al. Clinical outcome of immunonutrition in a heterogenous intensive care population. Intensive Care Med. 2005;31(4):524–32.
79. Chen W, Jiang H, Zhou ZY, et al. Is omega-3 fatty acids enriched nutrition support safe for critical ill patients? A systematic review and meta-analysis. Nutrients. 2014;6(6):2148–64.
80. Kagan I, Cohen J, Stein M, et al. Preemptive enteral nutrition enriched with eicosapentaenoic acid, gamma-linoleic acid and anti-oxidants in severe multiple trauma: a prospective, randomized double-blind study. Intensive Care Med. 2015;41(3):460–9.
81. Rice TW, Wheeler AP, Thompson BT, et al. Enteral omega-3 fatty acid, gamma-linoleic acid, and antioxidant supplementation in acute lung injury. JAMA. 2011;306(1):1574–81.
82. King JC. Physiology of pregnancy and nutrient metabolism. Am J Clin Nutr. 2000;71(5 Suppl):1218S–25S.
83. Calloway DH. Nitrogen balance during pregnancy. Curr Concepts Nutr. 1974;2:79–94.
84. Institute of Medicine, Food and Nutrition Board. Dietary reference intakes: energy, carbohydrates, fiber, fatty acids, cholesterol, protein and amino acids. Washington DC: The National Academy; 2005.
85. Stephens TV, Payne M, Ball RO, et al. Protein requirements of healthy pregnant women during early and late gestation are higher than current recommendations. J Nutr. 2015;145(1):73–8.
86. Imdad A, Bhutta ZA. Maternal nutrition and birth outcomes: the effect of balanced protein-energy supplementation. Paediatr Perinat Epidemiol. 2012;26(Suppl 1):178–90.
87. Maslova E, Rytter D, Bech BH, et al. Maternal protein intake during pregnancy and offspring overweight 20 years later. Am J Clin Nutr. 2014;100(4):1139–48.
88. Plank M, Fischer R, Geoghegan V, et al. Protein for the critically ill patients- what and when. Eur J Clin Nutr. 2013;67(5):565–8.
89. Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. N Engl J Med. 2008;358(13):1327–35.
90. McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: society of critical medicine (SCCM) and American society for parenteral and enteral nutrition (A.S.P.E.N.). J Parenter Enter Nutr. 2016;40(2):159–211.
91. Taylor S, Dumont N, Clemente R, et al. Critical care: meeting energy requirements without overfeeding energy. Clin Nutr. 2016;11:e1–8.
92. Ginguay A, De Bandt JP, Cynober L, et al. Indications and contraindications for infusing specific amino acids (leucine, glutamine, arginine, citrulline and taurine) in critical illness. Curr Opin Clin Nutr Metab Care. 2016;19(2):161–9.
93. Black RE. Micronutrients in pregnancy. Br J Nutr. 2001;85(Suppl 2):S193–7.
94. Bothwell TH. Iron requirements during pregnancy and strategies to meet them. Am J Clin Nutr. 2000;72(Suppl 1):257S–64S.
95. Geneva: World Health Organization (2012). Guideline: intermittent iron and folic acid supplementation in non-anaemic pregnant women. WHO guidelines approved by the guidelines review committee.
96. Berti C, Biealski HK, Gärtner R, et al. Micronutrients in pregnancy: current knowledge and unresolved questions. Clin Nutr. 2011;30(6):689–701.
97. Poston L, Brilet AL, Seed PT, et al. Vitamin C and vitamin E in pregnant women at risk for pre-eclampsia (VIP trial): a randomised placebo-controlled trial. Lancet. 2006;367(9517):1145–54.
98. Fall CHD, Fisher DJ, Osmond C, et al. Multiple micronutrient supplementation during pregnancy in low-income countries: a meta-analysis of effects on birth size and length of gestation. Food Nutr Bull. 2009;30(Suppl 4):533S–46S.

99. Casaer MP, Van Den Berghe G. Nutrition in the acute phase of critical illness. N Engl J Med. 2014;370(13):1227–36.
100. Manzanares W, Dhaliwal R, Jiang X, et al. Antioxidant micronutrients in the critically ill: a systematic review and meta-analysis. Crit Care. 2012;16(2):R66.
101. Singer P, Berger MM, Van Den Berghe G, et al. ESPEN guidelines on parenteral nutrition: intensive care. Clin Nutr. 2009;28(4):387–400.
102. Hernandez G, Velasco N, Wainstein C, et al. Gut mucosal atrophy after a short enteral fasting period in critically ill patients. J Crit Care. 1999;14(2): 73–7.
103. Scheppach W. Effects of short chain fatty acids on gut morphology and function. Gut. 1994;35(1 Suppl):S35–8.
104. Jabbar A, Chang WK, Dryden GW, et al. Gut immunology and the differential response to feeding and starvation. Nutr Clin Pract. 2003;18(6):461–82.
105. Gustafsson UO, Scott MJ, Schwenk W, et al. Guidelines for perioperative care in elective colonic surgery: enhanced recovery after surgery (ERAS(®)) society recommendations. World J Surg. 2013;37(2):259–84.
106. Bendavid I, Singer P, Theilla M, et al. NutritionDay ICU: a 7 year worldwide prevalence of nutrition practice in intensive care. Clin Nutr; 2016. pii: S0261-5614(16)30178–9.
107. Alkhawaja S, Martin C, Butler RJ, et al. Post-pyloric versus gastric tube feeding for preventing pneumonia and improving nutritional outcomes in critically ill adults. Cochrane Database Syst Rev. 2015;(8):CD008875.
108. Nally DM, Kelly EG, Clarke M, et al. Nasogastric feeding is efficacious in severe acute pancreatitis: a systematic review and meta-analysis. Br J Nutr. 2014;112(11):1769–78.
109. Kuslapuu M, Jõgela K, Starkopf J, et al. The reasons for insufficient enteral feeding in an intensive care unit: a prospective observational study. Intensive Crit Care Nurs. 2015;31(5):309–14.
110. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med. 2011;365(6):506–17.
111. Theilla M, Ławiński M, Cohen J, et al. Safety of home parenteral nutrition during pregnancy. Clin Nutr. 2017;36(1):288–92.
112. Yatabe T, Inoue S, Sakaguchi M, et al. The optimal target for acute glycemic control in critically ill patients: a network meta-analysis. Intensive Care Med. 2017;43(1):16–28.

33 Acute Fatty Liver of Pregnancy, Liver Failure, and Liver Transplantation

Chundamannil Eapen Eapen, Ashish Goel, and Subramani Kandasamy

Bullet Points

- Acute fatty liver of pregnancy (AFLP) is an uncommon, severe liver disorder leading to liver failure in women in late pregnancy.
- AFLP is characterized by defective fatty acid oxidation and consequent maternal "energy failure" and accumulation of toxic by-products.
- A high index of suspicion leading to early diagnosis, together with early institution of management, is imperative for good maternal outcome in AFLP.
- Any women presenting with severe liver dysfunction (jaundice and coagulopathy with or without encephalopathy and/or hypoglycemia) in late pregnancy should be suspected to have AFLP and should undergo appropriate evaluation.
- Diagnosis is confirmed by "Swansea" criteria. Presumptive diagnosis does not require liver biopsy.
- Urgent institution of delivery (with adequate precautions) remains the cornerstone of therapy for AFLP. Early appropriate supportive care should be instituted in parallel.
- The characteristic finding of AFLP in liver biopsy (which should be performed after delivery) is diffuse/perivenular microvesicular hepatic steatosis.
- There is small risk of recurrence of AFLP in future pregnancies.

33.1 Introduction

Acute fatty liver of pregnancy (AFLP) is an obstetric medical emergency that can occur at any time during pregnancy and labor. The diagnostic window to urgently terminate the pregnancy means that any delay in treatment can translate into worsening maternal liver failure and risk of maternal and fetal death/severe morbidity. In this chapter we review some of the recent insights into the pathogenesis of this fascinating disease, recent improvements in diagnosis, and newer advances in treatment.

C. E. Eapen (✉) · A. Goel
Hepatology Department, Christian Medical College, Vellore, Tamil Nadu, India
e-mail: eapen@cmcvellore.ac.in; drashishgoel@cmcvellore.ac.in

S. Kandasamy
Surgical Intensive Care Department, Christian Medical College, Vellore, TamilY India
e-mail: ksubramani9@hotmail.com

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_33

33.2 Epidemiology

A nationwide prospective population based study conducted in the United Kingdom (UK) in 2005–2006 estimated the incidence of AFLP to be 5/100,000 pregnancies (95% confidence interval 3.8–6.5/100,000). Twin pregnancies were at high risk of being complicated by AFLP (of the 57 women with AFLP, 18% had twin pregnancies) [1].

The predominant causes of liver dysfunction during pregnancy may differ according to geographic location. A prospective study from Wales in the UK noted that pregnancy-related liver diseases (pre-eclampsia, the HELLP syndrome [see details below], intrahepatic cholestasis of pregnancy, AFLP and hyperemesis gravidarum) are the predominant cause of liver dysfunction in pregnancy [2]. In contrast, in India, liver diseases unrelated to pregnancy are the predominant cause of liver dysfunction [3] and of liver-related maternal deaths [3–5].

33.3 Pathogenesis

33.3.1 The Hibernating Bear: A Good Analogy for AFLP Pathogenesis

Our current understanding of the pathogenesis of AFLP is best depicted by the analogy of a hibernating bear, as explained below [6, 7] (Fig. 33.1).

Fig. 33.1 Switch to fats as primary energy source during hibernation in bears and during late pregnancy in women may explain pathogenesis of acute fatty liver of pregnancy

AFLP is termed a mitochondrial hepatopathy. Ultrastructural mitochondrial alterations have been demonstrated in patients with AFLP [8, 9]. Defective functioning of the mitochondria (the powerhouse of the cells) in the liver leads to energy deficiency in the liver.

Genetic predisposition: One factor predisposing to AFLP is the presence of an autosomal recessive congenital defect in utilizing stored fats.

In an initial report of a woman with consecutive pregnancies complicated by AFLP, maternal liver function rapidly improved after delivery in both pregnancies. However, both babies died by 6 months of age with fatty infiltration of several organs. The authors suspected a familial defect in fatty acid oxidation, which in turn predisposed the mother to develop AFLP [10]. Subsequent reports confirmed fetal fatty acid oxidation defects to be associated with maternal AFLP. A study that compared 50 children with fatty acid oxidation disorders versus 1250 control children (without these disorders) reported that the risk of maternal liver diseases such as AFLP was increased 20-fold among pregnant women with children who themselves had fatty acid oxidation disorders [11].

Thus, AFLP is an example of maternal mitochondrial hepatopathy that is linked to fetal fatty acid oxidation disorders. Fetal fatty acid oxidation disorders are autosomal recessively inherited. Both the pregnant woman and her husband can only be heterozygotes for the fatty acid oxidation disorder. However, if the fetus is a compound heterozygote or a homozygote for this disorder, the mother is at risk for developing AFLP during that pregnancy. On the other hand, if the fetus is a simple heterozygote or wild type, the mother will not have liver dysfunction during pregnancy.

Fetal fatty acid oxidation disorders linked to AFLP and other maternal liver diseases include defects in long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) [12–15], medium-chain 3-hydroxyacyl-CoA dehydrogenase [16], short-chain 3-hydroxyacyl-CoA dehydrogenase (SCHAD) [17], and carnitine palmitoyltransferase I [18]. LCHAD deficiency is the most common fetal fatty acid oxidation disorder reported in association with AFLP [11]. Raised hydroxy-

acyl carnitine levels in patients with AFLP may suggest a defect in LCHAD or mitochondrial trifunctional protein [19].

However, pregnancies without evidence of fatty acid oxidation defects in the mother and baby have also been reported to be complicated by AFLP [20]. Centers studying women with AFLP have noted that the most prevalent LCHAD mutation, G1528C, was absent in several women [21, 22]. Therefore, although fetal fatty acid oxidation defects may be causative in some pregnant women with AFLP, currently there is insufficient evidence to instigate routine screening for fatty acid oxidation defects among all babies following maternal AFLP [23].

33.4 Acquired Predisposition

Diffuse hepatic microvesicular steatosis is an uncommon cause of liver failure. Reye's syndrome, precipitated by ingestion of aspirin, is an example of hepatic microvesicular steatosis and encephalopathy associated with fatty acid oxidation disorders [24]. In children and teenagers, avoidance of aspirin has been recommended in order to prevent the occurrence of Reye's syndrome in predisposed individuals. However, aspirin is commonly prescribed for preventing complications related to pre-eclampsia during pregnancy [25]. It has been hypothesized that non-steroidal anti inflammatory drugs (NSAIDs), including aspirin, can inhibit both the LCHAD enzyme and fatty acid oxidation during pregnancy, thus predisposing to AFLP [26]. Although an association between treatment with aspirin and the occurrence of AFLP has been reported in pregnancy [17, 27], this is uncommon and may be a chance association rather than a causative one.

33.5 Placental Pathogenesis

The dramatic postpartum improvement observed in maternal liver function raises questions regarding placental involvement in AFLP pathogenesis [28]. The placenta has the same genetic composition as the fetus, and LCHAD and SCHAD enzymes are both active in the human placenta. The activity of these enzymes inversely correlates with maternal gestational age in the second and third trimesters of pregnancy [29]. A rat model of valproate-induced hepatic microvesicular steatosis showed defective mitochondrial fatty acid oxidation and increased peroxisomal and microsomal oxidation in the liver [30]. Both the placenta and the serum of AFLP mothers show oxidant and nitrosative stress (in placental mitochondria and peroxisomes and in serum) compared to controls. Mitochondrial function was affected in the placentas of AFLP mothers. Raised arachidonic acid levels were seen in the placenta and serum of AFLP mothers. Such high arachidonic acid levels have been shown to induce oxidative stress and apoptosis in mitochondria and lipid deposition in hepatocytes grown in culture [31].

33.6 Timing of AFLP Manifestation: Why Does AFLP Manifest in Late Pregnancy?

An adult bear hibernates for about 3 months of the year, during which time the bear utilizes about 4000 kcal of energy each day. During hibernation, the bear eats no food and subsists on endogenous energy (fat) stores [6]. If a hypothetical bear had a defect in metabolizing fats or utilizing fat stores for energy needs, it would be expected to become sick during hibernation due to systemic energy depletion. Such problems in this hypothetical bear may occur due either to a genetic predisposition, to an acquired cause affecting fat metabolism, or both [32].

In the well-nourished non-obstetric population, the primary energy source after each meal (the subsequent 2–4 h) is glucose. Conversely, during late pregnancy, lipids are used as the maternal energy source, while glucose and amino acids are channeled to the fetus. The pregnant woman shares carbohydrates (her primary energy source in the nonpregnant state) with the fetus during her pregnancy. This dependence on fats as the primary energy source in pregnant women increases towards the latter part of pregnancy

[7]. Thus, using the analogy of the hibernating bear described above, late pregnancy forms the setting for the clinical manifestation of AFLP among pregnant woman with defective fatty acid oxidation.

33.7 Manifestations

The typical presentation of AFLP is a previously healthy woman presenting in the third trimester of pregnancy with a general description of "feeling unwell" and vomiting for the past 4 h. However, some pregnant women may present with signs and symptoms that overlap with pre-eclampsia (hypertension, pedal edema, proteinuria) together with liver dysfunction or hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). Liver function tests may show a mild-to-moderate rise in AST and ALT. Coagulopathy (prolongation of prothrombin time) is seen in almost all these patients. Hypoglycemia and encephalopathy are more rarely seen, as these are late manifestations of severe liver failure.

33.8 Diagnosis

A high index of suspicion is key in making an early diagnosis of AFLP. For a pregnant woman suspected to have AFLP, it is vital to rapidly exclude other potential causes of liver disease, as urgent termination of pregnancy may be required. Any woman with acute liver failure in late pregnancy (third or late second trimester) should therefore be suspected to be suffering from AFLP. Rapid diagnosis of AFLP and urgent termination of pregnancy have improved maternal survival. A recent UK study of 57 women with AFLP reported a case fatality rate of 1.8% and a perinatal mortality rate of 104/1000 births [1].

Once suspicion of AFLP has been raised, it is imperative to rapidly rule out common alternative differential diagnoses. The differential diagnoses to consider are either pregnancy-related liver disorders (HELLP syndrome and pre-eclamptic liver dysfunction) or other illnesses causing acute liver failure unrelated to pregnancy (e.g., acute viral hepatitis or drug-induced hepatitis). Since the infectious causes of acute liver failure that may mimic AFLP are varied (e.g. malaria, dengue, scrub typhus, viral hepatitis), diagnostic testing should be individualized, taking into consideration the epidemiology of the specific locale. Peripheral smear examination for the malaria parasite and serology for acute viral hepatitis A, B, and E are examples of tests that should be considered for diagnosing hepatic illnesses unrelated to pregnancy.

HELLP syndrome (presence of hemolysis-raised lactate dehydrogenase, elevation in aspartate aminotransferase, and thrombocytopenia) and pre-eclampsia (hypertension and proteinuria after 20 weeks of pregnancy) also constitute differential diagnoses. Although in theory these conditions should be simple to diagnose if the signs and symptoms are acknowledged, AFLP patients can often also be misclassified as suffering from HELLP syndrome or pre-eclamptic liver dysfunction. It is therefore difficult to differentiate between these disorders in an emergency setting.

The Swansea clinical criteria for diagnosing AFLP are comprised of 14 criteria including symptoms, laboratory parameters, and radiology and liver biopsy findings [2]. However, most pregnant women with AFLP have coagulopathy and thrombocytopenia (often severe), making it risky to perform a liver biopsy. In addition, the time taken to organize, obtain, and interpret a liver biopsy will delay initiation of management in these critically ill patients. Thus, although a liver biopsy showing microvesicular steatosis is the "gold standard" for diagnosis of AFLP, it is neither warranted nor necessary in the antepartum state. The authors of this chapter have studied the accuracy of the Swansea clinical criteria to predict diffuse hepatic microvesicular steatosis in pregnant women suspected to have AFLP who did undergo liver biopsy (postpartum or postmortem) [32]. Due to coexistent coagulopathy, most of the liver biopsies were performed via the transjugular route. Among 24 pregnant women with suspected AFLP, the negative predictive value for ruling out the presence of diffuse/perivenular microvesicular steatosis of the

liver was 100% using the Swansea clinical criteria [33]. Thus, these clinical criteria are appropriate for diagnosing AFLP in pregnant women. Based on these data, simplified criteria for diagnosing AFLP are proposed. These include (1) the setting of late pregnancy (third or late second trimester of pregnancy); (2) acute liver failure, jaundice with coagulopathy with/without hypoglycemia with/without encephalopathy; and (3) no other explanation for liver failure [34]. Once these simplified criteria are met, the woman should be considered suspect for AFLP and therefore at risk for rapid deterioration. Appropriate management should be rapidly initiated, preferably in an intensive care/high-dependency setting. Supporting this conservative approach is the fact that regardless of whether the cause of liver failure is AFLP, HELLP syndrome, or pre-eclamptic liver dysfunction, the management of liver dysfunction in all three conditions is essentially similar.

33.9 Management of AFLP (Fig. 33.2)

The managment of any woman presenting with jaundice in late pregnancy should be guided by the option that AFLP is the underlying disease.

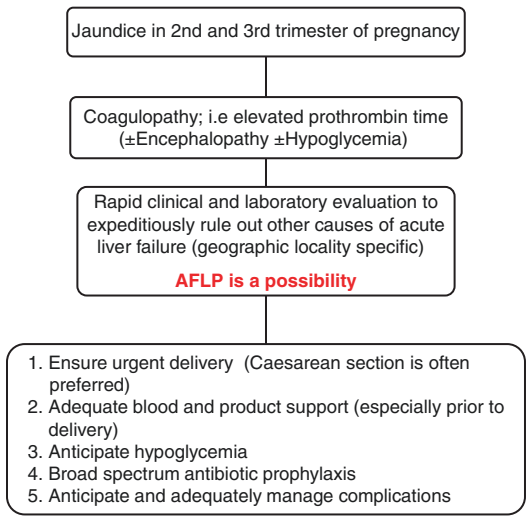


Fig. 33.2 Management algorithm for any woman presenting with jaundice in late pregnancy

The recommended management therefore includes the following steps:

1. Consider AFLP in the differential diagnosis. Quickly rule out alternative diagnoses which may present similarly, using suitable diagnostics as described above.
2. Ensure the availability of a multidisciplinary team, as more than one medical discipline is needed to manage pregnant women with AFLP. Some of these women are likely to need intensive care therapy and may require referral to a specialist liver unit.
3. Absence of specific symptomatology and paucity of laboratory indices make early diagnosis of AFLP difficult, and the mother can be sicker than expected. These patients can potentially develop multi-organ failure with or without sepsis and are likely to need aggressive management including ventilation, hemodynamic support, and dialysis. There should be a low threshold to admitting these mothers to high-dependency or intensive care units for close monitoring. Mothers can also be admitted to the ICU for stabilization and rapid treatment of coagulation abnormalities prior to termination of pregnancy.
4. Urgent delivery is the mainstay of current treatment. It is highly recommended that the patient undergo delivery as soon as feasible (see also the discussion below). AFLP can rapidly worsen (within hours), and there are no reports to date of any AFLP patient surviving without delivery.
5. The pregnant woman with AFLP needs appropriate management of the various complications likely to arise as a result of the disease. The standard recommendations for management of acute liver failure complications (e.g., mannitol for cerebral edema, etc.) remain the same and should be instituted as and when required. See below for greater detail on treatment of complications.
6. Following delivery, the neonate may need to be observed and treated in a neonatal intensive care or high-dependency care unit. We have proposed a management algorithm for patients with suspected AFLP (Fig. 33.2) [5].

33.10 Delivery Considerations

AFLP is a rapidly progressing illness. Poor maternal and fetal outcomes are to be expected if interventions are not performed early. As mentioned previously, in all cases of AFLP, it is of paramount importance to terminate the pregnancy at the earliest possible time. The medical team may be daunted by the prospect of undertaking cesarean delivery in a pregnant woman with AFLP in acute liver failure and coagulopathy, hence the importance of rapid workup and decision-making. As the disease is characterized by temporary shutdown of the liver mitochondria, opting for vaginal delivery in a pregnant women with AFLP can be considered equivalent to making a person who is in systemic energy deficiency run a marathon and should be expected to aggravate the systemic energy deficiency, leading to even more rapid patient deterioration.

A meta-analysis of 78 cohort and 2 case-control studies compared outcomes of cesarean versus vaginal delivery in pregnant women with AFLP. Maternal mortality was reduced 44% with cesarean delivery (relative risk [RR], 0.56 [0.41–0.76]) compared to vaginal delivery, as was the perinatal mortality rate (RR, 0.52 [0.38–0.71]). Maternal morbidity, including complications of liver failure (ascites, encephalopathy, etc.), renal failure, multiple organ failure, infection, or hemorrhage, was not significantly different in women who had cesarean versus vaginal delivery. Neonatal mortality rates (within 1 month after delivery) were unaffected by type of delivery (cesarean versus vaginal) (pooled RR, 0.93 [0.55–1.58]); Table 33.1 [35].

Table 33.1 The outcomes of cesarean versus vaginal delivery in pregnant women with AFLP—based on data from Wang et al. [35]

	Total number of studies	Total number of women included	Pooled unadjusted relative risk (95% CI)
Maternal death	39	517	0.56 (0.41–0.76)
Perinatal death	31	402	0.52 (0.38–0.71)
Neonatal death	19	263	0.93 (0.55–1.58)

Preparations for cesarean delivery in a pregnant woman with AFLP should parallel those for liver transplantation in a patient with acute liver failure. This requires a multidisciplinary and comprehensive approach.

Antibiotic coverage—Following diagnosis, blood should be sampled for cultures. and broad-spectrum prophylactic intravenous antibiotics, especially those covering gram-negative organisms, should be administered.

Correction of coagulation abnormalities—Sufficient blood products need to be prepared, and coagulation abnormalities should be corrected prior to delivery. As it is very difficult to fully normalize coagulation parameters, fresh frozen plasma and cryoprecipitate may be administered based on patient weight while preparing for an urgent delivery. Repeated coagulation parameter testing should not delay delivery.

Preparation for massive hemorrhage—Among six pregnant women with AFLP who underwent urgent termination of pregnancy, the median (range) of packed red cell units transfused was 6.5 (1–27) and of other blood products was 60 units (24–108). All but one woman underwent cesarean delivery, and two also underwent prophylactic bilateral uterine artery ligation. One woman required hysterectomy 2 days after delivery to control postpartum hemorrhage [36].

As massive transfusion is likely during cesarean delivery in these women, preparations should include preparation of an adequate amount of blood products, calcium and magnesium, as well as those items required for correction of hypothermia. Disseminated intravascular coagulation may occur with massive transfusion. In the presence of liver dysfunction, these mothers are also prone to citrate toxicity due to blood transfusions, leading to or exacerbating metabolic acidosis, hypocalcemia, and hypomagnesemia; these can lead to myocardial depression and cardiac arrhythmias. High levels of lactate can also chelate calcium which worsens hypocalcemia. Large-volume rapid transfusion can lead to hypothermia and dilutional coagulopathy. In addition to blood product supplementation, the correction of hypothermia, metabolic acidosis, and hypocalcemia are important cornerstones in the management of coagulopathy.

The use of viscoelastic global assessment of clotting parameters (e.g., thromboelastography) has not been well studied in pregnant women with AFLP but can guide transfusion policy intraoperatively. Postdelivery blood product support is limited to women with active bleeding or those who require additional invasive procedures.

Factor VIIa is a universal procoagulant manufactured using recombinant technology which has been used in various clinical settings. Although its use in postpartum hemorrhage is currently off-label due to reports of an increased risk of thromboembolic complications, it is still being used in some countries to control massive obstetric hemorrhage [37]. This practice is yielding a growing body of literature on the topic. One study demonstrated a significant reduction in blood and blood product requirements among postpartum women with AFLP with no thromboembolic complications, provided that the dose used was less than half that recommended (<45 μg/kg instead of 90 μg/kg) [36]. This short-acting procoagulant may therefore be considered in AFLP patients and is increasingly being used to control postpartum hemorrhage in this population [38].

33.10.1 Intensive Care Treatment

The complications of AFLP may be life-threatening, and many of the complications observed in pregnant women with AFLP require intensive care treatment and monitoring. Some of those most commonly seen are hereby described.

Hemorrhagic complications—Coagulopathy due to liver dysfunction and disseminated coagulopathy can lead to life-threatening hemorrhage before, during, and after delivery. Severe peri- and postpartum hemorrhage, intra-abdominal bleeding, and gastrointestinal bleeding have all been described [39, 40]. Coagulopathy should therefore be monitored using prothrombin time, international normalized ratio (INR), activated partial thromboplastin time, fibrinogen, and fibrin degradation products; abnormalities should be corrected if necessary. As noted above, thromboelastography may be used to guide blood product supplementation.

Similar to the peripartum scenario, should hemorrhage occur, a massive transfusion protocol may need to be activated as a large amount of both blood and blood products may be required. Pancreatitis complicating AFLP may present as hemorrhagic pancreatitis secondary to the coagulopathy [40]. Serum amylase and lipase should therefore be monitored. In general, diagnosis may be difficult in women with altered sensorium.

Hemodynamic instability—Shock may be caused by hypovolemia, bleeding, loss of intravascular volume due to hypoalbuminemia, myocardial depression secondary to metabolic acidosis, electrolyte abnormalities (e.g., hyperkalemia), or sepsis. The use of bedside ultrasonography and echocardiography will help in guiding fluid and inotropic therapy. The choice of resuscitation fluids should be guided by the characteristics of the individual case. Of note, excessive crystalloid use in the presence of hypoalbuminemia (which lowers plasma oncotic pressure) can worsen ascites and peripheral edema and can precipitate or worsen respiratory failure. Albumin may therefore be a better choice for volume resuscitation in these pregnant women.

Renal failure—Renal failure is common in AFLP and can be secondary to shock, hepatorenal syndrome (altered flow dynamics), sepsis, hyperuricemia, and abdominal compartment syndrome [41]. Abdominal compartment syndrome is caused by ascites secondary to hypoproteinemia with low plasma oncotic pressure and portal hypertension. Abdominal paracentesis may be necessary to decrease intra-abdominal pressure. Treatment of renal failure is targeted at the etiology. Renal replacement therapy may also be required (see also Chap. 31). However, renal replacement therapy can be complicated by the presence of coagulopathy. Therefore, decisions regarding access port insertion should be individualized. Continuous renal replacement therapy (CRRT) (see Chap. 31) may provide a more favorable hemodynamic profile and better fluid balance. Intermittent therapies [slow low efficiency dialysis (SLED) or extended daily dialysis (EDD)] are alternatives to consider if cost is a constraining factor. Given the coagulation abnormalities accompanying AFLP, citrate is preferred

for anticoagulation. However, citrate intoxication should be anticipated.

Metabolic complications—The metabolic complications seen with AFLP stem from both the liver failure itself and from the treatment. Metabolic complications include metabolic acidosis, lactic acidosis, and hypoglycemia. Metabolic acidosis may need renal replacement therapy (RRT). Lactic acidosis may not respond to RRT and usually settles once the liver dysfunction improves. Supplementation of thiamine should be considered in these patients. Hypoglycemia is frequent, demanding close monitoring and glucose supplementation as required.

Electrolyte imbalance can be life-threatening. Common electrolyte imbalances are hyperkalemia, hypocalcemia, and hypomagnesemia. The causes of hyperkalemia include metabolic acidosis, renal failure, and multiple blood transfusions. Medical management with beta-2 agonists and glucose insulin infusions may be attempted, but RRT may have to be instituted. Sodium levels as well need to be monitored closely as they can complicate encephalopathy.

Encephalopathy is a common metabolic complication of any liver disease. Encephalopathy may require airway protection with endotracheal intubation. Ventilation should be used to control intracranial pressure (via arterial carbon dioxide pressures) and prevent hypoxemia. The cerebral edema associated with hyperammonemia should be treated with routine measures (see chapter Bilotta). As ammonia is highly diffusible and its clearance is dependent on flow, high-flow CRRT and intermittent hemodialysis can also be used to decrease ammonia levels in extreme cases.

Infection and sepsis—Like other types of liver failure, AFLP is accompanied by immune suppression. Secondary infections may occur, and even fungal infections have been described [42]. Pregnant women with AFLP can develop sepsis and septic shock [43, 44]. Given the pre-existing predisposition to multi-organ dysfunction in AFLP, diagnosis should be prompt, and appropriate antibiotic therapy should rapidly be instituted to prevent additional deterioration.

Nutrition—Provision of nutrition is important in these mothers. Enteral feeding should include a minimal amount of proteins (to prevent the accompanying rise in ammonia levels). If parenteral nutrition is required, aromatic amino acids should be avoided, and branched chain amino acids should instead be provided for the same reason.

Direct treatment of AFLP with plasma exchange—Plasma exchange has been described in women with AFLP after delivery as an adjunct to treatment of multi-organ failure. Case reports suggest that plasma exchange is safe and effective in these women [45–49]. A retrospective analysis of 22 AFLP patients demonstrated a 19% versus 83% survival rate in 16 AFLP patients with standard medical therapy versus 6 AFLP patients with plasma exchange and perfusion as added therapy. The authors suggested that early initiation of plasma exchange and perfusion had a role in halting or reversing the progression of AFLP [50]. As AFLP is uncommon, randomized controlled trials on plasma exchange in this population do not exist, and most case series are rather small. It is difficult to derive meaningful conclusions from the existing literature; hence, plasma exchange currently remains a salvage treatment at most.

Liver rupture and liver transplant—Rupture of liver can be a fatal complication of AFLP and has been described in several cases [41].

There are very few reports of liver transplantation in AFLP [51–53]. Hence, specific listing criteria/indications for liver transplantation for AFLP have not been defined. Women undergoing liver transplantation were usually those in whom the diagnosis and treatment of AFLP were delayed. In this medical emergency, a delay of a few hours can translate to worsening maternal liver failure and its attendant complications. In a report of four AFLP patients who had liver transplantation, the King's College criteria for liver transplantation (used for any patient with acute liver failure) were considered inadequate for predicting the need for liver transplantation in AFLP [53]. The authors noted that the combination of hyperlactatemia and encephalopathy was a better predictor of the need for liver transplantation [53]. Auxiliary liver transplantation may be considered in AFLP patients [52].

33.11 Outcomes: Maternal and Fetal

Maternal Outcomes—Pregnant women with AFLP are expected to show rapid improvement (often within a few days) after delivery. Liver function tends to revert back to normal in most of these women [54]. In addition to delays in delivery, the severity of liver failure (high serum bilirubin, prolonged prothrombin time) and high serum creatinine determine the prognosis in these women [55–57]. With rapid diagnosis and urgent delivery, the authors of this chapter have noted a steady decline in the contribution of AFLP (and other pregnancy-related liver disorders) to maternal mortality in their practice [5]. Similar results have been replicated across various studies [1, 58], and the maternal mortality due to pregnancy-related severe liver disorders (including AFLP) is now expected to be <10% [23].

Increased awareness of AFLP among obstetricians as well as emergency/acute medicine physicians has led to early recognition of AFLP at medical centers with subsequently improving maternal outcomes. A woman suspected to have AFLP is categorized as "high risk." This leads to institution of a management protocol derived in consultation with the different specialties involved. In an audit of the treatment of woman with biopsy-proven AFLP (n = 17), nine underwent cesarean delivery, and most (n = 12) women delivered within 24 h of hospital admission. The median delay between the onset of symptoms to delivery was 5 days. With this active management, only two (12%) mothers died. The average length of stay in hospital in these women was 11 ± 4 days, and 18 ± 15 blood products were required per patient. The 15 women who survived showed a steady improvement in liver dysfunction with a normalization in coagulopathy in the majority by the 10th day postpartum (authors' unpublished data).

Fetal Outcomes—Stillbirths and abortion are more common in mothers with AFLP [23]. Fetal outcomes remain dismal, despite the steady improvement in maternal outcome. Ensuring an adequate supply of glucose to the fetus by providing sufficient and appropriate nutrition to the mother is currently the only suggestion that may be made to positively affect fetal outcome.

The neonatal presentation of fatty acid oxidation disorders includes hypoketotic hypoglycemia [14], hepatic failure, metabolic acidosis, and cardiomyopathy. Later presentations include episodic myopathy, neuropathy, retinopathy, and arrhythmias. Growth restriction and premature births occur in babies with fatty acid oxidation defects delivered by mothers who had AFLP [59].

33.12 Conclusion

Acute fatty liver of pregnancy (AFLP) is an uncommon, severe liver disorder leading to liver failure in women in late pregnancy. Increasingly, it is being recognized as an important preventable cause of maternal death.

Better understanding of pathogenesis, early diagnosis followed by rapid delivery of the fetus, and better supportive multi-disciplinary intensive management have led to improvement in maternal mortality secondary to AFLP.

Ensuring an adequate supply of glucose to the mother, and hence to the fetus, may improve the hitherto dismal fetal outcome.

Acknowledgment We wish to thank Ms. Silvia for the artwork.

References

1. Knight M, Nelson-Piercy C, Kurinczuk JJ, Spark P, Brocklehurst P, UK Obstetric Surveillance System. A prospective national study of acute fatty liver of pregnancy in the UK. Gut. 2008;57:951–6.
2. Ch'ng CL, Morgan M, Hainsworth I, Kingham JG. Prospective study of liver dysfunction in pregnancy in Southwest Wales. Gut. 2002;51(6):876–80.
3. Solanke D, Rathi C, Pandey V, Patil M, Phadke A, Sawant P. Etiology, clinical profile, and outcome of liver disease in pregnancy with predictors of maternal mortality: a prospective study from Western India. Indian J Gastroenterol. 2016;35:450–8.
4. Bhatia V, Singhal A, Panda SK, Acharya SK. A 20-year single-center experience with acute liver

failure during pregnancy: is the prognosis really worse? Hepatology. 2008;48:1577–85.
5. Goel A, Jamwal KD, Ramachandran A, Balasubramanian KA, Eapen CE. Pregnancy-related liver disorders. J Clin Exp Hepatol. 2014;4:151–62.
6. Tysen P. Bear essentials of hibernation. NOVA; 2000. http://www.pbs.org/wgbh/nova/nature/bear-essentials-of-hibernation.html. Last Accessed 6 Jun 2018.
7. Butte NF. Carbohydrate and lipid metabolism in pregnancy: normal compared with gestational diabetes mellitus. Am J Clin Nutr. 2000;71:1256S–61S.
8. Rolfes DB, Ishak KG. Acute fatty liver of pregnancy: a clinicopathologic study of 35 cases. Hepatology. 1985;5:1149–58.
9. Eapen CE, Ramakrishna B, Jose R, Loganathan G, Chandy G. Liver failure during pregnancy. Gut. 2008;57:83.
10. Schoeman MN, Batey RG, Wilcken B. Recurrent acute fatty liver of pregnancy associated with a fatty-acid oxidation defect in the offspring. Gastroenterology. 1991;100:544–8.
11. Browning MF, Levy HL, Wilkins-Haug LE, Larson C, Shih VE. Fetal fatty acid oxidation defects and maternal liver disease in pregnancy. Obstet Gynecol. 2006;107:115–20.
12. Kobayashi T, Minami S, Mitani A, Tanizaki Y, Booka M, Okutani T, Yamaguchi S, Ino K. Acute fatty liver of pregnancy associated with fetal mitochondrial trifunctional protein deficiency. J Obstet Gynaecol Res. 2015;41:799–802.
13. Lamireau D, Feghali H, Redonnet-Vernhet I, Mesli S, Carles D, Brissaud O. Acute fatty liver in pregnancy: revealing fetal fatty acid oxidation disorders. Arch Pediatr. 2012;19:277–81.
14. Gutiérrez Junquera C, Balmaseda E, Gil E, Martínez A, Sorli M, Cuartero I, Merinero B, Ugarte M. Acute fatty liver of pregnancy and neonatal long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) deficiency. Eur J Pediatr. 2009;168:103–6.
15. Treem WR, Rinaldo P, Hale DE, Stanley CA, Millington DS, Hyams JS, Jackson S, Turnbull DM. Acute fatty liver of pregnancy and long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency. Hepatology. 1994;19:339–45.
16. Santos L, Patterson A, Moreea SM, Lippiatt CM, Walter J, Henderson M. Acute liver failure in pregnancy associated with maternal MCAD deficiency. J Inherit Metab Dis. 2007;30:103.
17. Samuel R, Eapen CE, Pulimood A, Jose R, Kurian G. Acute fatty liver of pregnancy occurring in a woman on long term aspirin. J Gastroenterol Hepatol. 2004;19:A809.
18. Innes AM, Seargeant LE, Balachandra K, Roe CR, Wanders RJ, Ruiter JP, Casiro O, Grewar DA, Greenberg CR. Hepatic carnitine palmitoyltransferase I deficiency presenting as maternal illness in pregnancy. Pediatr Res. 2000;47:43–5.
19. Eskelin PM, Laitinen KA, Tyni TA. Elevated hydroxyacylcarnitines in a carrier of LCHAD deficiency during acute liver disease of pregnancy—a common feature of the pregnancy complication? Mol Genet Metab. 2010;100:204–6.
20. Tan AC, van Krieken JH, Peters WH, Steegers EA. Acute fatty liver in pregnancy. Neth J Med. 2002;60:370–3.
21. Kong XF, Zhang XX, Yu YY, Shi Q, La DD, Zhu-Ge CD, Deng L, Gong QM, Shen BY, Peng CH, Li HW. No mutation was found in the alpha-subunit of the mitochondrial tri-functional protein in one patient with severe acute fatty liver of pregnancy and her relatives. J Gastroenterol Hepatol. 2007;22:2107–11.
22. Raghupathy V, Goel A, Thangaraj KR, Eapen CE, Balasubramanian KA, Regi A, Jose R, Benjamin SJ, Ramachandran A. Absence of G1528C mutation in long-chain 3-hydroxyacyl-CoA dehydrogenase in four Indian patients with pregnancy-related liver disease. Indian J Gastroenterol. 2014;33:387–9.
23. Liu J, Ghaziani TT, Wolf JL. Acute fatty liver disease of pregnancy: updates in pathogenesis, diagnosis, and management. Am J Gastroenterol. 2017;112:838–46.
24. Uppala R, Dudiak B, Beck ME, Bharathi SS, Zhang Y, Stolz DB, Goetzman ES. Aspirin increases mitochondrial fatty acid oxidation. Biochem Biophys Res Commun. 2017;482:346–51.
25. Rolnik DL, Wright D, Poon LC, O'Gorman N, Syngelaki A, de Paco MC, Akolekar R, Cicero S, Janga D, Singh M, Molina FS, Persico N, Jani JC, Plasencia W, Papaioannou G, Tenenbaum-Gavish K, Meiri H, Gizurarson S, Maclagan K, Nicolaides KH. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. NEJM. 2017;377:613–22.
26. Baldwin GS. Do NSAIDs contribute to acute fatty liver of pregnancy? Med Hypotheses. 2000;54:846–9.
27. Saygan-Karamürsel B, Kizilkiliç-Parlakgümüş A, Deren O, Onderoğlu L, Durukan T. Acute fatty liver of pregnancy after aspirin intake. J Matern Fetal Neonatal Med. 2004;16:65–6.
28. Natarajan SK, Thangaraj KR, Goel A, Eapen CE, Balasubramanian KA, Ramachandran A. Acute fatty liver of pregnancy: an update on mechanisms. Obstet Med. 2011;4:99–103.
29. Rakheja D, Bennett MJ, Foster BM, Domiati-Saad R, Rogers BB. Evidence for fatty acid oxidation in human placenta, and the relationship of fatty acid oxidation enzyme activities with gestational age. Placenta. 2002;23:447–50.
30. Natarajan SK, Eapen CE, Pulimood AB, Balasubramanian KA. Oxidative stress in experimental liver microvesicular steatosis: role of mitochondria and peroxisomes. J Gastroenterol Hepatol. 2006;21:1240–9.
31. Natarajan SK, Thangaraj KR, Eapen CE, Ramachandran A, Mukhopadhya A, Mathai M, Seshadri L, Peedikayil A, Ramakrishna B, Balasubramanian KA. Liver injury in acute fatty liver of pregnancy: possible link to placental mitochondrial dysfunction and oxidative stress. Hepatology. 2010;51:191–200.
32. Zachariah U, Goel A, Balasubramanian KA, Eapen CE. The hibernating bear-a good analogy to explain

why acute fatty liver of pregnancy manifests in late pregnancy. Am J Gastroenterol. 2018;113:307–8.
33. Goel A, Ramakrishna B, Zachariah U, Ramachandran J, Eapen CE, Kurian G, Chandy G. How accurate are the Swansea criteria to diagnose acute fatty liver of pregnancy in predicting hepatic microvesicular steatosis? Gut. 2011;60:138–9.
34. Goel A, Ramakrishna B, Madhu K, Zacharaiah U, Eapen CE, Chandy G. Simplified diagnostic criteria for acute fatty liver of pregnancy. J Gastroenterol Hepatol. 2010;25:A113. https://onlinelibrary.wiley.com/doi/epdf/10.1111/j.1440-1746.2009.06464.x. Last Accessed 31 Jul 2018.
35. Wang HY, Jiang Q, Shi H, Xu YQ, Shi AC, Sun YL, Li J, Ning Q, Shen GX. Effect of caesarean section on maternal and foetal outcomes in acute fatty liver of pregnancy: a systematic review and meta-analysis. Sci Rep. 2016;6:28826.
36. Goel A, Nair SC, Viswabandya A, Masilamani VP, Rao SV, George A, Regi A, Jose R, Zachariah U, Subramani K, Eapen CE, Chandy G. Preliminary experience with use of recombinant activated factor VII to control postpartum hemorrhage in acute fatty liver of pregnancy and other pregnancy-related liver disorders. Indian J Gastroenterol. 2013;32:268–71.
37. Welsh A, McLintock C, Gatt S, Somerset D, Popham P, Ogle R. Guidelines for the use of recombinant activated factor VII in massive obstetric haemorrhage. Aust N Z J Obstet Gynaecol. 2008;48:12–6.
38. Supriya K, Thunga S, Narayanan A, Singh P. Recombinant activated factor VII in the management of acute fatty liver of pregnancy: a case report. J Obstet Gynaecol Res. 2015;41:1122–5.
39. Riely CA, Latham PS, Romero R, Duffy TP. Acute fatty liver of pregnancy. A reassessment based on observations in nine patients. Ann Intern Med. 1987;106:703–6.
40. Moldenhauer JS, O'brien JM, Barton JR, Sibai B. Acute fatty liver of pregnancy associated with pancreatitis: a life-threatening complication. Am J Obstet Gynecol. 2004;190(2):502–5.
41. Minuk GY, Lui RC, Kelly JK. Rupture of the liver associated with acute fatty liver of pregnancy. Am J Gastroenterol. 1987;82:457–60.
42. Goel A, Rao SV, Mathews MS, George A, Kurien M, Amritanand A, Masilamani VP, Zachariah U, Eapen CE. Rhino-orbital zygomycosis in a patient with pregnancy related liver disease and multi-organ failure. Indian J Gastroenterol. 2011;30:49–50.
43. Ko HH, Yoshida E. Acute fatty liver of pregnancy. Can J Gastroenterol. 2006;20:25–30.
44. Ranjan V, Smith NC. Acute fatty liver of pregnancy. J Obstet Gynaecol. 1997;17:285–6.
45. Martin JN Jr, Briery CM, Rose CH, Owens MT, Bofill JA, Files JC. Postpartum plasma exchange as adjunctive therapy for severe acute fatty liver of pregnancy. J Clin Apher. 2008;23:138–43.
46. Chu YF, Meng M, Zeng J, Zhou HY, Jiang JJ, Ren HS, Zhang JC, Zhu WY, Wang CT. Effectiveness of combining plasma exchange with continuous hemodiafiltration on acute fatty liver of pregnancy complicated by multiple organ dysfunction. Artif Organs. 2012;36:530–4.
47. Yu CB, Chen JJ, Du WB, Chen P, Huang JR, Chen YM, Cao HC, Li LJ. Effects of plasma exchange combined with continuous renal replacement therapy on acute fatty liver of pregnancy. Hepatobiliary Pancreat Dis Int. 2014;13:179–83.
48. Jin F, Cao M, Bai Y, Zhang Y, Yang Y, Zhang B. Therapeutic effects of plasma exchange for the treatment of 39 patients with acute fatty liver of pregnancy. Discov Med. 2012;13:369–73.
49. Seyyed Majidi MR, Vafaeimanesh J. Plasmapheresis in acute fatty liver of pregnancy: an effective treatment. Case Rep Obstet Gynecol. 2013;2013:615975.
50. Ding J, Han LP, Lou XP, Geng LN, Liu D, Yang Q, Gao S. Effectiveness of combining plasma exchange with plasma perfusion in acute fatty liver of pregnancy: a retrospective analysis. Gynecol Obstet Investig. 2015;79:97–100.
51. Remiszewski P, Pawlak J, Skwarek A, Grzelak I, Patkowski W, Grodzicki M, Krawczyk M, Giercuszkiewicz D, Podciechowski L, Wilczyński J. Orthotopic liver transplantation for acute liver failure resulting from "acute fatty liver of pregnancy". Ann Transplant. 2003;8:8–11.
52. Ringers J, Bloemenkamp K, Francisco N, Blok JJ, Arbous MS, van Hoek B. Auxiliary or orthotopic liver transplantation for acute fatty liver of pregnancy: case series and review of the literature. BJOG. 2016;123:1394–8.
53. Westbrook RH, Yeoman AD, Joshi D, Heaton ND, Quaglia A, O'Grady JG, Auzinger G, Bernal W, Heneghan MA, Wendon JA. Outcomes of severe pregnancy-related liver disease: refining the role of transplantation. Am J Transplant. 2010;10:2520–6.
54. Xiong HF, Liu JY, Guo LM, Li XW. Acute fatty liver of pregnancy: over six months follow-up study of twenty-five patients. World J Gastroenterol. 2015;21:1927–31.
55. Zhang YP, Kong WQ, Zhou SP, Gong YH, Zhou R. Acute fatty liver of pregnancy: a retrospective analysis of 56 cases. Chin Med J. 2016;129:1208–14.
56. Meng J, Wang S, Gu Y, Lv H, Jiang J, Wang X. Prenatal predictors in postpartum recovery for acute fatty liver of pregnancy: experiences at a tertiary referral center. Arch Gynecol Obstet. 2016;293:1185–91.
57. Gao Q, Qu X, Chen X, Zhang J, Liu F, Tian S, Wang C. Outcome and risk factors of patients with acute fatty liver of pregnancy: a multicenter retrospective study. Singapore Med J. 2018;59(8):425–30. https://doi.org/10.11622/smedj.2018001.
58. Fesenmeier MF, Coppage KH, Lambers DS, Barton JR, Sibai BM. Acute fatty liver of pregnancy in 3 tertiary care centers. Am J Obstet Gynecol. 2005;192:1416–9.
59. Tyni T, Ekholm E, Pihko H. Pregnancy complications are frequent in long-chain 3-hydroxyacyl-coenzyme a dehydrogenase deficiency. Am J Obstet Gynecol. 1998;178:603–8.

Part X

Surgical Dilemmas in Critically Ill Women

Trauma During Pregnancy

34

Hen Y. Sela and Misgav Rottenstreich

Bullet Points

- During routine antenatal care, all pregnant women should be screened for intimate partner violence (IPV) and educated about the proper use of seat belts as well as about the risk of falling.
- All injured women of childbearing age should be screened for pregnancy upon assessment in the emergency department.
- All injured pregnant women should be screened for intimate partner violence (IPV); certain injuries should increase the suspicion for IPV.
- Severely injured pregnant woman should be screened for use of alcohol and drugs.
- Maternal health takes priority over fetal health even when gestational age is greater than 23–24 weeks.
- ATLS primary and secondary surveys should be performed prior to assessment of fetal well-being.
- Adaptations made to the ATLS guidelines include early oxygen supplementation, insertion of intravenous access in the upper limbs, and, after 20 weeks of gestation, either maternal left lateral tilt or uterine displacement to the left.
- Fetal assessment should begin after maternal stabilization and should include fetal heart rate assessment for 2–6 h and, when indicated, admission for longer periods of time.
- Obstetrical ultrasound is an adjunct tool that assists in identifying the number of fetuses, gestational age, and fetal well-being; however, its use for detecting placental abruption is discouraged.
- When maternal condition mandates radiographic examinations and/or computed tomography, neither should be postponed nor delayed.
- If cardiac arrest occurs in an injured pregnant woman, perimortem cesarean delivery (PMCD) should be initiated within 4 min of initiation of resuscitation efforts. However, PMCD should only be provided if the gestational age is greater than 20 weeks and there is no return of spontaneous circulation.
- Adverse fetal outcome may extend beyond the admission immediately following trauma.

H. Y. Sela (✉) · M. Rottenstreich
Department of Obstetrics and Gynecology, Shaare Zedek Medical Center in Jerusalem, Hebrew University School of Medicine, Jerusalem, Israel
e-mail: hysela@szmc.org.il; misgavr@gmail.com

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_34

34.1 Introduction

Trauma is the leading cause of non-obstetric maternal death [1] and is thought to complicate up to 8% of all pregnancies [2–4]. Motor vehicle accidents and domestic partner violence are the most frequent causes of major maternal trauma. Other causes include falls, homicide, penetrating trauma, suicide, toxic exposure, and burns [5].

The complexity of managing two endangered lives simultaneously requires a coordinated multidisciplinary effort [6–8]. Furthermore, severe injury is associated with adverse maternal and fetal/neonatal outcomes [9], but obstetric complications may also occur with less severe injuries.

34.2 The Unique Physiology of Pregnancy

Widespread functional and anatomical changes occur during normal pregnancy. These are described in detail throughout this book. In the trauma setting, knowledge of these changes is crucial for discriminating between normal and abnormal clinical and laboratory findings. The following section will review the changes most relevant to trauma management of the pregnant woman in accordance with the sequence recommended in the trauma management algorithm.

Airway maintenance and cervical spine protection—All pregnant women are considered at high risk for difficulty in airway management. Rapid weight gain accompanied by respiratory tract soft tissue edema and mucosal congestion poses clinical challenges when urgent establishment of a safe airway is necessary [10]. Obstetric patients have a higher rate of difficult laryngoscopy (1.6%) compared with non-obstetric patients (0.5%), $p = 0.023$ [11]. This situation is compounded by the high risk of gastric aspiration due to increased intraabdominal pressure and decreased lower esophageal sphincter tone.

Breathing and ventilation—Pregnant women develop hypoxemia and desaturation more rapidly than nonpregnant woman. Several causes underlie these ventilation changes. Oxygen consumption increases by about 35% [12]. Diaphragmatic rise, widening of the subcostal angle, and an increase in the transverse diameter of the thoracic cage lead to a reduction in functional residual capacity and residual volume [13, 14]. From the first trimester of pregnancy, minute ventilation increases from the nonpregnancy values by about 30% and remains stable at these values thereafter [14, 15]. At the same time, tidal volume and respiratory drive increase, thereby potentially causing hyperventilation and chronic respiratory alkalosis [14].

Circulation and hemorrhage control—Maternal heart rate, blood pressure, hemoglobin and platelet levels, and coagulation differ somewhat from those of nonpregnant women; this may lead to normal vital signs up until a class 3 shock appears, whereupon rapid maternal deterioration will likely occur [16]. Systemic vascular resistance decreases gradually from 8 weeks of gestation, resulting in a decrease in mean blood pressure of 10–15 mmHg and an increase in pulse rate of 15–20 beats per minute. As a result, cardiac output (CO) increases until the third trimester, when it plateaus at approximately 50% above baseline [17–19].

At the end of the first trimester of pregnancy, plasma volume has expanded by approximately 15% [20]. The peak increase in plasma volume (by approximately 50%) is accompanied by a lesser increase in total red cell mass (20–30%) resulting in hemodilution [21]. This leads to normal hemoglobin levels in the second and third trimester of 10.5 g/dL and 11 g/dL, respectively [22].

A decrease in thrombocytes to about 150,000/mm^3 is often observed in pregnancy. More severe thrombocytopenia may occur in 5% of pregnant women at term and is still considered normal [23]. The leukocyte count increases to 12,200/mm^3 in the second trimester and to 20,000/mm^3 in the third trimester [22]. Fibrinogen levels also rise during pregnancy (350–600 mg/dL during the third trimester) [24, 25]. The transfusion goals for fibrinogen, platelets, and hemoglobin are likely different in pregnant women, but these have yet to be defined [26, 27],

34.2.1 Additional Anatomical Considerations

The presence of the enlarged uterus should be taken into consideration when treating the pregnant woman after trauma. The size of the uterus provides information not only regarding fetal viability but also about potential effects on maternal hemodynamic parameters.

Uterine blood flow increases to approximately 600 mL/min in the third trimester; thus traumatic bleeding from the uterus in the third trimester can cause rapid exsanguination.

Since gestational age may impact critical decisions, accurate determination is of utmost importance in the setting of trauma. For example, the gestational age may determine the need to perform perimortem cesarean delivery (PMCD). Figure 34.1 describes the method of approximating gestational age in the pregnant woman after trauma.

Supine positioning is usually advocated for treatment of trauma patients. From the late second trimester and onward, supine positioning may be associated both with a decrease in venous return and reflex tachycardia. Despite the physiological attempt to correct cardiac output with both increased heart rate and blood volume during pregnancy, cardiac output may decrease in some women [28], leading to hypotension [29]. Whether the preferred position remains supine for the injured pregnant woman should therefore be determined on a case-by-case basis (see below in primary survey).

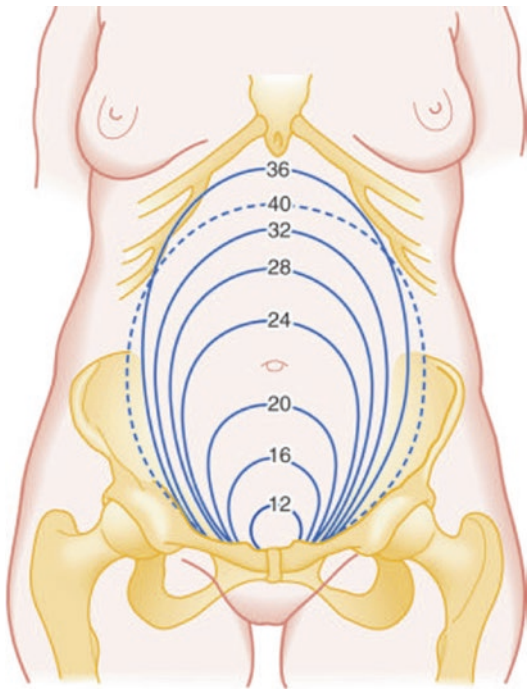


Fig. 34.1 Clinical assessment of gestational age

34.3 The Epidemiology of Trauma in Pregnancy

Approximately 5–8% of all pregnancies are complicated by trauma [2–4]. The most frequent causes of injury in pregnancy are motor vehicle accident (MVAs) or falls; most studies report MVAs as the most common mechanism [30–35], while others report falls [36] . This may be related to the populations being studied, the trimester of injury, and the source of data [e.g., information derived from hospital admission vs. visits to the department of emergency medicine (ED)]. The reported incidence of injury by type of trauma during pregnancy and in the general population is described in Table 34.1.

Table 34.1 Estimated incidence of injury by type of trauma [5]

Mechanism of injury	During pregnancy	Outside of pregnancy
Domestic violence	8307/100,000 live births	5239/100,000 women
Motor vehicle crashes	207/100,000 live births	1104/100,000 women
Falls and slips	48.9/100,000 live births	3029/100,000 women
Toxic exposure	25.8/100,000 person-years	115.3/100,000 person-years
Penetrating trauma	3.27/100,000 live births	3.4/100,000 women
Homicide	2.9/100,000 live births	2.3/100,000 women
Suicide	2/100,000 live births	8.8/100,000 population
Burns	0.17/100,000 person-years	2.6/100,000 person-years

Data from the USA Nationwide Inpatient Sample (across 35 states, approximately 87% of all admissions) showed that the rate of injury hospitalizations of pregnant women was 4.1/1000 deliveries. The rate of assault in this study was 5% for delivered and 10% for non-delivered pregnant women. Hence, a high index of suspicion regarding the option of domestic violence should be maintained when treating pregnant women after trauma.

Severity of injury: Fortunately, most trauma incidents during pregnancy result in minor injury. In one report, 41.2% of pregnant women arriving to the ED after trauma were barely injured [ISS (injury severity score) 0] [37]. The rate of severe maternal injury (ISS >8) varies in different reports between 9.2 and 73.0%. This extreme variability does not differ from the nonpregnant population [30, 31, 36, 37] and probably stems from differences in case mix and denominator (population-based data vs. ED arrivals vs. hospital admissions). Among pregnant women who are admitted to the hospital, severe maternal injury is more common with MVAs (31%) in comparison to falls (0%) or assaults (22%) [37]. A population-based study from Sweden reported that 1% (15/1721) of the women involved in an MVA sustained fatal injuries, 15% (251/1721) sustained a major injury, 85% (1455/1721) sustained minor injuries, and another 549 were not injured at all [32].

Maternal mortality associated with trauma: Worldwide, trauma is a major cause of maternal death during pregnancy. In Sweden, the rate of maternal death from MVA is 6:1000 among MVAs and 1.4:100,000 pregnancies [32]. In Canada, the rate of maternal death due to MVA was similar, 1.5:100,000 pregnancies [38]. Smaller studies, which include more select pregnant populations (e.g., women admitted to Level I trauma centers; women with penetrating trauma), report higher maternal mortality rates of 2–7% [30, 39]. A recent population-based study from Japan reported that trauma was a cause of maternal mortality in 5% of all maternal deaths (10/213) [40]. Maternal mortality is higher with severe trauma (ISS $\geq$ 8) than with minor trauma (ISS < 9) (6% vs. 0%) [41].

Maternal mortality is particularly high when cesarean delivery was required during the index trauma admission. A study of all consecutive maternal trauma admissions during an 8-year period (1986–1994, nine Level I trauma centers in the USA) found that among 441 cases, 32 underwent emergency cesarean delivery. These women were in critical condition as evidenced by the mean maternal ISS which was 25. In this context, maternal mortality was 28% [39].

Maternal trauma as a cause for intensive care unit admission: Maternal ICU admission occurs in approximately 1 in 300 pregnancies [42]. However, the most common reasons for ICU admission are major obstetric hemorrhage, hypertensive disorders of pregnancy, and maternal sepsis [43, 44].

34.4 Initial Management of Maternal Trauma

The following section will discuss prevention, general management at the time of ED arrival, performance of the primary and secondary surveys in pregnant women, and initial fetal assessment.

Prevention: The reported rate of seatbelt use among pregnant women remains lower than expected, likely due to concerns regarding possible fetal injury by the belt. Lack of—or improper use of—seat belts is unequivocally associated with increased maternal and fetal mortality and morbidity [33, 34, 37, 45–50]. Conversely, wearing a seat belt while pregnant has been demonstrated in simulations to reduce pressure exerted on the abdomen during impact in an MVA [51]. Benjamin Franklin famously wrote, "an ounce of prevention is worth a pound of cure." The National Highway Traffic Safety Administration and the American College of Obstetricians and Gynecologists (ACOG) recommend that pregnant women use lap and shoulder seat belts [52, 53]. The restraint probably prevents contact between the abdomen and the steering wheel. Wearing a seat belt while pregnant reduces the risk of both maternal and fetal mortality and morbidity in the setting of MVAs according to a study

performed on crash test dummies as well as in several single-center studies [35, 51, 54]. In the context of critical care, the injuries sustained during an MVA differ when the casualty has worn a seatbelt or not. Information regarding seatbelt use is therefore prerequisite when treating the injured pregnant woman. Furthermore, knowledge of the different patterns of injury is important for early detection and treatment of life-threatening maternal injuries.

General management after ED arrival: The general principles of care following ED arrival include trauma team activation (TTA), performance of a pregnancy workup, and a toxicology workup, eliciting the mechanism of injury and multidisciplinary care. Figure 34.2 outlines the

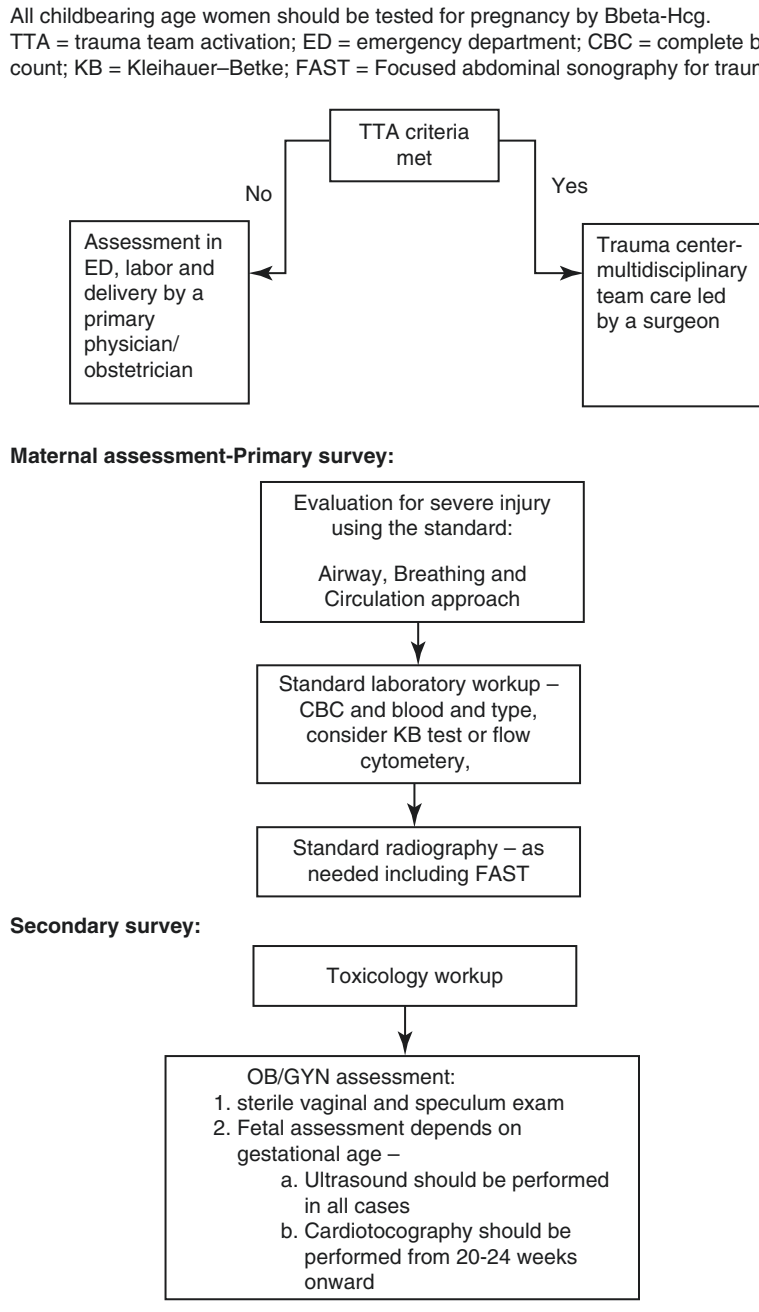


Fig. 34.2 Flowchart of maternal and fetal assessment following maternal trauma. Author Hen Y Sela. All childbearing age women should be tested for pregnancy by beta-HCG. *TTA* trauma team activation, *ED* emergency department, *CBC* complete blood count, *KB* Kleihauer-Betke, *FAST* focused abdominal sonography for trauma

Table 34.2 Minimum criteria for trauma team activation according to the American College of Surgeons

1	Systolic blood pressure less than 90 in adults and hypotension in children
2	Gunshot wounds to the neck, chest, or abdomen or extremities proximal to the elbow/knee
3	Glasgow coma scale score less than nine attributed to trauma
4	Intubated patients transferred from the scene
5	Patients who have respiratory compromise or are in need of an emergent airway
6	Emergency physician's discretion

flowchart of assessment when maternal trauma occurs.

In 2011, the National Expert Panel on Field Triage suggested that when injury occurs during pregnancy, a gestational age exceeding 20 weeks is sufficient for considering transport to a trauma center [55]. Since this declaration, several studies that assessed whether pregnancy alone justifies trauma team activation have shown that with such practice, most women transferred to trauma centers had lower ISSs than those who met other TTA criteria and did not require immediate operative intervention [56, 57]. Consequentially, when the American College of Surgeons (ACS) published an instructive tool in 2014 regarding resources for optimal care of the injured patient, pregnancy was not defined as a criterion for TTA [58]. Accordingly, TTA should be reserved for pregnant women who meet general TTA criteria; these criteria are detailed in Table 34.2.

All women of childbearing age injured during pregnancy should undergo pregnancy testing when arriving to the ED. One study demonstrated that 8% of women who were admitted due to trauma had a surprise positive pregnancy test [59].

All pregnant women who arrive to the ED after trauma should also undergo testing for alcohol and illicit drug levels. In the general population, the pooled rate of positive alcohol and illicit drug tests may be as high as 42% among severely injured patients (6% among non-severely injured patients) [60]. Studies of pregnancy-related traumas report that 12.9% are associated with the use of alcohol and 19.6% with illicit drug use [61].

Both the ACOG and the ACS recommend that all women of childbearing age be screened for intimate partner violence (IPV) during pregnancy [6, 61–63]. Repeated ED visits for trauma and/or a vague or inconsistent story regarding the circumstances of the trauma should raise suspicion of IPV. Other known risk factors for IPV include low socioeconomic and education statuses, substance abuse, unintended pregnancy, and a history of IPV in previous close relationships [61–63]. Pregnant women who have been identified as high risk for IPV should be appropriately referred [64].

A systematic and multidisciplinary approach is required for optimizing management of maternal trauma. The injured pregnant patient should be assessed as if she were not pregnant [6]. There is clear consensus that maternal health takes priority over interventions for the fetus. Therefore, the injured pregnant woman should undergo a primary and secondary survey and only then should attention be given to fetal evaluation.

34.4.1 The Primary and Secondary Survey

Treating the injured pregnant woman appropriately is beneficial for both the mother and the fetus. Guidelines addressing the management of pregnant women involved in trauma were last published by the ACOG in 1998 [8], by the ACS (ATLS) in 2012 [6], and by the Society of Obstetricians and Gynaecologists of Canada (SOGC) in 2015 [7]. Of note, both the ACOG and the SOGC have endorsed ATLS guidelines for treating injured pregnant women. These guidelines provide a systematic, concise approach to the care of trauma patients that has been shown to improve patient outcomes [65, 66].

The primary survey should therefore include evaluation for severe maternal injury using the standard airway, breathing, and circulation approach. Reduced maternal oxygen reserves and increased oxygen consumption should lower the threshold for administration of supplemental oxygen. Given the possibility of reduced venous return, intravenous access should, if possible, be obtained above the diaphragm. In order to avoid supine hypotension, women with a gesta-

tional age exceeding 20 weeks should either be tilted approximately 15° to the left or their uterus should be displaced manually to the left.

Laboratory investigation of the injured pregnant woman should follow the standard trauma protocol, including complete blood counts and type and screen [6].

A recent study from Australia demonstrated that only 19% of high risk MVA obstetric patients underwent appropriate imaging studies [67]. Efforts to decrease exposure of the injured pregnant woman to radiation should not manifest as nonperformance of tests when indicated. Instead, the clinician should apply critical thinking with regard to the indications for each test and the yield of alternative modes of imaging. When maternal benefit mandates performance of standard radiography or computed tomography tests, neither should be delayed. Therefore, the imaging adjuncts recommended by the ACS (ATLS) as part of the primary survey (i.e., plain radiographs of the cervical spine, chest, and pelvis) should not be withheld from the injured pregnant woman when indicated. Imaging should be performed according to routine indications [6–8]. Focused abdominal sonography for trauma (FAST) should be applied when possible (See also Chap. 13). FAST has been shown to be as accurate in pregnant women as it is in nonpregnant populations [68–70].

The secondary survey requires that the injured pregnant woman undergo a thorough physical examination and additional imaging as required. One may reduce fetal exposure to ionizing radiation during regular x-rays by using a posterior-anterior approach. This approach increases the distance of the radiation source from the anterior uterus. During computed tomography, slice thickness may be increased (thereby reducing the number of slices performed), and current may be reduced or pitch increased. Lead apron shielding may also be used [71, 72].

Only after the primary and secondary surveys have been completed should the pregnant women also undergo an obstetric workup. The obstetric workup includes examination of the entire body for bruising, examination of the abdomen for signs and symptoms of peritoneal irritation, palpation of the uterus to diagnose tenderness and the frequency of contractions, a sterile vaginal examination to determine the degree of cervical dilation and effacement, and a sterile examination with a speculum to directly visualize possible trauma, assess whether vaginal fluid is present, and ascertain its source.

The quality of maternal trauma care after an MVA may be poorer than expected due to the distracting presence of the fetus [73, 74]. Maternal and fetal survival relies on maternal well-being. Therefore, maternal care should take priority over assessment of fetal condition. Fetal assessment should be withheld until both primary and secondary surveys of the injured pregnant woman have been completed.

34.4.2 Fetal Assessment

Fetal assessment should be initiated immediately following maternal stabilization, if not simultaneously. An important benefit of fetal assessment is that it may provide an early indirect indication of impending maternal decompensation (e.g., hypoxemia, hypovolemia).

Fetal evaluation depends on gestational age. The fetus is considered viable at gestational age above 23–24 weeks. Following maternal stabilization, uterine activity should be monitored for signs of placental abruption or preterm labor; this is usually performed when gestational age is greater than 20–24 weeks. Both ultrasound and cardiotocography (CTG) have roles in assessing fetal and maternal status following maternal trauma and are complementary to each other. Table 34.3 compares advantages and disadvantages of cardiotocography, which records fetal heart rate and uterine contractions and ultrasound during pregnancy. Ultrasound may aid in detecting the number of fetuses, ascertaining viability and gestational age, locating the placenta and excluding placenta previa, assessing fetal well-being, and measuring cervical length as a screening tool for preterm labor [7]. Placental abruption may occur shortly during or after physical trauma [39, 75]. Ultrasonography has only a 24% sensitivity versus a 96% specificity for detecting placental abruption and is therefore not the preferred

Table 34.3 Advantages and disadvantages of cardiotocography and ultrasound for assessment of maternal and fetal condition following trauma

	Cardiotocography	Ultrasound
Advantages	Assess both fetal condition and uterine activity simultaneously	Detects number of fetuses
	High sensitivity for detection of placental abruption	Ascertain fetal viability
	Detects uterine contraction and risk of preterm labor	Ascertain gestational age
	Once attached gives continuous information	Ascertain placental location
		Assess fetal well-being
		May be used for uterine cervical length measurement as an adjunct tool for predicting preterm labor
		May be performed by an obstetrician or a radiologist
Disadvantages		
	Needs to be attached for at least 20 min	Not sensitive for detecting placental abruption
	Usually is read by an obstetrician	Dos not give information about uterine activity
		Records fetal condition accurately for the moment performed

tool for diagnosing this complication [76]. CTG is more sensitive for detecting placental abruption than ultrasound and may be performed at the bedside in both the ED and the ICU. Rapid or continuous uterine contractions or late fetal heart rate decelerations on CTG are suggestive of placental abruption. In these cases, prompt assessment of maternal condition is extremely important. Uncontrolled placental hemorrhage constitutes an indication to perform cesarean delivery rapidly in order to save both the mother and the unborn child. If imperative, i.e., in the presence of maternal instability or fetal jeopardy (severe non-reassuring fetal status), the premature baby can be delivered and resuscitated outside of the uterus. Trauma centers and ICUs should be equipped and prepared for both cesarean and vaginal delivery in order to enable immediate delivery on location. The Royal College of Obstetricians and Gynaecologists (RCOG) states that the only essential equipment required for perimortem cesarean delivery (PMCD) is a scalpel [77]; however the American Heart Association (AHA) recommends that the equipment contents of the emergency cesarean delivery tray include the following: scalpel with No. 10 blade, lower end of a Balfour retractor, pack of sponges, two Kelly clamps, needle driver, Russian forceps, sutures, and suture scissors [78]. When maternal status dictates delivery, the neonate may be in jeopardy as well; hence a neonatologist should attend the delivery.

If the mother is stable and gestational age is greater than 23–24 weeks, assessment of fetal condition with electronic fetal heart rate monitoring may be performed [6–8]. Once the mother has been cleared by the trauma team, in a viable pregnancy with reassuring initial fetal evaluation, further assessment is recommended to rule out delayed obstetrical complications. An abnormal fetal heart rate tracing and uterine contractions should suggest placental abruption and/or preterm labor even if they occur hours or days after the physical insult. The decision regarding need for observation may be based upon maternal and fetal condition (Table 34.4).

34.4.3 Extracorporeal Membrane Oxygenation for Maternal Salvage

Extracorporeal membrane oxygenation (ECMO) is an extracorporeal technique for providing respiratory and cardiac support in cases of respiratory or cardiac failure. ECMO can be used safely during pregnancy and is of value when indicated. According to the Extracorporeal Life

Table 34.4 Indications for prolonged maternal/fetal observation based on three sources: the American College of Surgeons trauma guidelines, the American College of Obstetricians and Gynecologists and the Society of Obstetricians and Gynaecologists of Canada

	ATLS [6]	ACOG [8]	SOGC [7]
Uterine tenderness	+	+	+
Significant abdominal pain	+	–	+
Vaginal bleeding	+	+	+
Sustained contractions (>1/10 min),	–	+	+
Rupture of the membranes	+	+	+
Abnormal fetal heart rate pattern	+	+	+
High risk mechanism of injury	+	–	+
Serum fibrinogen <200 mg/dL	–	–	+
Serious maternal injury	–	+	–
Hypovolemia	+	–	–
Maternal heart rate > 110	+	–	–
ISS > 9	+	–	–

Key: *ATLS* advanced trauma life support, *ACOG* American College of Obstetricians and Gynecologists, *SOGC* Society of Obstetricians and Gynaecologists of Canada, *ISS* injury severity score

Support Organization (ELSO), pregnancy is not a contraindication to ECMO therapy [79]. However, in the trauma setting, ECMO is controversial and has not been well described [80, 81]. Although a recent series of more than 40 cases of ECMO in the setting of trauma has been published [80], a search of the literature revealed only 1 case report describing the use of ECMO in the setting of maternal trauma [81]. It appears that ECMO in the setting of maternal trauma should be the last resort, until further evidence for its safety and efficacy is accrued and reported (see Chap. 14).

34.4.4 Perimortem Cesarean Delivery

Maternal resuscitation guidelines propose that perimortem cesarean delivery (PMCD) be performed if good quality resuscitation has been ongoing for 4 min and there is no evidence of return of spontaneous circulation [6, 78]. These guidelines are predicated on reports of PMCD mostly outside the context of trauma. However, two studies have suggested that in the setting of maternal resuscitation, both maternal and neonatal outcomes may improve with PMCD [82, 83]. The proposed mechanism was that PMCD performed after 20–24 weeks may alleviate aortocaval compression, thereby improving maternal cardiac preload. For pregnant women with a gestational age greater than 23–24 weeks with cardiac arrest, the recommendation for timely PMCD therefore stands in the setting of trauma as well [78]. Recently, it has been suggested that in the setting of a viable fetus with obviously fatal maternal injury (when resuscitative measures are unlikely to succeed), an interval shorter than 4 min may even be preferable [84].

34.5 Management in the Intensive Care Unit

Pregnant women who are involved in trauma may suffer both trauma-related issues unrelated to pregnancy and pregnancy-related complications. Regarding the former, pregnant women suffer from similar patterns and severities of injury as nonpregnant patients [3, 30, 85] and should be treated similarly with few caveats. The following section addresses several of the complications specific to the injuries of pregnant women (which may be diagnosed at any time during maternal admission), special considerations in treatment of conventional trauma, and prognosis.

34.5.1 Complications Specific to the Injuries of Pregnant Women

In case of ongoing maternal instability, fetal and uterine monitoring should be extended at least until maternal stability has been restored. Table 34.3 presents the variables associated with increased risk for maternal, obstetrical, or fetal/

neonatal complications. Fetal and uterine monitoring should be continued for at least 24 h in cases with increased risk. Pregnant women with a potentially viable fetus who require prolonged sedation should be monitored periodically, either continuously or two to three times daily.

Placental abruption—Placental abruption occurs in 3.5–11% [49, 86–88] of maternal trauma cases. It is almost ten times more common following trauma during pregnancy than in uninjured pregnant women (odds ratio 9.22; 95% CI: 7.79–10.91) [89]. Acceleration-deceleration mechanisms may shear the placenta away from the uterus; hence placental abruption may occur during MVA or a fall even without apparent maternal injury [90, 91]. The severity of injury increases the risk of placental abruption, even though placental abruption may occur with minor trauma alone [37]. A retrospective cohort study compared pregnancy outcome for all pregnant women admitted with injury in Washington State (USA) versus randomly selected non-injured pregnant women. Placental abruption occurred in 1.4% (170/12,578) without injury, in 4.9% (13/266) with non-severe injuries, and in 25% (7/28) of severely injured women [37].

Symptoms of placental abruption include acute abdominal pain, vaginal bleeding, and/or severely painful contractions. On physical examination, a tender and/or rigid uterus and vaginal bleeding may be present. Delayed placental abruption is unlikely if the frequency of uterine contraction is lower than once every 10 min, vaginal bleeding and abdominal pain are absent, and fetal heart rate activity is normal over 4–6 h of observation.

Testing for fetal maternal hemorrhage (FMH) should be performed in all injured pregnant women with a severe mechanism of injury if signs of fetal anemia are evident on CTG or ultrasound or when the mother is Rh negative. The optimal test to assess for FMH is unclear. Either the Kleihauer-Betke (KB) test or flow cytometry may be used. FMH may follow placental abruption and any trauma during pregnancy. A positive Kleihauer-Betke (KB) test indicates the presence of fetal blood cells in the maternal circulation. In one study, 54% of women tested for KB following MVA during pregnancy were positive, and positive KB testing was associated with increased risk of preterm labor [92]. Flow cytometry, an alternative test for fetal blood cells, must be performed in the central hospital laboratory. This method is more simple, objective, and precise than KB testing [93]. Massive FMH may cause fetal anemia (suspected with cardiotocography and diagnosed by obstetric ultrasound) and necessitate fetal blood transfusion or delivery [94].

Significant placental abruption may jeopardize both the mother and her fetus [95]. Placental abruption inhibits the flow of oxygen to the fetus and causes carbon dioxide accumulation in utero, resulting in hypoxia and acidosis and leading to fetal distress [95]. Sustained uterine contractions induced by intrauterine hemorrhage also inhibit uterine blood flow, further contributing to fetal hypoxia. Maternal disseminated intravascular coagulation (DIC) and hemorrhagic shock have been described in the setting of placental abruption [96]. Appropriate therapy in cases of maternal disseminated intravascular coagulation (DIC) and/or fetal death consists of maternal stabilization and prompt delivery. Expectant management can be instituted for mild placental abruption remote from term and without maternal DIC or intrauterine fetal death, provided that maternal hemodynamic condition and fetal well-being are closely monitored [90, 91]. When expected management is practiced, it should be remembered that placental abruption is a risk factor for early postpartum hemorrhage (up to 24 h post-delivery) [97].

Uterine rupture and penetration: Uterine rupture is an obstetrical emergency that is accompanied by massive hemorrhage that may be lethal to both mother and fetus. A population-based study in Sweden revealed a prevalence of uterine rupture of 0.3% in pregnant MVA patients [32]. Uterine rupture has not been reported to occur in the ICU. However, a nationwide population-based study of 371,000 pregnancies from the Netherlands has shown that 12% of women with uterine rupture will be admitted to the ICU [98]. Uterine rupture usually results from a severe mechanism of injury; therefore additional severe injuries should always be sought once this injury has been identi-

fied. Uterine penetration has also been described in penetrating trauma. Exploratory laparotomy is recommended in high-speed projectile injuries [99]. However, exploratory laparotomy is not necessarily an indication for immediate caesarian delivery if the fetus is stable, particularly if the fetus is extremely preterm [8].

34.5.2 Massive Transfusion

In the setting of any trauma with severe, acute blood loss (obstetric or non-obstetric), O-negative blood should be transfused in order to avoid Rh sensitization in Rh-negative women until type-specific or cross-matched donor blood becomes available. Transfusion ratios of one unit of packed red blood cells to one unit fresh frozen plasma have been associated with better outcomes in the general trauma population [100–103]. A similar ratio of 1:1 packed red blood cells to fresh frozen plasma has also been recommended empirically for postpartum hemorrhage [104, 105].

34.5.3 Delivery Considerations

All pregnant women are at increased risk of delivery during hospital admission for trauma. Data from the USA Nationwide Inpatient Sample showed that slightly more than one-third of the pregnant women admitted after trauma (37.7%) delivered during the index trauma admission [106]. Other studies concur that about 38% of pregnant women admitted after trauma actually undergo delivery [33, 34]. Among the women who deliver during admission, 31% will have presented after a fall and 15% after an MVA [106].

Preterm uterine contractions, preterm delivery (PTD), and preterm premature rubture of membranes (PPROM): All of these may affect neonatal outcome. A retrospective cohort study of pregnant women hospitalized for trauma in California (1991–1999) revealed that 14.4% of women delivering during the index trauma admission delivered prematurely, compared to 7% of uninjured women, and 2.7% of women who were admitted and discharged following trauma [89]

Among women with uterine contractions and/or signs of preterm delivery, an attempt to prolong pregnancy and to "buy time" to prepare the fetus is a legitimate strategy. Preterm delivery is a concern between gestational ages 24–37 weeks. Preparation for this untoward development includes a course of antenatal steroids to boost fetal lung maturity and to reduce complications of prematurity. Between 24 and 32 weeks, it is also common to administer magnesium sulfate, as this may impart some fetal neuroprotection [107, 108]. When preterm labor starts following trauma, tocolysis is considered to be relative contraindicated [109].

Cesarean delivery: Maternal trauma is associated with an increased risk of cesarean delivery. Whether this risk may be attributed to the trauma per se is controversial. Data from California suggest that among women who deliver during the index trauma admission, the risk of cesarean delivery was doubled compared to women who were still pregnant when discharged home after the trauma admission (OR 2.18, 95% CI (1.98–2.4), $p < 0.0001$) [89]. A study from Washington State showed that the likelihood of cesarean delivery was particularly high in pregnant women who had been severely injured compared to pregnant women who were not involved in an MVA (cesarean delivery rate 31% vs. 19.5%, respectively; relative risk 1.6; 95% CI 1.1,2.4) [110]. This finding was corroborated in another study showing that pregnant women with severe injury (ISS $\geq$ 9) that were admitted for >48 h had higher immediate delivery rates [16.7% (83/495) vs. 5.7% (41/713)] and higher cesarean delivery rates (81% vs. 51%, $p < 0.0001$) than women with lower ISSs [41].

The specific indications for performing cesarean delivery are not detailed in most studies on this topic. Data from a registry from nine USA Level I trauma centers described 32/441 (7.2%) cesarean deliveries among pregnant trauma patients. The most common indications for cesarean delivery were fetal distress (59%), severe maternal condition (13%), or both (28%). The average time from hospital arrival to cesarean delivery was 5.6 h [39].

Pregnant women with a viable fetus (i.e., gestational age greater than 24 weeks) who are

admitted to the ward after trauma (e.g., to surgery, orthopedics, or the ICU) should undergo periodic CTG monitoring to assess both fetus well-being and uterine activity. Ideally, CTG should be performed two to three times daily. The CTG should be interpreted by an obstetrician; hence the women will be assessed every 8–12 h. Exceptions to this rule are women with signs of preterm delivery, placental abruption, or maternal instability; in these cases, the obstetrician should be involved immediately.

34.5.4 Special Considerations in Treatment of Conventional Trauma

In general, maternal vaccination confers immunity to both the mother and the fetus. Therefore, when vaccination is indicated, it should be administered. For instance, pregnant women should receive tetanus toxoid if indicated, as administration of this vaccine during pregnancy has been shown to be safe [111]. With regards to antibiotics, penicillins and cephalosporins may also be administered as required (see Chap. 38). Some antibiotics are considered unsafe during pregnancy. When in doubt, consultation with a microbiologist or obstetrician is suggested [112].

34.6 Repetitive Imaging

Ultimately, two factors determine whether exposure to radiation will incur fetal damage: the gestational age of the fetus and the radiation dose [113]. The fetus is generally most vulnerable to the teratogenic effects of radiation during the first trimester of pregnancy. Exposure to radiation at a gestational age of 10–25 weeks increases the risk of mental retardation [114, 115]. Intrauterine exposure to radiation has also been associated with an increased risk of childhood cancer regardless of trimester. However, the risk of fetal malformation or childhood cancer is unlikely to be increased if the dose of radiation does not exceed 50 mSv. Most diagnostic imaging exposes the fetus to far less than this dose [71, 116].

The pretest probability of a positive finding ultimately determines the likelihood of a pathological finding in any test. For example, chest radiographs that are performed "on demand" are almost twice more likely to yield abnormal findings and have a much greater impact on patient care than those performed as "routine" tests [117]. If repetitive, accurate diagnostic imaging is required nonetheless and concerns are raised that such imaging may be associated with an excessively high radiation dose, the option of substituting MRI for CT imaging should be given consideration. MRI provides better soft tissue imaging than either ultrasound or CT and is not associated with radiation exposure. MRI appears to be safe even in the first trimester. Of note, the use of gadolinium is controversial and may be associated with fetal harm during all trimesters, as it crosses the placenta [118].

34.6.1 Predicting Maternal and Pregnancy Outcomes Following Trauma

Maternal outcomes—Although virtually all the variables that may predict outcomes among injured pregnant women have been challenged, certain variables are consistently associated with worse maternal outcomes (Table 34.5). Early identification of pregnant women at risk for a poor outcome may enable timely implementation of corrective measures and reduce maternal morbidity and mortality [37, 119]. Trauma scores are often used to describe the severity of injury and to predict mortality in non-obstetric trauma victims. The most commonly used scoring methods include the injury severity score (ISS), new injury severity score (NISS), revised trauma scores (RTS), and the trauma and injury severity score (TRISS) [120]. None of these have been validated for injured pregnant women. However, several studies have shown that the ISS or the RTS may be used to predict maternal mortality. In one of these studies, pregnant women who died compared to those who were admitted or discharged had higher ISS (44.4 vs. 11.49 vs. 2.66; $p < 0.001$) and lower RTS (0.5 vs. 7.49 vs. 7.83; $p < 0.001$) [34].

Table 34.5 Variables assessed for prediction of maternal outcome in trauma

Variable	Outcome	OR	95% CI	*p*-value	References
Demographic characteristics					
Maternal age > 41 years	Death	2.86	1.6–5.1	0.000	[122]
Gestational age > 35 weeks	Uterine contractions, preterm labor, vaginal bleeding	3.7	2.1–6.7	NA	[130]
Mechanism of injury					
Gun shot	Severe maternal injury	50%			[30]
MVA		31%			
Assaults		22%			
Falls		0%			
Injury characteristics					
Intracranial injury	Death	11.1	1.6–76	0.014	[122]
Internal injury	Death	15.0	1.9–117	0.01	
ISS > 9	Death	14.6	1.5–143	0.002	
Lower revised trauma score	Death (each decrease point of RTS)	0.0004	NA	0.006	[54]
ISS > 8	Placental abruption	9;17	4.7–17; 6.2–46.8	NA	[30, 37]
	Preterm delivery	3.8	1.4–10.3	NA	[30]
	Cesarean delivery	1.6; 3.8	1.1–2.4; 2.1–6.9	NA	[30, 37]

Key: *MVA* motor vehicle accident, *ISS* injury severity score, *OR* odds ratio, *CI* confidence interval, *ISS* injury severity score, *NA* nonavailable, *RTS* revised trauma score

Only one study in a Level I trauma center reported ICU admissions among injured pregnant women; 22/188 (11.7%) of pregnant women in the USA during the 9-year study period were admitted to the ICU. The ED categorized women as severely injured or non-severely injured. The 42 severely injured women were almost evenly distributed between direct ICU admission ($n = 22$) and transfer from the ED to the operating room ($n = 20$). Unfortunately, ICU outcomes were not reported [48].

Fetal and neonatal outcomes—Fetal morbidity and death usually occur secondary to preterm delivery. Preterm delivery may be precipitated directly by the trauma, or indirectly due to premature rupture of the membranes or placental abruption. During maternal trauma, the fetus may also sustain direct traumatic injury (e.g., in penetrating trauma) or indirect injury due to maternal instability (e.g., due to maternal anemia, hypoxemia, hypovolemia). Crash severity, improper/lack of maternal seat belt use, poor maternal condition at the time of admission (e.g., tachycardia, hypotension, hypoxemia, coagulopathy, low fibrinogen, increased base deficit, low serum bicarbonate), serious maternal abdominal injury necessitating emergency laparotomy, poor maternal outcomes (i.e., death or coma), and poor fetal condition as evident by category II or III fetal heart rate tracing during admission have all been associated with poor fetal outcomes during admission [33, 37, 46, 48, 51]. Increasing maternal ISS has also been associated with an increased likelihood of fetal death (85.7% sensitivity, 70.9% specificity) [101].

Fetal morbidity—Direct fetal injury is uncommon and complicates less than 1% of pregnancies with blunt trauma [120]. Fetal injuries are most likely to occur after direct and severe abdominal or pelvic impact, during the second half of pregnancy, and when the fetal head is engaged in the maternal pelvis [121, 122]. Direct fetal injuries that have been reported include fetal splenic rupture, subarachnoid hemorrhage, subdural hemorrhage, brain edema with reversal of diastolic flow, ischemic changes, hypoxic ischemic encephalopathy, cerebellar hemorrhage, contusions, and skull fractures [123, 124]. Hypoxic injuries may

also occur secondary to disruption of the fetal vascular supply from a placental abruption.

Adverse fetal outcomes may extend beyond the index admission. Maternal trauma is associated with higher rates of preterm deliveries, low birth weight infants, placental abruption, fetal distress, fetal demise, maternal thrombotic events, and cesarean deliveries, all potentially due to a subclinical partial abruption; these can occur even after hospital discharge [89, 121, 125, 126]. The risk of these complications is higher with increasing severity of maternal injury and among those injured early in gestation [126].

Fetal Mortality—The rate of fetal death following injury of pregnant women varies between 0.3 and 10%, and, as with maternal trauma, the greatest proportion of fetal deaths occurs following MVAs. A retrospective study of fetal death certificates from 16 states (approximately 50% of all live births in the USA between 1995 and 1997) revealed an annual number of about 143 traumatic fetal deaths, the majority of which occurred due to MVA [127]. A population-based study from Sweden showed that the risk of fetal/neonatal death in pregnant MVA patients was 3.55 times higher than the risk during pregnancy uncomplicated by involvement in an MVA [32].

Placental abruption is the leading cause of fetal death after blunt trauma [128]. When the mother sustains life-threatening injuries, the likelihood of fetal demise is 40–50%. However, since minor trauma is much more common, 30–70% of fetal losses after trauma follow minor injury [32, 76, 129]. Fetal demise that occurs during trauma admission is mostly associated with severe maternal injury (ISS $\geq$ 9); conversely, fetal demise following hospital discharge occurs more commonly when injury is not as severe (ISS < 9) [89]. This has important implications for follow-up assessment of the pregnant woman after trauma.

34.7 Summary

Trauma during pregnancy is common; when it occurs, both the mother and the fetus/newborn are at risk of morbidity and mortality. Hence, evaluation and management presents a unique challenge, and appropriate care should involve a coordinated multidisciplinary team that follows ATLS guidelines. One major principle guides the treatment in these situations: maternal health takes priority over interventions for the fetus.

References

1. Fildes J, Reed L, Jones N, Martin M, Barrett J. Trauma: the leading cause of maternal death. J Trauma. 1992;32(5):643–5.
2. Harland KK, Saftlas AF, Yankowitz J, Peek-Asa C. Risk factors for maternal injuries in a population-based sample of pregnant women. J Womens Health (Larchmt). 2014;23(12):1033–8. https://doi.org/10.1089/jwh.2013.4560.
3. Periyanayagam U, Crandall M. The cost of injury: hospital charges for pregnant trauma patients, 1999 to 2003. Am J Surg. 2014;208(1):130–5. https://doi.org/10.1016/j.amjsurg.2013.10.018.
4. Fischer PE, Zarzaur BL, Fabian TC, Magnotti LJ, Croce MA. Minor trauma is an unrecognized contributor to poor fetal outcomes: a population-based study of 78,552 pregnancies. J Trauma. 2011;71(1):90–3. https://doi.org/10.1097/TA.0b013e31821cb600.
5. Mendez-Figueroa H, Dahlke JD, Vrees RA, Rouse DJ. Trauma in pregnancy: an updated systematic review. Am J Obstet Gynecol. 2013;209(1):1–10. https://doi.org/10.1016/j.ajog.2013.01.021.
6. ATLS, advanced trauma life support for doctors: student course manual. 9th ed. American College of Surgeons. Committee on Trauma.; 2012.
7. Jain V, Chari R, Maslovitz S, et al. Guidelines for the management of a pregnant trauma patient. J Obstet Gynaecol Can. 2015;37(6):553–74. https://doi.org/10.1016/S1701-2163(15)30232-2.
8. ACOG educational bulletin. Obstetric aspects of trauma management. Number 251, September 1998 (replaces Number 151, January 1991, and Number 161, November 1991). American College of Obstetricians and Gynecologists. Int J Gynaecol Obstet. 1999;64(1):87–94.
9. Lavery JP, Staten-McCormick M. Management of moderate to severe trauma in pregnancy. Obstet Gynecol Clin N Am. 1995;22(1):69–90.
10. Bobrowski RA. Pulmonary physiology in pregnancy. Clin Obstet Gynecol. 2010;53(2):285–300. https://doi.org/10.1097/GRF.0b013e3181e04776.
11. Heinrich S, Irouschek A, Prottengeier J, Ackermann A, Schmidt J. Adverse airway events in parturient compared with non-parturient patients. Is there a difference? Results from a quality management project. J Obstet Gynaecol Res. 2015;41(7):1032–9. https://doi.org/10.1111/jog.12677.
12. Pernoll ML, Metcalfe J, Kovach PA, Wachtel R, Dunham MJ. Ventilation during rest and exer-

cise in pregnancy and postpartum. Respir Physiol. 1975;25(3):295–310.
13. Wise RA, Polito AJ, Krishnan V. Respiratory physiologic changes in pregnancy. Immunol Allergy Clin N Am. 2006;26(1):1–12. https://doi.org/10.1016/j.iac.2005.10.004.
14. McAuliffe F, Kametas N, Costello J, Rafferty GF, Greenough A, Nicolaides K. Respiratory function in singleton and twin pregnancy. BJOG. 2002;109(7):765–9.
15. Milne JA, Howie AD, Pack AI. Dyspnoea during normal pregnancy. Br J Obstet Gynaecol. 1978;85(4):260–3.
16. Pacagnella RC, Souza JP, Durocher J, et al. A systematic review of the relationship between blood loss and clinical signs. PLoS One. 2013;8(3):e57594. https://doi.org/10.1371/journal.pone.0057594.
17. Flo K, Wilsgaard T, Vartun A, Acharya G. A longitudinal study of the relationship between maternal cardiac output measured by impedance cardiography and uterine artery blood flow in the second half of pregnancy. BJOG. 2010;117(7):837–44. https://doi.org/10.1111/j.1471-0528.2010.02548.x.
18. Duvekot JJ, Cheriex EC, Pieters FA, Menheere PP, Peeters LH. Early pregnancy changes in hemodynamics and volume homeostasis are consecutive adjustments triggered by a primary fall in systemic vascular tone. Am J Obstet Gynecol. 1993;169(6):1382–92.
19. Mabie WC, DiSessa TG, Crocker LG, Sibai BM, Arheart KL. A longitudinal study of cardiac output in normal human pregnancy. Am J Obstet Gynecol. 1994;170(3):849–56.
20. Bernstein IM, Ziegler W, Badger GJ. Plasma volume expansion in early pregnancy. Obstet Gynecol. 2001;97(5 Pt 1):669–72.
21. Whittaker PG, Macphail S, Lind T. Serial hematologic changes and pregnancy outcome. Obstet Gynecol. 1996;88(1):33–9. https://doi.org/10.1016/0029-7844(96)00095-6.
22. Abbassi-Ghanavati M, Greer LG, Cunningham FG. Pregnancy and laboratory studies: a reference table for clinicians. Obstet Gynecol. 2009;114(6):1326–31. https://doi.org/10.1097/AOG.0b013e3181c2bde8.
23. Cines DB, Levine LD. Thrombocytopenia in pregnancy. Blood. 2017;130:2271. https://doi.org/10.1182/blood-2017-05-781971.
24. Bonnet MP, Deneux-Tharaux CB-CM. Critical care and transfusion management in maternal deaths from postpartum haemorrhage. Eur J Obs Gynecol Reprod Biol. 2011;158:183–8.
25. Liu XH, Jiang YM, Shi H, Yue XA, Wang YF, Yang H. Prospective, sequential longitudinal study of coagulation changes during pregnancy in Chinese women. Int J Gynaecol Obstet. 2009;105:240–3.
26. Shaylor R, Weiniger CF, Austin N, Tzabazis A, Shander A, Goodnough LTBA. National and international guidelines for patient blood management in obstetrics: a qualitative review. Anesth Analg. 2017;124:216–32.
27. de Lloyd L, Bovington R, Kaye A, Collis RE, Rayment R, Sanders J, Rees ACP. Standard haemostatic tests following major obstetric haemorrhage. Int J Obstet Anesth. 2011;20:135–41.
28. Pearlman MFS. Obstetric septic shock: a pathophysiologic basis for management. Clin Obstet Gynecol. 1990;33(3):482–92.
29. Rossi A, Cornette J, Johnson MR, et al. Quantitative cardiovascular magnetic resonance in pregnant women: cross-sectional analysis of physiological parameters throughout pregnancy and the impact of the supine position. J Cardiovasc Magn Reson. 2011;13:31. https://doi.org/10.1186/1532-429X-13-31.
30. Battaloglu E, McDonnell D, Chu J, Lecky F, Porter K. Epidemiology and outcomes of pregnancy and obstetric complications in trauma in the United Kingdom. Injury. 2016;47(1):184–7. https://doi.org/10.1016/j.injury.2015.08.026.
31. Aboutanos SZ, Aboutanos MB, Dompkowski D, Duane TM, Malhotra AK, Ivatury RR. Predictors of fetal outcome in pregnant trauma patients: a five-year institutional review. Am Surg. 2007;73(8):824–7.
32. Kvarnstrand L, Milsom I, Lekander T, Druid H, Jacobsson B. Maternal fatalities, fetal and neonatal deaths related to motor vehicle crashes during pregnancy: a national population-based study. Acta Obstet Gynecol Scand. 2008;87(9):946–52. https://doi.org/10.1080/00016340802302184.
33. Klinich KDS, Flannagan CAC, Rupp JD, Sochor M, Schneider LW, Pearlman MD. Fetal outcome in motor-vehicle crashes: effects of crash characteristics and maternal restraint. Am J Obstet Gynecol. 2008;198(4):450.e1–9.
34. Weinberg L, Steele RG, Pugh R, Higgins S, Herbert M, Story D. The pregnant trauma patient. Anaesth Intensive Care. 2005;33(2):167–80.
35. Brookfield KF, Gonzalez-Quintero VH, Davis JS, Schulman CI. Maternal death in the emergency department from trauma. Arch Gynecol Obstet. 2013;288(3):507–12. https://doi.org/10.1007/s00404-013-2772-5.
36. Distelhorst JT, Krishnamoorthy V, Schiff MA. Association between hospital trauma designation and maternal and neonatal outcomes after injury among pregnant women in Washington state. J Am Coll Surg. 2016;222(3):296–302. https://doi.org/10.1016/j.jamcollsurg.2015.12.010.
37. Schiff MA, Holt VL, Daling JR. Maternal and infant outcomes after injury during pregnancy in Washington state from 1989 to 1997. J Trauma. 2002;53(5):939–45. https://doi.org/10.1097/01.TA.0000033750.65011.BC.
38. Health Canada. Special Report on Maternal Mortality and Severe Morbidity in Canada—Enhanced Surveillance: The Path to Prevention. Ottawa: Minister of Public Works and Government Services Canada; 2004. http://publications.gc.ca/Collection/H39-4-44-2004E.pdf. Last Accessed 3 Sep 2018.

39. Morris JAJ, Rosenbower TJ, Jurkovich GJ, et al. Infant survival after cesarean section for trauma. Ann Surg. 1996;223(5):481–91.
40. Hasegawa J, Sekizawa A, Tanaka H, et al. Current status of pregnancy-related maternal mortality in Japan: a report from the maternal death exploratory committee in Japan. BMJ Open. 2016;6(3):e010304. https://doi.org/10.1136/bmjopen-2015-010304.
41. Schuster M, Becker N, Young A, Paglia MJ, Mackeen AD. Trauma in pregnancy: a review of the Pennsylvania trauma systems foundation database. Trauma. 2018;20(1):30–7.
42. Einav S, Bromiker R, Sela HY. Maternal critical illness. Curr Anesthesiol Rep. 2017;7(1):55–66. https://doi.org/10.1007/s40140-017-0198-5.
43. Zwart JJ, Dupuis JRO, Richters A, Öry F, Van Roosmalen J. Obstetric intensive care unit admission: a 2-year nationwide population-based cohort study. Intensive Care Med. 2010;36(2):256–63. https://doi.org/10.1007/s00134-009-1707-x.
44. Leung NYW, Lau ACW, Chan KKC, Yan WW. Clinical characteristics and outcomes of obstetric patients admitted to the intensive care unit: a 10-year retrospective review. Hong Kong Med J. 2010;16(1):18–25.
45. Hyde LK, Cook LJ, Olson LM, Weiss HB, Dean JM. Effect of motor vehicle crashes on adverse fetal outcomes. Obstet Gynecol. 2003;102(2):279–86.
46. Wolf ME, Alexander BH, Rivara FP, Hickok DE, Maier RV, Starzyk PM. A retrospective cohort study of seatbelt use and pregnancy outcome after a motor vehicle crash. J Trauma. 1993;34(1):116–9.
47. Crosby WM, Costiloe JP. Safety of lap-belt restraint for pregnant victims of automobile collisions. N Engl J Med. 1971;284(12):632–6. https://doi.org/10.1056/NEJM197103252841203.
48. Crosby WM, King AI, Stout LC. Fetal survival following impact: improvement with shoulder harness restraint. Am J Obstet Gynecol. 1972;112(8):1101–6.
49. Curet MJ, Schermer CR, Demarest GB, Bieneik EJ 3rd, Curet LB. Predictors of outcome in trauma during pregnancy: identification of patients who can be monitored for less than 6 hours. J Trauma. 2000;49(1):15–8.
50. Patteson SK, Snider CC, Meyer DS, et al. The consequences of high-risk behaviors: trauma during pregnancy. J Trauma. 2007;62(4):1015–20. https://doi.org/10.1097/01.ta.0000221554.95815.2e.
51. Motozawa Y, Hitosugi M, Abe T, Tokudome S. Effects of seat belts worn by pregnant drivers during low-impact collisions. Am J Obstet Gynecol. 2010;203(1):62.e1–8. https://doi.org/10.1016/j.ajog.2010.02.047.
52. American College of Obstetricians and Gynecologists. Car safety for you and your baby. https://www.acog.org/-/media/For-Patients/faq018.pdf?dmc=1&ts=20170806T1015448574. Last Accessed 4 Sep 2018.
53. National Highway Traffic Safety Administration. If You're pregnant: seat belt recommendations for drivers and passengers. https://www.nhtsa.gov/sites/nhtsa.dot.gov/files/documents/pregnant-seat-belt-use.pdf. Last Accessed 4 Sep 2018
54. Luley T, Fitzpatrick CB, Grotegut CA, Hocker MB, Myers ER, Brown HL. Perinatal implications of motor vehicle accident trauma during pregnancy: identifying populations at risk. Am J Obstet Gynecol. 2013;208(6):466.e1–5. https://doi.org/10.1016/j.ajog.2013.02.032.
55. Sasser SM, Hunt RC, Faul M, Sugerman D, Pearson WS, Dulski T, Wald MM, Jurkovich GJ, Newgard CD, Lerner EB, Centers for Disease Control and Prevention (CDC). Guidelines for field triage of injured patients: recommendations of the National Expert Panel on Field Triage, 2011. MWR Recomm Rep. 2012;61(RR-1):1–20.
56. Aufforth R, Edhayan E, Dempah D. Should pregnancy be a sole criterion for trauma code activation: a review of the trauma registry. Am J Surg. 2010;199(3):387–90. https://doi.org/10.1016/j.amjsurg.2009.09.008.
57. Greene W, Robinson L, Rizzo AG, et al. Pregnancy is not a sufficient indicator for trauma team activation. J Trauma. 2007;63(3):550–4. discussion 554–5.
58. American College of Surgeons. Resources for the optimal care of the injured patient. Chicago IL: American College of Surgeons; 2014. https://www.facs.org/quality-programs/trauma/tqp/center-programs/vrc/resources. Last Accessed 4 Sep 2018.
59. Bochicchio GV, Napolitano LM, Haan J, Champion H, Scalea T. Incidental pregnancy in trauma patients. J Am Coll Surg. 2001;192(5):566–9. https://doi.org/10.1016/S1072-7515(01)00818-3.
60. Dunham CM, Chirichella TJ. Trauma activation patients: evidence for routine alcohol and illicit drug screening. PLoS One. 2012;7(10):1–6. https://doi.org/10.1371/journal.pone.0047999.
61. Ikossi DG, Lazar AA, Morabito D, Fildes J, Knudson MM. Profile of mothers at risk: an analysis of injury and pregnancy loss in 1,195 trauma patients. J Am Coll Surg. 2005;200(1):49–56. https://doi.org/10.1016/j.jamcollsurg.2004.09.016.
62. Tinker SC, Reefhuis J, Dellinger AM, Jamieson DJ, National Birth Defects Prevention Study. Epidemiology of maternal injuries during pregnancy in a population-based study, 1997-2005. J Womens Health (Larchmt). 2010;19(12):2211–8. https://doi.org/10.1089/jwh.2010.2160.
63. American College of Surgeons. Trauma in pregnancy and intimate partner violence. In: Advanced trauma life support student course manual. 9th ed. Chicago Ill; 2012 . https://www.44c.in.ua/files/book11.pdf. Last Accessed 4 Sep 2018.
64. [No authors listed]. ACOG Committee Opinion No. 518: intimate partner violence. Obstet Gynecol. 2012;119(2 Pt 1):412–417. https://doi.org/10.1097/AOG.0b013e318249ff74.
65. Magnone S, Allegri A, Belotti E, et al. Impact of ATLS guidelines, trauma team introduction, and 24-hour mortality due to severe trauma in a busy,

metropolitan Italian hospital: a case control study. Ulus Travma Acil Cerrahi Derg. 2016;22(3):242–6. https://doi.org/10.5505/tjtes.2015.19540.
66. Navarro S, Montmany S, Rebasa P, Colilles C, Pallisera A. Impact of ATLS training on preventable and potentially preventable deaths. World J Surg. 2014;38(9):2273–8. https://doi.org/10.1007/s00268-014-2587-y.
67. Shakerian R, Thomson BN, Judson R, Skandarajah AR. Radiation fear. J Trauma Acute Care Surg. 2015;78(1):88–93. https://doi.org/10.1097/TA.0000000000000497.
68. Sirlin CB, Casola G, Brown MA, et al. Us of blunt abdominal trauma: importance of free pelvic fluid in women of reproductive age. Radiology. 2001;219(1):229–35. https://doi.org/10.1148/radiology.219.1.r01ap45229.
69. Goodwin H, Holmes JF, Wisner DH. Abdominal ultrasound examination in pregnant blunt trauma patients. J Trauma. 2001;50(4):689–93. discussion 694.
70. Richards JR, Ormsby EL, Romo MV, Gillen MA, McGahan JP. Blunt abdominal injury in the pregnant patient: detection with US. Radiology. 2004;233(2):463–70. https://doi.org/10.1148/radiol.2332031671.
71. Lockwood D, Einstein DDW. Diagnostic imaging: radiation dose and patients' concerns. Cleve Clin J Med. 2006;73(6):583–6.
72. Mock C, Nguyen S, Quansah R, Arreola-Risa C, Viradia R, Joshipura M. Evaluation of trauma care capabilities in four countries using the WHO-IATSIC Guidelines for Essential Trauma Care. World J Surg. 2006;30(6):946–56. https://doi.org/10.1007/s00268-005-0768-4.
73. Sela HY, Weiniger CF, Hersch M, Smueloff A, Laufer N, Einav S. The pregnant motor vehicle accident casualty: adherence to basic workup and admission guidelines. Ann Surg. 2011;254(2):346–52. https://doi.org/10.1097/SLA.0b013e31822638d4.
74. Bowman M, Giles W, Deane S. Trauma during pregnancy—a review of management. Aust N Z J Obstet Gynaecol. 1989;29(4):389–93.
75. Shah KH, Simons RK, Holbrook T, Fortlage D, Winchell RJ, Hoyt DB. Trauma in pregnancy: maternal and fetal outcomes. J Trauma. 1998;45(1):83–6.
76. Murphy NJ, Quinlan JD. Trauma in pregnancy: assessment, management, and prevention. Am Fam Physician. 2014;90(10):717–22.
77. Royal College of Obstetricians and Gynaecologists. Maternal collapse in pregnancy and the puerperium. Green–top guideline no. 56; 2011. https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_56.pdf. Last Accessed 4 Sep 2018.
78. Jeejeebhoy FM, Zelop CM, Lipman S, et al. Cardiac arrest in pregnancy: a scientific statement from the American Heart Association. Circulation. 2015;132(18):1747–73. https://doi.org/10.1161/CIR.0000000000000300.
79. Moore SA, Dietl CA, Coleman DM. Extracorporeal life support during pregnancy. J Thorac Cardiovasc Surg. 2016;151(4):1154–60. https://doi.org/10.1016/j.jtcvs.2015.12.027.
80. Ahmad SB, Menaker J, Kufera J, O'Connor J, Scalea TM, Stein DM. Extracorporeal membrane oxygenation after traumatic injury. J Trauma Acute Care Surg. 2107;82(3):587–91.
81. Plotkin JS, Shah JB, Lofland GK, DeWolf AM. Extracorporeal membrane oxygenation in the successful treatment of traumatic adult respiratory distress syndrome: case report and review. J Trauma. 1994;37:127–30.
82. Katz V, Balderston K, Defreest M, Nageotte M, Parer J. Perimortem cesarean delivery: were our assumptions correct? Am J Obstet Gynecol. 2005;192(6):1916–21. https://doi.org/10.1016/j.ajog.2005.02.038.
83. Einav S, Kaufman N, Sela HY. Maternal cardiac arrest and perimortem caesarean delivery: evidence or expert-based? Resuscitation. 2012;83(10):1191–200. https://doi.org/10.1016/j.resuscitation.2012.05.005.
84. Benson MD, Padovano A, Bourjeily G, Zhou Y. Maternal collapse: challenging the four-minute rule. EBioMedicine. 2016;6:253–7. https://doi.org/10.1016/j.ebiom.2016.02.042.
85. Manoogian S. Comparison of pregnant and non-pregnant occupant crash and injury characteristics based on national crash data. Accid Anal Prev. 2015;74:69–76. https://doi.org/10.1016/j.aap.2014.10.017.
86. Schiff MA, Holt VL. The injury severity score in pregnant trauma patients: predicting placental abruption and fetal death. J Trauma. 2002;53(5):946–9. https://doi.org/10.1097/01.TA.0000022386.27159.64.
87. Towery R, English TP, Wisner D. Evaluation of pregnant women after blunt injury. J Trauma. 1993;35(5):731–6.
88. Rogers FB, Rozycki GS, Osler TM, et al. A multi-institutional study of factors associated with fetal death in injured pregnant patients. Arch Surg. 1999;134(11):1274–7.
89. El Kady D, Gilbert WM, Anderson J, Danielsen B, Towner D, Smith LH. Trauma during pregnancy: an analysis of maternal and fetal outcomes in a large population. Am J Obstet Gynecol. 2004;190(6):1661–8. https://doi.org/10.1016/j.ajog.2004.02.051.
90. Hladky K, Yankowitz J, Hansen WF. Placental abruption. Obstet Gynecol Surv. 2002;57(5):299–305.
91. Oyelese Y, Ananth CV. Placental abruption. Obstet Gynecol. 2006;108(4):1005–16. https://doi.org/10.1097/01.AOG.0000239439.04364.9a.
92. Muench MV, Baschat AA, Reddy UM, et al. Kleihauer-betke testing is important in all cases of maternal trauma. J Trauma. 2004;57(5):1094–8. https://doi.org/10.1097/01.TA.0000096654.37009.B7.
93. Porra V, Bernaud J, Gueret P, et al. Identification and quantification of fetal red blood cells in

maternal blood by a dual-color flow cytometric method: evaluation of the fetal cell count kit. Transfusion. 2007;47(7):1281–9. https://doi.org/10.1111/j.1537-2995.2007.01271.x.
94. Wylie BJ, D'Alton ME. Fetomaternal hemorrhage. Obstet Gynecol. 2010;115(5):1039–51. https://doi.org/10.1097/AOG.0b013e3181da7929.
95. Nasiell J, Papadogiannakis N, Löf E, Elofsson F, Hallberg B. Hypoxic ischemic encephalopathy in newborns linked to placental and umbilical cord abnormalities. J Matern Fetal Neonatal Med. 2016;29(5):721–6. https://doi.org/10.3109/14767058.2015.1015984.
96. Rattray DD, O'Connell CM, Baskett TF. Acute disseminated intravascular coagulation in obstetrics: a tertiary centre population review (1980 to 2009). J Obstet Gynaecol Can. 2012;34(4):341–7.
97. Practice Bulletin No. 183: Postpartum hemorrhage. Obstet Gynecol. 2017;130(4):e168–e186. https://doi.org/10.1097/AOG.0000000000002351.
98. Zwart JJ, Richters JM, Ory F, de Vries JIP, Bloemenkamp KWM, van Roosmalen J. Severe maternal morbidity during pregnancy, delivery and puerperium in the Netherlands: a nationwide population-based study of 371,000 pregnancies. BJOG. 2008;115(7):842–50. https://doi.org/10.1111/j.1471-0528.2008.01713.x.
99. Awwad JT, Azar GB, Seoud MA, Mroueh AM, Karam KS. High-velocity penetrating wounds of the gravid uterus: review of 16 years of civil war. Obstet Gynecol. 1994;83(2):259–64.
100. Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma. JAMA. 2015;313(5):471–82. https://doi.org/10.1001/jama.2015.12.
101. Schuster KM, Davis KA, Lui FY, Maerz LL, Kaplan LJ. The status of massive transfusion protocols in United States trauma centers: massive transfusion or massive confusion? Transfusion. 2010;50(7):1545–51. https://doi.org/10.1111/j.1537-2995.2010.02587.x.
102. Cotton BA, Au BK, Nunez TC, Gunter OL, Robertson AM, Young PP. Predefined massive transfusion protocols are associated with a reduction in organ failure and postinjury complications. J Trauma. 2009;66(1):41–8. https://doi.org/10.1097/TA.0b013e31819313bb. discussion 48–9.
103. Dente CJ, Shaz BH, Nicholas JM, et al. Improvements in early mortality and coagulopathy are sustained better in patients with blunt trauma after institution of a massive transfusion protocol in a civilian level I trauma center. J Trauma. 2009;66(6):1616–24. https://doi.org/10.1097/TA.0b013e3181a59ad5.
104. Brookfield KF, Goodnough LT, Lyell DJ, Butwick AJ. Perioperative and transfusion outcomes in women undergoing cesarean hysterectomy for abnormal placentation. Transfusion. 2014;54(6):1530–6. https://doi.org/10.1111/trf.12483.
105. Pasquier P, Gayat E, Rackelboom T, et al. An observational study of the fresh frozen plasma: red blood cell ratio in postpartum hemorrhage. Anesth Analg. 2013;116(1):155–61. https://doi.org/10.1213/ANE.0b013e31826f084d.
106. Kuo C, Jamieson DJ, McPheeters ML, Meikle SF, Posner SF. Injury hospitalizations of pregnant women in the United States, 2002. Am J Obstet Gynecol. 2007;196(2):161.e1–6. https://doi.org/10.1016/j.ajog.2006.09.015.
107. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2017;3:CD004454. https://doi.org/10.1002/14651858.CD004454.pub3.
108. Magee L, Sawchuck D, Synnes A, von Dadelszen P, SOGC Clinical Practice Guideline. Magnesium sulphate for fetal neuroprotection. J Obstet Gynaecol Can. 2011;33(5):516–29.
109. Hösli I, Sperschneider C, Drack G, Zimmermann R, Surbek D, Irion O. Tocolysis for preterm labor: expert opinion. Arch Gynecol Obstet. 2014;289(4):903–9. https://doi.org/10.1007/s00404-013-3137-9.
110. Schiff MA, Holt VL. Pregnancy outcomes following hospitalization for motor vehicle crashes in Washington state from 1989 to 2001. Am J Epidemiol. 2005;161(6):503–10. https://doi.org/10.1093/aje/kwi078.
111. Keller-Stanislawski B, Englund JA, Kang G, et al. Safety of immunization during pregnancy: a review of the evidence of selected inactivated and live attenuated vaccines. Vaccine. 2014;32(52):7057–64. https://doi.org/10.1016/j.vaccine.2014.09.052.
112. Mylonas I. Antibiotic chemotherapy during pregnancy and lactation period: aspects for consideration. Arch Gynecol Obstet. 2011;283(1):7–18. https://doi.org/10.1007/s00404-010-1646-3.
113. ACR practice guideline for imaging pregnant or potentially pregnant adolescents and women with ionizing radiation. http://www.who.int/tb/advisory_bodies/impact_measurement_taskforce/meetings/prevalence_survey/imaging_pregnant_arc.pdf. Last Accessed 4 Sep 2018.
114. Nguyen CP, Goodman LH. Fetal risk in diagnostic radiology. Semin Ultrasound CT MR. 2012;33(1):4–10. https://doi.org/10.1053/j.sult.2011.09.003.
115. Schull WJ, Otake M. Cognitive function and prenatal exposure to ionizing radiation. Teratology. 1999;59(4):222–6.
116. Tremblay E, Thérasse E, Thomassin-Naggara I, Trop I. Quality initiatives: guidelines for use of medical imaging during pregnancy and lactation. Radiographics. 2012;32(3):897–911. https://doi.org/10.1148/rg.323115120.
117. Lakhal K, Serveaux-Delous M, Lefrant JY, Capdevila X, Jaber S. Chest radiographs in 104 French ICUs: current prescription strategies and clinical value (the RadioDay study). Intensive Care Med. 2012;38(11):1787–99. https://doi.org/10.1007/s00134-012-2650-9.

118. Ray JG, Vermeulen MJ, Bharatha A, Montanera WJ, Park AL. Association between MRI exposure during pregnancy and fetal and childhood outcomes. JAMA. 2016;316(9):952–61. https://doi.org/10.1001/jama.2016.12126.
119. MacKenzie EJ, Rivara FP, Jurkovich GJ, et al. A national evaluation of the effect of trauma-center care on mortality. N Engl J Med. 2006;354(4):366–78. https://doi.org/10.1056/NEJMsa052049.
120. Van Hook JW. Trauma in pregnancy. Clin Obstet Gynecol. 2002;45(2):414–24.
121. El Kady D. Perinatal outcomes of traumatic injuries during pregnancy. Clin Obstet Gynecol. 2007;50(3):582–91. https://doi.org/10.1097/GRF.0b013e31811eab82.
122. Muench MV, Canterino JC. Trauma in pregnancy. Obstet Gynecol Clin N Am. 2007;34(3):555–83,. xiii. https://doi.org/10.1016/j.ogc.2007.06.001.
123. Breysem L, Cossey V, Mussen E, Demaerel P, Van de Voorde W, Smet M. Fetal trauma: brain imaging in four neonates. Eur Radiol. 2004;14(9):1609–14. https://doi.org/10.1007/s00330-004-2357-6.
124. Strigini FA, Cioni G, Canapicchi R, Nardini V, Capriello P, Carmignani A. Fetal intracranial hemorrhage: is minor maternal trauma a possible pathogenetic factor? Ultrasound Obstet Gynecol. 2001;18(4):335–42. https://doi.org/10.1046/j.0960-7692.2001.00486.x.
125. Weiss HB, Sauber-Schatz EK, Cook LJ. The epidemiology of pregnancy-associated emergency department injury visits and their impact on birth outcomes. Accid Anal Prev. 2008;40(3):1088–95. https://doi.org/10.1016/j.aap.2007.11.011.
126. Sperry JL, Casey BM, McIntire DD, Minei JP, Gentilello LM, Shafi S. Long-term fetal outcomes in pregnant trauma patients. Am J Surg. 2006;192(6):715–21. https://doi.org/10.1016/j.amjsurg.2006.08.032.
127. Weiss HB, Songer TJ, Fabio A. Fetal deaths related to maternal injury. JAMA. 2001;286(15):1863–8.
128. Barraco RD, Chiu WC, Clancy TV, et al. Practice management guidelines for the diagnosis and management of injury in the pregnant patient: the EAST practice management guidelines work group. J Trauma. 2010;69(1):211–4. https://doi.org/10.1097/TA.0b013e3181dbe1ea.
129. Weiss HB, Lawrence B, Miller T. Prevalence and risk of hospitalized pregnant occupants in car crashes. Annu Proc Assoc Adv Automot Med. 2002;46:355–66.
130. Stone IK. Trauma in the obstetric patient. Obstet Gynecol Clin North Am. 1999 Sep;26(3):459–67.

Non-obstetric Intra-Abdominal Surgery During Pregnancy

35

Sorina Grisaru-Granovsky

Bullet Points

- 1–2% of pregnant women undergo non-obstetric intra-abdominal surgery.
- Appendicitis is the most common non-obstetric surgery performed in pregnant women.
- Focus on fetal well-being may erroneously dominate care decisions for pregnant women with intra-abdominal pathology; delayed surgery is associated with worse maternal and neonatal outcomes.
- Diagnostic imaging may require special considerations; however, pregnant women who have an indication for x-ray studies should not be denied them.
- Most imaging techniques, including CT, use an ionizing radiation dose below 50 mGy and should be offered to pregnant women if required for diagnosis.
- The American College of Obstetrics and Gynecologists (ACOG) recommends that MRI be utilized despite pregnancy when appropriate in both elective and emergency situations.
- Invasive radiology may be performed during pregnancy, including ERCP; some modifications may be introduced to minimize procedure duration and radiation exposure.
- The anesthetic technique and the medications used for anesthesia should be selected as guided by patient condition and the type of surgery required.
- Intraoperative fetal monitoring should be reserved for cases where an obstetrician is available and prepared, and intervention for fetal indications is possible without endangering the mother during the surgical procedure.
- Laparoscopy is safe and feasible during any trimester of pregnancy.

35.1 Introduction

The estimated incidence of non-obstetric intra-abdominal surgery is approximately 1–2% among all pregnant women [1]. Incidental non-obstetric surgery has been described at every stage of pregnancy: 42%, 35%, and 23% during the first, second, and third trimesters, respectively [2, 3]. Although fetal/neonatal teratogenicity

S. Grisaru-Granovsky (✉)
Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Shaare Zedek Medical Center, Hebrew University Jerusalem, Jerusalem, Israel
e-mail: sorina@szmc.org.il

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_35

concerns may be relevant, including the hazard of possible preterm birth, surgery should never be delayed if indicated according to nonpregnant criteria. The general consensus is that a pregnant woman should not be denied any requisite surgery, regardless of gestational age. The timing and choice of surgery should be based on urgency and diagnosis (i.e., solely the maternal indications for surgery).

Despite its relative rarity and some overlapping reports, overall 12,452 non-obstetric surgeries during pregnancy were reported in the literature between 1996 and 2002 [2]. Appendicitis and biliary tract disorders constitute the most common non-obstetric intra-abdominal conditions requiring abdominal surgery during pregnancy (excluding adnexa/ovarian and trauma surgery which is discussed in Chap. 34) [2].

35.2 Pre-surgery Diagnostic Imaging

Management of acute abdominal pain in a pregnant woman is a difficult diagnostic and clinical task, requiring a systematic evaluation of the entire abdomen (Fig. 35.1). The anatomical and physiological alterations which take place during pregnancy include changes in vital signs, cranial displacement of the appendix, and altered laboratory values, e.g., physiologic leukocytosis. Imaging may be limited due to the enlarged uterus and the conception products. In parallel, concerns may arise regarding maternal and fetal radiation exposure dose and the safety of iodinated and gadolinium-based contrast agents. Practitioners may unjustifiably hesitate to utilize radiologic techniques in the pregnant woman even in emergency conditions; such hesitation could lead to delayed diagnosis of life-threatening conditions.

35.2.1 Ionizing Radiation Techniques

X-ray studies: Pregnant women who have an indication for x-ray studies should not be denied them due to pregnancy. Exposure to ionizing radiation doses of less than 50 mGy has not been associated with more adverse pregnancy outcomes than exposure to contemporary life background radiation alone. Most diagnostic imaging techniques use an ionizing radiation dose below 50 mGy and should be offered to pregnant women if appropriate to the diagnostic goal and the facilities available [4, 5].

The teratogenic and carcinogenic effects of ionizing radiation on the developing fetus have been ascertained and are addressed in guidelines released by the American College of Radiology (ACR) [6, 7]. Radiation teratogenicity is dose-dependent. In the preimplantation-organogenesis stages, an embryo radiation dose of 50–100 mGy may cause failure of implantation and spontaneous abortion. The developing fetus between 8 and 15 weeks of gestation is most sensitive to radiation; fetal radiation doses above 100–200 mGy are associated with intrauterine growth restriction, microcephaly, and neuro-developmental impairment. After the 15th gestational week, the fetus is less sensitive to radiation effects on the central nervous system. An increased risk of malformation has been reported at fetal doses above 150–200 mGy, and fetal damage has been reported to occur at exposures greater than 500 mGy [8]. The carcinogenic risk of ionizing radiation is still controversial at doses less than 100 mSv. The association of exposure to radiation on the risk of developing childhood cancers may be greater if exposure occurs earlier in the pregnancy [8].

Computerized tomography (CT): CT is an essential imaging modality in the acute setting where it can serve as a triage tool, thus preventing delays in diagnoses that might result in increased morbidity and mortality. The diagnostic use of CT has increased in the general population and is also acceptable for pregnant women [9, 10]. In any clinical setting, emergent or otherwise, this diagnostic modality should not be denied in pregnancy when indicated. However, radiation dose reduction techniques, for example, thicker slices, may be utilized [11].

Ultrasound is useful in diagnosing acute appendicitis in pregnant women and may prevent unnecessary surgery [12, 13]. However, despite encouraging reports in the literature [14, 15], the rate of visualization of the appendix on ultra-

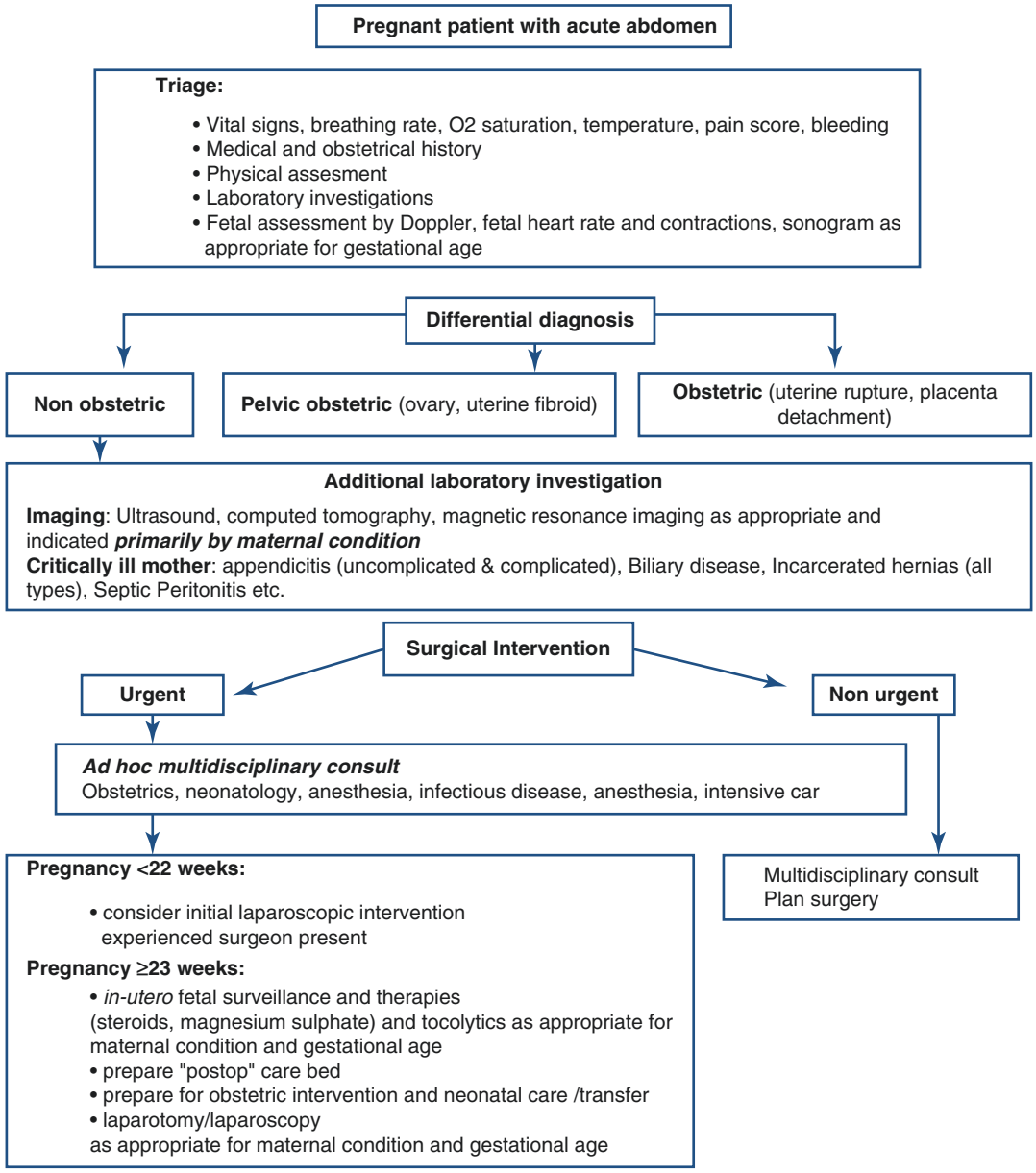


Fig. 35.1 Diagnostic algorithm for pregnant woman with acute abdomen

sound remains low among pregnant women at an advanced gestational age. The ability of ultrasound to diagnose other nonpregnancy-related abdominal pathologies such as colitis, distended stool-filled colon, diverticulitis, omental infarct, partial small bowel obstruction, and terminal ileitis is also relatively limited. Therefore the focus of imaging in pregnant women with abdominal pain has shifted to MRI.

Magnetic resonance imaging (MRI): Noncontrast MRI has become an integral part of the workup of abdominal pain in pregnancy and the initial triage assessment [16–19]. The American College of Obstetrics and Gynecologists (ACOG) recommends that MRI be utilized despite pregnancy when appropriate in either elective or emergency situations. More recent ACR guidelines state that MRI may be used in

pregnant women regardless of gestational age when the benefit outweighs the risks, as determined by an experienced MRI radiologist [20].

Although MRI has hitherto not been associated with known adverse fetal effects [7], the potential risk of heating effects from radiofrequency pulses, and the effects of acoustic noise on the human fetus have not been thoroughly or systematically evaluated [21–27]. The International Radiation Protection Association (ICNIRP) initially recommended postponing elective MRI until after the first trimester in pregnant women; however, this conservative recommendation was issued before the widespread application of this technique and its benefits to maternal soft tissue contrast and intracranial vascular diagnoses [28].

In order to determine the risk-benefit ratio of performing an MRI during pregnancy, the ACR recommends that three questions be answered:

1. Could the information be obtained by ultrasound?
2. Will this study likely impact or change the care of the patient?
3. Could this study be postponed until the patient is no longer pregnant?

Alternative options are more relevant in the earlier stages of pregnancy when the uterus and fetus do not obscure the abdominal viscera and vasculature. Furthermore, in most acute/emergency situations, the potential diagnostic benefit derived from use of MRI is believed to outweigh the risks even in the first trimester.

The optimal MRI protocol for investigating abdominal pain during pregnancy remains unclear. Until it is clarified, there are means of modifying the MRI protocol in order to decrease the likelihood of fetal risk without compromising the mother. For example, one study showed in a large cohort of pregnant patients that MRI has high diagnostic value in the workup of acute appendicitis: 100% negative predictive value and sensitivity and 99.5% specificity [29]. In pregnant patients with suspected appendicitis, the diagnostic performance of MRI remained unchanged if sagittal or both coronal and sagittal SSH-T2WI were omitted [30]. Furthermore, performance of MRI may prevent unnecessary surgery in pregnant women; one study showed that this imaging modality provided an alternative diagnosis for abdominal pain in nearly half of the exams deemed negative for appendicitis in this population, leading to reevaluation of therapeutic options [29].

Intravenous contrast media: Current knowledge regarding the effects of gadolinium and iodinated contrast agents on the human embryo or fetus is limited. Iodinated contrast material crosses the human placenta and is absorbed into the fetal thyroid. It may therefore cause neonatal hypothyroidism. However, this effect is unlikely with a single dose, thus it seems even less likely that a single dose would be teratogenic [31, 32]. The fetal half-life of gadolinium is unknown. Animal studies show that gadolinium crosses the placenta and appears in the fetal bladder. These models are currently used to extrapolate findings as to the effects of gadolinium in humans, which is at this point hypothetical. In these models, once gadolinium has passed the placenta it remains in the amniotic fluid; the fetus can excrete, swallow, and reabsorb gadolinium via the gastrointestinal tract for an indefinite amount of time [22, 23]. Limited evidence from animal studies suggests that gadolinium does have a teratogenic effect [33]. Thus, gadolinium should be used during pregnancy only if considered justified for maternal benefit by experts.

Some procedures such as endoscopic retrograde cholangiopancreatography (ERCP) have typically been avoided in pregnancy. However, when faced with an explicit indication such as cholangitis, biliary pancreatitis or symptomatic choledocholithiasis, ERCP is a less invasive approach than surgery for bile duct pathology [34]. Furthermore, postponement of ERCP carries significant maternal morbidity and increases the risk for preterm delivery as well as for adverse fetal and neonatal outcomes [34]. Strategies to perform ERCP in pregnancy with minimal fluoroscopy exposure include using modern equipment, minimizing the exposure time, minimizing exposure, maintaining the image intensifier close to the patient and the required image site, limiting use of the enhanced modes (boost and magnifica-

tion), and using a low frame rate [35]. Additional suggestions to limit exposure include use in the manual mode with higher kV (at least 75) and lower mA settings and keeping time for the endoscopist in order to increase awareness and potentially limit exposure time. Pregnancy appears to be an independent risk factor for post-ERCP pancreatitis, with an odds ratio 2.8, (95%CI 2.1–3.8) [36]. This may be related to the attempts to limit fluoroscopy during cannulation or to an inherent mechanism associated with pregnancy.

35.3 Maternal Considerations and Outcomes

A focus on fetal well-being may erroneously dominate care decisions for pregnant women with intra-abdominal pathology. This is a concern and may contribute to surgical care that differs in pregnancy when compared to the nonpregnant state.

35.3.1 Maternal Morbidity

A study of 9714 pregnant women with biliary disease demonstrated advantages to surgical management of pregnant women (i.e., with cholecystectomy); these women had significantly lower rates of maternal (4 vs 17%) and fetal (6 vs 17%) complications versus women managed conservatively. In the same study, after matching pregnant women to nonpregnant controls (according to age and primary diagnosis), a higher likelihood of open (rather than laparoscopic) cholecystectomy was reported, while there were more surgical complications among women undergoing an open procedure [37].

35.3.2 Maternal Mortality

Among 2000 pregnant women who underwent non-obstetric surgery as reported by Erekson et al., the mortality rate was 0.25% [38]. Four of the five women who died had intra-abdominal surgery; preoperative risk factors for death included emergency surgery, systemic inflammatory response syndrome and septic shock [38]. A literature search [39, 40] revealed only one report of maternal death following laparoscopic cholecystectomy in the 20th week of pregnancy. This mother died due to massive intra-abdominal hemorrhage 2 weeks postoperatively. However, maternal "near miss" events are underreported following surgery (see also Chap. 3). The diagnosis may be delayed and related to hemorrhage, obesity, other related thromboembolic phenomena, sepsis due to delayed diagnosis, and surgery for perforation of viscus [41].

35.4 Fetal and Neonatal Outcomes

Pregnant women who must undergo non-obstetrical surgery should be informed of the risks to their pregnancy, but at the same time it must be clarified that these considerations are always superseded by maternal well-being.

35.4.1 Miscarriage

Women may be concerned about the risk of miscarriage following intra-abdominal surgery. Overall, 6% of pregnant women who undergo any surgical intervention will report miscarriages [2]. Pregnant women exposed to a surgical intervention during the first trimester had a high (10.5%) reported rate of miscarriage [2]. It is difficult to assess the relative contributions of the surgical condition, the surgical technique, and individual maternal risk factors (e.g., age, previous reproductive techniques to achieve pregnancy, comorbidities); thus, these miscarriage reports should interpreted with caution when counseling pregnant women who require non-obstetric intra-abdominal surgery.

35.4.2 Preterm Delivery

Many studies have reported an increased incidence of premature delivery after non-obstetric surgery [42, 43] .This finding may be attributed

to the surgery itself, to manipulation of the uterus or to maternal underlying conditions (i.e., sterile inflammation, infectious inflammation, sepsis). The most recent estimate of the overall rate of prematurity related to non-obstetric surgery is approximately 8.2% [2], which is actually comparable/lower than the overall preterm birth rate in the developed world, which ranges between 5.5 and 11.5% [42, 43].

Unfortunately, there is little recent progress for prevention of preterm birth. Traditionally, open abdominal techniques and surgeries that do not manipulate the uterus have been associated with the lowest risk for preterm labor during the second trimester [44]. Given the newer evidence regarding the rates of preterm delivery and potential maternal complications stemming from modified surgical techniques, an informed discussion should be conducted with the mother regarding the preferred mode of surgery.

35.5 Anesthesia Considerations

Patient positioning and resuscitation: Increased intra-abdominal pressure can lead to decreased inferior vena caval return, resulting in decreased cardiac output and subsequent maternal hypotension or hypoxia. The fetus is dependent on maternal hemodynamic stability [45]. Therefore, to minimize surgical risk, gravid patients with hemodynamic compromise should optimally be positioned in a 15° left-tilted supine position. Minimizing the degree of reverse Trendelenburg position for upper abdominal surgery may also further reduce uterine compression of the vena cava. If a laparoscopic technique is used, gas insufflation should be limited as noted above. If required, maternal resuscitation should be conducted vigorously following standard protocols (for additional details see Chaps. 7, 27 and 28) as management principles are similar.

Choice of antibiotics: Surgical site infection is an ongoing concern in pregnant women undergoing non-obstetric surgery. As noted above, the laparoscopic approach has been associated with a lower rate of infectious complications than the open approach in both appendectomies and cholecystectomies in pregnant women [46]. Multiple studies have shown that delaying antibiotic administration until after cord clamping during obstetric surgery (namely, cesarean delivery) results in significantly increased rates of composite maternal postpartum infectious morbidity as compared with administration before surgery; this, without affecting neonatal outcomes [47]. As the fetus is intended to remain in situ, there is no point in delaying antibiotic treatment to any time other than that recommended by the guidelines for the general population. To date there is no support for a change in the routine antibiotic therapies, and pregnant women should receive those recommended for the non-obstetric population (see Chap. 38). Future studies should be directed toward protocols and safety of prophylactic antibiotics for non-obstetric surgery during pregnancy [39].

Anesthetic technique: The choice of anesthetic technique and the selection of appropriate anesthetic drugs should be guided by patient condition and the type of surgery required. Anesthetic considerations for the critically ill patient including aspiration risk and management of the obstetric airway are detailed elsewhere in this book (see Chap. 21).

Fetal preparation and monitoring: Once a decision has been made that a pregnant woman requires non-obstetric intra-abdominal surgery, several measures should be undertaken to optimize neonatal outcome. These include administration of steroids to promote fetal lung maturation until 34 weeks gestation, tocolytics, and neuroprotective magnesium sulfate administered intravenously as a 6 g bolus followed by a constant infusion of 1–2 g/h for up to 12 h between 24 and 31 + 6 weeks [48–50]. High-dose steroids may depress the normal physiologic immune response to sepsis. Tocolytics and magnesium may cause vasodilation, causing an additional, secondary decrease in blood pressure in an already septic patient. On the other hand, the effects of steroids on fetal lung maturation occur hours after administration. As the potential side effects of these drugs could endanger the mother if given unnecessarily, decisions regarding the timing of their administration should be preceded by multidisciplinary discussion of their potential risks versus their benefits. However, if any of the above inter-

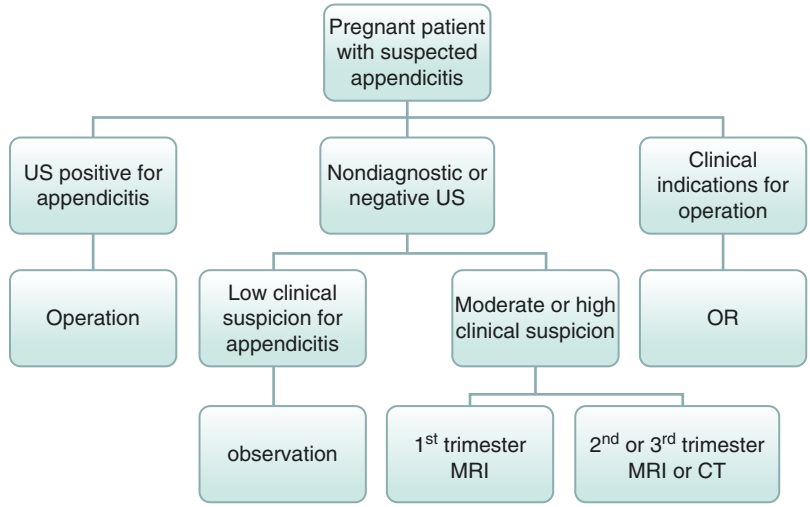


Fig. 35.2 Diagnostic algorithm for pregnant woman with suspected appendicitis. Reproduced with permission from Freeland M, King E, Safcsak K, Durham R. Diagnosis of appendicitis in pregnancy. The American Journal of Surgery, 2009; 198:753–758

ventions are not immediately available, surgery should not be delayed for their administration.

If the fetus is considered previable, the fetal heart rate should be ascertained by Doppler before and after the surgical procedure. In cases where the fetus is considered to be viable, electronic fetal heart rate and contraction monitoring should be performed before and after the surgical procedure. The decision whether to perform electronic fetal monitoring intraoperatively is not always easy. This decision should be guided by the surgical technique required and discussed in a multidisciplinary setting. Intraoperative monitoring should be reserved for cases where an obstetrician is available and prepared to intervene during the surgical procedure for fetal indications. Such intervention should never endanger the mother. The gestational age must be appropriate and neonatal care must be available. These considerations are outlined in the Committee Opinion on Non-obstetric Surgery During Pregnancy of the American Society of Anesthesiologists [51].

35.6 Specific Intra-abdominal Surgical Conditions

35.6.1 Appendicitis

Suspected appendicitis is the most common indication for non-obstetric surgery in pregnancy; it occurs in approximately 1:500–2000 pregnancies annually [52], accounting for one-quarter of all non-obstetric indications for surgery during pregnancy, Fig. 35.2. The first and second trimester are the most common periods for appendicitis; 7.4 and 7.3/10,000 person years, respectively, and it is less frequent during the third trimester (4.6/10,000 person years) [53]. The diagnosis of appendicitis is particularly difficult during pregnancy due to blunting of the signs of peritonitis and altered appendix location. Typically, appendicitis in pregnancy is associated with right lower quadrant pain and direct abdominal tenderness is frequently noted; however, rebound and guarding may be absent. As noted above, anatomical and physiological changes complicate diagnosis; the increase in uterine volume displaces the appendix, and the presence of physiological leukocytosis is also misleading. Pain may present in the back or flank, suggesting renal pathologies. Psoas irritation may be absent altogether [52].

As note above, clinicians may mistakenly be reluctant to use imaging techniques to advance the diagnosis. After diagnosis is made there may also be some hesitation to operate, particularly in women with advanced gestational age. Such hesitation may lead to unnecessary delays in diagnosis and treatment. The risk of appendix perforation is high, particularly when surgery is delayed for more than 24 h after onset of symptoms [54]. Reports describe perforation rates ranging between 14 and 43% among pregnant women undergoing appendectomy [55, 56]. A ruptured

appendix is subsequently 3–10 times more common in women, and specifically in pregnant women in the third trimester of pregnancy and the immediate postpartum period, versus the reported rate for the general adult population [57–63].

Recent suggestions of conservative antibiotic therapy for patients with uncomplicated appendicitis may appeal to those reluctant to perform surgery during pregnancy [64]. Furthermore, the diagnosis of "uncomplicated versus complicated" appendicitis in pregnancy may prove difficult to ascertain. However, non-operative management of appendicitis may lead to high maternal morbidity. One study compared patients with appendicitis managed using conservative versus surgical management; 6% of the study cohort was pregnant. Among these pregnant women, there were statistically significant higher rates of maternal morbidity with conservative management. These included a sixfold increase in the risk of septic shock (OR 6.3; 95% CI 1.9, 20.8), a one-and-a-half times higher likelihood of peritonitis (OR 1.6; 95%CI 1.3,2.1) and a greater than twofold increase in venous thromboembolism [65]. In a UK cohort of 362,219 pregnancies with appendicitis, the third trimester was reportedly a challenging period to diagnose appendicitis [53].

The complications related to appendicitis even with appendectomy are significantly higher in pregnant women as compared to nonpregnant women. One study showed that the rates of peritonitis were 20.3% in pregnant women with appendicitis versus 16.1% in nonpregnant women with appendicitis (OR 1.3; 95%CI 1.2, 1.4); sepsis and septic shock were also more common in the pregnant population. The rates of transfusion, bowel obstruction, pneumonia, and other postoperative infections, as well a hospital stay of more than 3 days, were also increased [65]. Additionally, an open surgical approach is more often chosen when surgery is performed during pregnancy, especially when the enlarged uterus poses a challenge to the laparoscopic approach. The increased maternal morbidity associated with appendicitis in pregnancy may therefore be explained not only by the increased rate of peritonitis but also by a twofold increase in laparotomy as compared to the general population; laparoscopy is used in only 43–58% of women with appendicitis [65, 66]. For women who remain pregnant, the risk of dehiscence of the appendectomy incision during labor and vaginal delivery is unlikely to be increased when the aponeurosis is properly approximated [67]. A study using a US database found that among 7114 pregnancies complicated by appendicitis, preterm birth and cesarean delivery were significantly more likely in women with peritonitis, reflecting a delayed diagnosis or more severe disease [68]. Maternal mortality is estimated to be low when appendicitis is promptly diagnosed and treated [69, 70].

35.6.2 Recommended Surgical Approach to Appendectomy

Regardless of the surgical procedure at hand, the choice to apply laparoscopy during pregnancy is best determined by the anatomical point of access, the length of the procedure and subsequent duration of exposure to anesthetics, the difficulty of patient positioning for optimal respiratory support, maternal and fetal oxygenation demands, and ultimately, the training and experience of the surgeon (Fig. 35.3). The complexity of surgical intervention increases with gestational age. Laparoscopy during pregnancy is best performed by an experienced surgeon in a tertiary medical center, with facilities to manage delivery and the neonate if the pregnancy is viable [51]. If no such option exists and the mother has been admitted to a medical center with limited laparoscopic surgery experience, open surgery may be the better option [71, 72].

The optimal surgical approach to a pregnant woman with suspected appendicitis is through a transverse incision in McBurney's point. Equally good alternatives surgical approaches to the diagnosis and treatment of surgical conditions that may mimic appendicitis include incision at the point of maximum sensitivity or a midline vertical incision from the umbilicus to the ramus pubis. Uterine traction and handling of the uterus should be minimal.

Both early and later reports agree that laparoscopic appendectomy can be performed during all trimesters with few maternal complications

Ultrasongraphic imaging during pregnancy is safe and useful in identifying the cause of acute abdominal pain in the pregnant patient (moderate; strong).
Expeditious and accurate diagnosis should take precedence over concerns for ionizing radiation. Cumulative radiation dosage should be limited to 5–10 rads during pregnancy (moderate; strong).
Contemporary multidetector computed tomography protocols deliver a low radiation dose to the fetus and may be used judiciously during pregnancy (moderate; weak).
MRI without intravenous gadolinium can be performed at any stage of pregnancy (low; strong).
Adminidtration of radionucleotides for diagnostic studies is generally safe for mother and fetus (low; weak).
Intraoperative and endoscopic cholangiography exposes the mother and fetus to minimal radiation and may be used selectively during pregnancy. The lower abdomen should be shielded when performing cholongiography during pregnancy to decrease the radiation exposure to the fetus (low; weak).
Diagnostic laparoscopy is well tolerated and effective when used selectively in the workup and treatment of acute abdominal processes in pregnancy (moderate; strong).
Laparoscopic treatment of acute abdominal disease has the same indications in pregnant and nonpregnant patients (moderate; strong).
Laparoscopy can be safely performed during any trimester of pregnancy (moderate; strong).
Gravid patients should be placed in the left lateral decubitus position to minimize compression of the vena cava (moderate; strong).
Initial abdominal access can be safely performed with an open (Hasson) technique, Veress needle, or optical trocar, if the location is adjusted according to fundal height and previous incisions (moderate; weak).
CO_2 insufflation of 10–15 mmHg can be safely used for laparoscopy in the pregnant patient (moderate; strong).
Intraoperative CO_2 monitoring by capnography should be used during laparoscopy in the pregnant patient (moderate; strong).
Intraoperative and postoperative pneumatic compression devices and early postoperative ambulation are recommended prophylaxis for deep venous thrombosis in the gravid patient (moderate; strong).
Laparoscopic cholecystectomy is the tratment of choice in the pregnant patient with gallbladder disease, regardless of trimester (moderate; strong).
Choledochlithiasis during pregnancy may be managed with preoperative endoscopic retrograde cholangiopancreatography with sphincterptomy followed by laparoscopic cholecystectomy, laparodcopic comman bile duct exploration, or postoperative endoscopic retrograde cholangiopancreatography (moderate; strong).
Laparoscopic appendectomy may be performed safely in pregnant patients with appendicitis (moderate; strong).
Laparoscopic adrenalectomy, nephrectomy, splenectomy, and mesenteric cyst excision are well tolerated procedures in pregnant patients (low; weak).
Laparoscopy is a well tolerated and effective treatment in gravid patients with symptomatic ovarian cystic masses. Observation is acceptable for all other cystic provided ultrasound is not concerning for malignancy and tumor markers are normal. Initial obeservation is warranted for most cystic lesions <6 cm in size (low; strong).
Laparoscopy is recommended for both diagnosis and treatment of adnexal torsion unless clinical severity warrants laparotomy (low; strong).
Fetal heart monitoring should occur pre and postoperatively in the setting of urgent abdominal surgery during pregnancy (moderate; strong).
Obstetric consultation can be obtained pre and/or postoperatively based on the severity of the patient's disease and availability (moderate; strong).
Tocolytics should not be used prophyloctically in pregnant women undergoing surgery but should be considered perioperatively when signs of preterm labor are present (high; strong).

Fig. 35.3 Guidelines for laparoscopic surgery suring pregnancy, developed under the auspices of the Society of American Gastrointestinal Endoscopic Surgeons (taken from non-obstetric anesthesia during pregnancy, Heesen et al. Curr Opin Anesthesiol 2016, 29:297–303)

[73–77] even after perforation [46]. A systematic review [78] of laparoscopic management for non-specific abdominal pain and suspected appendicitis among pregnant women concluded that laparoscopy was beneficial, with a high rate of specific diagnoses and a low rate of removal of normal appendices compared with open appendectomy. To minimize risk, use of any instruments in the cervix should be avoided altogether. Trocar insertion should only be performed under direct vision, and the location of insertion should take into account uterine size. Gas insufflation should be minimized and insufflation pressures should not exceed 10–15 mmHg.

While there are some reports of an increased rate of fetal loss when compared with open appendectomy (OR 1.91, 95% CI 1.31–2.77%) [79, 80], none of those studies are adjusted for confounders (e.g., maternal age, gestational age, complicated appendicitis, surgeon experience).

35.7 Biliary Tract Disease

Approximately 0.05–0.8% of pregnant women have symptomatic gallstones [81]. Among 1,064,089 pregnancies, 1882 (0.2%) had gallstone disease. Of these, 239 (13%) had an antepartum

cholecystectomy and 1643 (87%) were managed conservatively. Of those managed conservatively, 319 (19%) had a postpartum cholecystectomy [82]. Biliary surgery and biliary procedure type should not be delayed and indications should be as for nonpregnant patients. Delays are associated with worse outcomes [39]. Surgery may be required for perforated gallbladder, common bile duct obstruction or for repeated attacks of biliary colic and biliary pancreatitis, as for any patient. Current evidence supports selecting a treatment approach similar to one acceptable for the general population.

In the general population, a conservative approach with administration of antibiotic therapy alone has been associated with poorer outcomes than in an open surgical approach, and both are associated with poorer outcomes than closed drainage [83]. Nonsurgical (conservative) management, including antibiotics and intravenous fluid supplementation, has also been reported in pregnant women. In this population too this approach has been associated with high rates of symptom recurrence and disease progression [52, 84, 85]. Furthermore, pregnant women with biliary tract disease who were managed conservatively had a higher risk of maternal readmission (ARR [absolute risk reduction] 4.7, 99% CI 4.2, 5.3) and one in five (19%) eventually underwent postpartum cholecystectomy [82]. Although most women with gallstones are managed conservatively during pregnancy, surgical management decreases the readmission rates [82]. Despite this, most women with biliary tract disease during pregnancy remain managed conservatively [86].

No differences have been observed in mode of delivery or preterm birth rates for women treated surgically versus conservatively. However, pregnant women with symptomatic gallstones causing biliary pain or with biliary complications such as acute cholecystitis or pancreatitis have a higher risk of planned preterm birth as compared to women with an incidental finding of gallstones (ARR (absolute risk reduction) 1.6, 99%CI 1.2, 2.1). This likely reflects caregiver anxiety rather than the natural course of the disease or therapy [86].

Despite the fact that symptomatic biliary tract disease is a leading indication for emergency non-obstetric surgery, fetal death has not been reported in association with this type of surgery. This may be based on the natural course of the disease, which rarely causes viscus perforation, or on timely and accurate diagnosis of biliary complications when compared to the diagnosis of appendicitis [81, 87, 88]. However, one cohort study did report an increased risk of preterm birth, jaundice, small-for-gestational age, respiratory distress syndrome, and intrauterine fetal death associated with pancreatitis secondary to gallstone disease during pregnancy, regardless of surgical management [82]. While these are rare complications, the mother should be informed of these risks, and they should not be disregarded.

35.7.1 Recommended Surgical Approach to Cholecystectomy

The operative management of symptomatic cholelithiasis (biliary colic, acute and chronic cholecystitis, choledocholithiasis, and biliary pancreatitis) during pregnancy can be either laparoscopic or open cholecystectomy. Traditionally, the timing of laparoscopic or open biliary tract surgery in pregnancy was determined mainly by gestational age; if the disease presented during early pregnancy, the thought was that nonemergency surgery could be delayed until the second trimester (Fig. 35.3). By this time, the risk of miscarriage was believed to be lower, the risk incurred by exposure to anesthetics decreased, and there was still the benefit of operating in an abdomen without an overly large gravid uterus [87]. A recent meta-analysis compared the surgical laparoscopic approach to the open approach and reported that laparoscopic surgery is associated with significantly fewer maternal and fetal complications, less surgical complications, and a shorter hospital stay despite similar duration of surgery [40]. However, 91% of the women in this meta-analysis were in the first or second trimester at the time of surgery [40], and most cholecystectomies (63.4%) were performed during the

Table 35.1 Differential diagnosis for right upper quadrant pain in pregnancy

Appendicitis
Cholangitis
Cholecystitis
Cholelithiasis
Hepatitis
Liver hematoma
Pancreatitis
Peptic ulcer
Pneumonia
Pyelonephritis

second trimester. As pregnancies advanced into the third trimester, there was an increasingly greater likelihood of open surgery [40]. Although the reasons for performing open surgery in advanced pregnancies were not stated in any of the studies, they are presumably related to technical considerations. These may include limited operative space, difficulties in managing the required surgery with the required alteration in laparoscopic port placement and poorer visualization of the operative field due to obstruction by the gravid uterus. Regardless of cause, this finding supports early intervention for symptomatic gallstones (i.e., in the first and second trimester), as at this time a laparoscopic approach is more likely to be used. The one caveat to this recommendation is the fact that the only maternal death report was in the laparoscopic group (0.001%). The rate of preterm delivery seemed slightly higher after laparoscopic surgery, but this finding did not reach statistical significance. Whether this finding stemmed from the limited sample size or from actual lack of increased risk remains unclear [40] (Table 35.1).

35.8 Hernias

Another cause of emergency non-obstetric surgery during pregnancy is hernias that may become incarcerated or strangulated due to increased intra-abdominal pressure [89, 90]. Superficial surgical site infection was the most common morbidity in pregnant women undergoing open umbilical hernia repair [91]. The long-term recurrence rate of urgent complicated umbilical hernia repair performed in pregnant women has not been evaluated to date.

35.9 Obesity and Bariatric Surgery

Obesity and bariatric surgery have become increasingly common and thus merit special attention during pregnancy [91, 92]. During the first pregnancy after bariatric surgery, the rate of surgery for intestinal obstruction was 1.5% among women that had undergone bariatric surgery versus 0.02% among women with similar Body Mass Index and no previous surgery. The rate of diagnostic laparoscopy or laparotomy was also significantly higher (1.5 versus 0.1%) [93]. Young women who are considering bariatric surgery should be informed that this could potentially be an issue during pregnancy.

35.10 Robotic Surgery

At the time of this writing, the use of robotics for acute abdominal surgery has not been reported for pregnant women. There is a single report on the use of robotic surgery in ovarian cystectomy during pregnancy. Lower levels of intra-abdominal pressure were required for performing the six successful procedures described [94]. The authors postulated that the use of robotics increases dexterity, similar to an open procedure. They also postulated that performing laparoscopy in these women would likely have been accompanied by increased blood loss and even conversion to laparotomy.

35.11 Conclusions

Diagnosing the non-obstetric causes of acute abdominal/pelvic symptoms during pregnancy is challenging. Imaging should be used as required to optimize decision-making and to reduce the incidence of unfavorable maternal and fetal

outcomes. The most significant maternal risks are engendered by delays in treatment. The course of the intra-abdominal disease and overall maternal well-being will also determine fetal outcome. Fetal death is highest in perforated appendicitis (resulting from delayed care).

Non-obstetric surgery during pregnancy requires a multidisciplinary approach, including availability of neonatologists and specialized neonatal care. Anesthesia during intra-abdominal surgery in pregnant women is a challenge regardless of gestational age, as the intra-abdominal pathology compounds the risks of airway and circulatory compromise. Laparoscopy is safe and feasible in any trimester of pregnancy and may improve maternal outcomes without adversely affecting pregnancy outcomes.

References

1. Crowhurst JA. Anaesthesia for non-obstetric surgery during pregnancy. Acta Anaesthesiol Belg. 2002;53(4):295–7.
2. Cohen-Kerem R, Railton C, Oren D, Lishner M, Koren G. Pregnancy outcome following non-obstetric surgical intervention. Am J Surg. 2005;190(3):467–73.
3. Mazze RI, Källén B. Reproductive outcome after anesthesia and operation during pregnancy: a registry study of 5405 cases. Am J Obstet Gynecol. 1989;161(5):1178–85.
4. Wang PI, Chong ST, Kielar AZ, Kelly AM, Knoepp UD, Mazza MB, Goodsitt MM. Imaging of pregnant and lactating patients: part 1, evidence-based review and recommendations. Am J Roentgenol. 2012;198(4):778–84.
5. Mettler FA Jr, Huda W, Yoshizumi TT, Mahesh M. Effective doses in radiology and diagnostic nuclear medicine: a catalog. Radiology. 2008;248(1):254–63.
6. Wagner LK, Applegate K. ACR practice guideline for imaging pregnant or potentially pregnantadolescents and women with ionizing radiation. https://www.who.int/tb/advisory_bodies/impact_measurement_taskforce/meetings/prevalence_survey/imaging_pregnant_arc.pdf. Last Accessed 13 Dec 2018.
7. [No authors listed]. Committee opinion no. 723 summary: guidelines for diagnostic imaging during pregnancy and lactation. Obstet Gynecol. 2017;130(4):933–4.
8. Doll R, Wakeford R. Risk of childhood cancer from fetal irradiation. Br J Radiol. 1997;70:130–9.
9. Lazarus E, Debenedectis C, North D, Spencer PK, Mayo-Smith WW. Utilization of imaging in pregnant patients: 10-year review of 5270 examinations in 3285 patients--1997-2006. Radiology. 2009;251(2):517–24.
10. Goldberg-Stein S, Liu B, Hahn PF, Lee SI. Body CT during pregnancy: utilization trends, examination indications, and fetal radiation doses. AJR Am J Roentgenol. 2011;196(1):146–51.
11. Wagner LK, Huda W. When a pregnant woman with suspected appendicitis is referred for a CT scan, what should a radiologist do to minimize potential radiation risks? Pediatr Radiol. 2004;34(7):589–90.
12. Bendeck SE, Nino-Murcia M, Berry GJ, Jeffrey RB Jr. Imaging for suspected appendicitis: negative appendectomy and perforation rates. Radiology. 2002;225(1):131–6.
13. Long SS, Long C, Lai H, Macura KJ. Imaging strategies for right lower quadrant pain in pregnancy. AJR Am J Roentgenol. 2011;196(1):4–12.
14. Lim HK, Bae SH, Seo GS. Diagnosis of acute appendicitis in pregnant women: value of sonography. AJR Am J Roentgenol. 1992;159(3):539–42.
15. Lehnert BE, Gross JA, Linnau KF, Moshiri M. Utility of ultrasound for evaluating the appendix during the second and third trimester of pregnancy. Emerg Radiol. 2012;19(4):293–9.
16. Oto A, Ernst RD, Ghulmiyyah LM, Nishino TK, Hughes D, Chaljub G, Saade G. MR imaging in the triage of pregnant patients with acute abdominal and pelvic pain. Abdom Imaging. 2009;34(2):243–50.
17. Pedrosa I, Lafornara M, Pandharipande PV, Goldsmith JD, Rofsky NM. Pregnant patients suspected of having acute appendicitis: effect of MR imaging on negative laparotomy rate and appendiceal perforation rate. Radiology. 2009;250(3):749–57.
18. Rapp EJ, Naim F, Kadivar K, Davarpanah A, Cornfeld D. Integrating MR imaging into the clinical workup of pregnant patients suspected of having appendicitis is associated with a lower negative laparotomy rate: single-institution study. Radiology. 2013;267(1):137–44.
19. Theilen LH, Mellnick VM, Longman RE, Tuuli MG, Odibo AO, Macones GA, Cahill AG. Utility of magnetic resonance imaging for suspected appendicitis in pregnant women. Am J Obstet Gynecol. 2015;212(3):345.e1–6.
20. Kanal E, Barkovich AJ, Bell C, Borgstede JP, Bradley WG Jr, Froelich JW, Gilk T, Gimbel JR, Gosbee J, Kuhni-Kaminski E, Lester JW Jr, Nyenhuis J, Parag Y, Schaefer DJ, Sebek-Scoumis EA, Weinreb J, Zaremba LA, Wilcox P, Lucey L, Sass N, ACR Blue Ribbon Panel on MR Safety. ACR guidance document for safe MR practices: 2007. AJR Am J Roentgenol. 2007;188(6):1447–74.
21. Shellock FG, Kanal E. Policies, guidelines, and recommendations for MR imaging safety and patient management. SMRI safety committee. J Magn Reson Imaging. 1991;1(1):97–101.
22. Novak Z, Thurmond AS, Ross PL, Jones MK, Thornburg KL, Katzberg RW. Gadolinium-DTPA transplacental transfer and distribution in fetal tissue in rabbits. Investig Radiol. 1993;28(9):828–30.

23. Chapon C, Franconi F, Roux J, Le Jeune JJ, Lemaire L. Prenatal evaluation of kidney function in mice using dynamic contrast-enhanced magnetic resonance imaging. Anat Embryol (Berl). 2005;209(4):263–7.
24. Coakley FV, Glenn OA, Qayyum A, Barkovich AJ, Goldstein R, Filly RA. Fetal MRI: a developing technique for the developing patient. AJR Am J Roentgenol. 2004;182(1):243–52.
25. Baker PN, Johnson IR, Harvey PR, Gowland PA, Mansfield P. A three-year follow-up of children imaged in utero with echo-planar magnetic resonance. Am J Obstet Gynecol. 1994;170(1 Pt 1):32–3.
26. Glover P, Hykin J, Gowland P, Wright J, Johnson I, Mansfield P. An assessment of the intrauterine sound intensity level during obstetric echo-planar magnetic resonance imaging. Br J Radiol. 1995;68(814):1090–4.
27. Kanal E. Pregnancy and the safety of magnetic resonance imaging. Magn Reson Imaging Clin N Am. 1994;2(2):309–17.
28. Kotecha HM, McIntosh LJ, Lo HS, Chen BY, Dupuis CS. What to expect when they are expecting: magnetic resonance imaging of the acute abdomen and pelvis in pregnancy. Curr Probl Diagn Radiol. 2017;46(6):423–31.
29. Kereshi B, Lee KS, Siewert B, Mortele KJ. Clinical utility of magnetic resonance imaging in the evaluation of pregnant females with suspected acute appendicitis. Abdom Radiol (NY). 2018;43(6):1446–55.
30. Shin I, Chung YE, An C, Lee HS, Kim H, Lim JS, Kim MJ. Optimisation of the MR protocol in pregnant women with suspected acute appendicitis. Eur Radiol. 2018;28(2):514–21.
31. Webb JA, Thomsen HS, Morcos SK, Members of Contrast Media Safety Committee of European Society of Urogenital Radiology (ESUR). The use of iodinated and gadolinium contrast media during pregnancy and lactation. Eur Radiol. 2005;15(6):1234–40.
32. Bourjeily G, Chalhoub M, Phornphutkul C, Alleyne TC, Woodfield CA, Chen KK. Neonatal thyroid function: effect of a single exposure to iodinated contrast medium in utero. Radiology. 2010;256(3):744–50.
33. Okuda Y, Sagami F, Tirone P, Morisetti A, Bussi S, Masters RE. Reproductive and developmental toxicity study of gadobenate dimeglumine formulation (E7155) (3)—study of embryo-fetal toxicity in rabbits by intravenous administration. Article in Japanese. J Toxicol Sci. 1999;24(Suppl 1):79–87.
34. Magno-Pereira V, Moutinho-Ribeiro P, Macedo G. Demystifying endoscopic retrograde cholangiopancreatography (ERCP) during pregnancy. Eur J Obstet Gynecol Reprod Biol. 2017;219:35–9.
35. Amis ES. Risks of radiation exposure in the endoscopy suite: principles, cautions, and risks to patients and endoscopy staff. Techn Gastrointest Endosc. 2007;9(4):213–7.
36. Inamdar S, Berzin TM, Sejpal DV, Pleskow DK, Chuttani R, Sawhney MS, Trindade AJ. Pregnancy is a risk factor for pancreatitis after endoscopic retrograde cholangiopancreatography in a National Cohort Study. Clin Gastroenterol Hepatol. 2016;14(1):107–14.
37. Kuy S, Roman SA, Desai R, Sosa JA. Outcomes following cholecystectomy in pregnant and nonpregnant women. Surgery. 2009;146(2):358–66.
38. Erekson EA, Brousseau EC, Dick-Biascoechea MA, Ciarleglio MM, Lockwood CJ, Pettker CM. Maternal postoperative complications after nonobstetric antenatal surgery. J Matern Fetal Neonatal Med. 2012;25(12):2639–44.
39. Sedaghat N, Cao AM, Eslick GD, Cox MR. Laparoscopic versus open cholecystectomy in pregnancy: a systematic review and meta-analysis. Surg Endosc. 2017;31(2):673–9.
40. Estadella J, Español P, Grandal B, Gine M, Parra J. Laparoscopy during pregnancy: case report and key points to improve laparoscopic management. Eur J Obstet Gynecol Reprod Biol. 2017;217:83–8.
41. Barone JE, Bears S, Chen S, Tsai J, Russell JC. Outcome study of cholecystectomy during pregnancy. Am J Surg. 1999;177(3):232–6.
42. Saunders P, Milton PJ. Laparotomy during pregnancy: an assessment of diagnostic accuracy and fetal wastage. Br Med J. 1973;3(5872):165–7.
43. Magro Malosso ER, Saccone G, Simonetti B, Squillante M, Berghella V. US trends in abortion and preterm birth. J Matern Fetal Neonatal Med. 2018;31(18):2463–7.
44. Nadeau-Vallée M, Obari D, Palacios J, Brien MÈ, Duval C, Chemtob S, Girard S. Sterile inflammation and pregnancy complications: a review. Reproduction. 2016;152(6):R277–92.
45. Gaitán HG, Reveiz L, Farquhar C, Elias VM. Laparoscopy for the management of acute lower abdominal pain in women of childbearing age. Cochrane Database Syst Rev. Cochrane Database Syst Rev. 2014;(5):CD007683. https://doi.org/10.1002/14651858.CD007683.pub3. PMID: 24848893.
46. Cox TC, Huntington CR, Blair LJ, Prasad T, Lincourt AE, Augenstein VA, Heniford BT. Laparoscopic appendectomy and cholecystectomy versus open: a study in 1999 pregnant patients. Surg Endosc. 2016;30(2):593–602.
47. Mackeen AD, Packard RE, Ota E, Berghella V, Baxter JK. Timing of intravenous prophylactic antibiotics for preventing postpartum infectious morbidity in women undergoing cesarean delivery. Cochrane Database Syst Rev. 2014;(12):CD009516. https://doi.org/10.1002/14651858.CD007683.pub3.
48. Shepherd E, Salam RA, Middleton P, Makrides M, McIntyre S, Badawi N, Crowther CA. Antenatal and intrapartum interventions for preventing cerebral palsy: an overview of Cochrane systematic reviews. Cochrane Database Syst Rev. 2017;8:CD012077.
49. Crowther CA, Middleton PF, Voysey M, Askie L, Duley L, Pryde PG, Marret S, Doyle LW, AMICABLE Group. Assessing the neuroprotective benefits for babies of antenatal magnesium sulphate: an individual participant data meta-analysis. PLoS Med. 2017;14(10):e1002398.

50. AMICABLE Group. Antenatal magnesium individual participant data international collaboration: assessing the benefits for babies using the best level of evidence (AMICABLE). Syst Rev. 2012;1:21.
51. Committee on Obstetric Practice and the American Society of Anesthesiologists. Committee opinion no. 696: nonobstetric surgery during pregnancy. Obstet Gynecol. 2017;129(4):777–8.
52. Augustin G, Majerovic M. Non-obstetrical acute abdomen during pregnancy. Eur J Obstet Gynecol Reprod Biol. 2007;131(1):4–12.
53. Zingone F, Sultan AA, Humes DJ, West J. Risk of acute appendicitis in and around pregnancy: a population-based cohort study from England. Ann Surg. 2015;261(2):332–7.
54. Tamir IL, Bongard FS, Klein SR. Acute appendicitis in the pregnant patient. Am J Surg. 1990;160:571–6.
55. Andersen B, Nielsen TF. Appendicitis in pregnancy: diagnosis, management and complications. Acta Obstet Gynecol Scand. 1999;78(9):758–62.
56. Yilmaz HG, Akgun Y, Bac B, Celik Y. Acute appendicitis in pregnancy—risk factors associated with principal outcomes: a case control study. Int J Surg. 2007;5(3):192–7.
57. Holzer T, Pellegrinelli G, Morel P, Toso C. Appendectomy during the third trimester of pregnancy in a 27-year old patient: case report of a "near miss" complication. Patient Saf Surg. 2011;5(1):11.
58. Keller M, Felderhoff-Mueser U, Lagercrantz H, Dammann O, Marlow N, Hüppi P, Buonocore G, Poets C, Simbruner G, Guimaraes H, Mader S, Merialdi M, Saugstad OD. Policy benchmarking report on neonatal health and social policies in 13 European countries. Acta Paediatr. 2010;99(11):1624–9.
59. Franca Neto AH, Amorim MM, Nóbrega BM. Acute appendicitis in pregnancy: literature review. Rev Assoc Med Bras (1992). 2015;61(2):170–7.
60. Guttman R, Goldman RD, Koren G. Appendicitis during pregnancy. Can Fam Physician. 2004;50:355–7.
61. Bickell NA, Aufses AH Jr, Rojas M, Bodian C. How time affects the risk of rupture in appendicitis. J Am Coll Surg. 2006;202(3):401–6.
62. Livingston EH, Woodward WA, Sarosi GA, Haley RW. Disconnect between incidence of nonperforated and perforated appendicitis: implications for pathophysiology and management. Ann Surg. 2007;245(6):886–92.
63. Wadhawan D, Singhal S, Sarda N, Arora R. Appendicitis in postpartum period: a diagnostic challenge. J Clin Diagn Res. 2015;9(10):QD10–1.
64. Joo JI, Park HC, Kim MJ, Lee BH. Outcomes of antibiotic therapy for uncomplicated appendicitis in pregnancy. Am J Med. 2017;130(12):1467–9.
65. Abbasi N, Patenaude V, Abenhaim HA. Management and outcomes of acute appendicitis in pregnancy—population-based study of over 7000 cases. BJOG. 2014;121:1509–14.
66. Silvestri MT, Pettker CM, Brousseau EC, Dick MA, Ciarleglio MM, Erekson EA. Morbidity of appendectomy and cholecystectomy in pregnant and nonpregnant women. Obstet Gynecol. 2011;118(6):1261–70.
67. Varadhan KK, Neal KR, Lobo DN. Safety and efficacy of antibiotics compared with appendicectomy for treatment of uncomplicated acute appendicitis: meta-analysis of randomised controlled trials. BMJ. 2012;344:e2156.
68. Abbasi N, Patenaude V, Abenhaim HA. Evaluation of obstetrical and fetal outcomes in pregnancies complicated by acute appendicitis. Arch Gynecol Obstet. 2014;290(4):661–7.
69. Halvorsen AC, Brandt B, Andreasen JJ. Acute appendicitis in pregnancy: complications and subsequent management. Eur J Surg. 1992;158:603–6.
70. Kumamoto K, Imaizumi H, Hokama N, Ishiguro T, Ishibashi K, Baba K, Seki H, Ishida H. Recent trend of acute appendicitis during pregnancy. Surg Today. 2015;45(12):1521–6.
71. Allegaert K, van den Anker JN. Perinatal and neonatal use of paracetamol for pain relief. Semin Fetal Neonatal Med. 2017;22(5):308–13.
72. Pearl JP, Price RR, Tonkin AE, Richardson WS, Stefanidis D. SAGES guidelines for the use of laparoscopy during pregnancy. Surg Endosc. 2017;31(10):3767–82.
73. Stuart A, Källen K. Risk of abdominal surgery in pregnancy among women who have undergone bariatric surgery. Obstet Gynecol. 2017;129(5):887–95.
74. Curet MJ, Allen D, Josloff RK, Pitcher DE, Curet LB, Miscall BG, Zucker KA. Laparoscopy during pregnancy. Arch Surg. 1996;131(5):546–50. discussion 550–1.
75. Gurbuz AT, Peetz ME. The acute abdomen in the pregnant patient. Is there a role for laparoscopy? Surg Endosc. 1997;11(2):98–102.
76. Donkervoort SC, Boerma D. Suspicion of acute appendicitis in the third trimester of pregnancy: pros and cons of a laparoscopic procedure. JSLS. 2011;15(3):379–83.
77. Machado NO, Grant CS. Laparoscopic appendicectomy in all trimesters of pregnancy. JSLS. 2009;13(3):384–90.
78. Wilasrusmee C, Sukrat B, McEvoy M, Attia J, Thakkinstian A. Systematic review and meta-analysis of safety of laparoscopic versus open appendicectomy for suspected appendicitis in pregnancy. Br J Surg. 2012;99(11):1470–8.
79. Sadot E, Telem DA, Arora M, Butala P, Nguyen SQ, Divino CM. Laparoscopy: a safe approach to appendicitis during pregnancy. Surg Endosc. 2010;24(2):383–9.
80. Walsh CA, Tang T, Walsh SR. Laparoscopic versus open appendicectomy in pregnancy: a systematic review. Int J Surg. 2008;6(4):339–44.
81. Date RS, Kaushal M, Ramesh A. A review of the management of gallstone disease and its complications in pregnancy. Am J Surg. 2008;196(4):599–608.
82. Ibiebele I, Schnitzler M, Nippita T, Ford JB. Outcomes of gallstone disease during pregnancy: a population-

based data linkage study. Paediatr Perinat Epidemiol. 2017;31(6):522–30.
83. Dhupar R, Smaldone GM, Hamad GG. Is there a benefit to delaying cholecystectomy for symptomatic gallbladder disease during pregnancy? Surg Endosc. 2010;24(1):108–12.
84. Othman MO, Stone E, Hashimi M, Parasher G. Conservative management of cholelithiasis and its complications in pregnancy is associated with recurrent symptoms and more emergency department visits. Gastrointest Endosc. 2012;76(3):564–9.
85. Jorge AM, Keswani RN, Veerappan A, Soper NJ, Gawron AJ. Non-operative management of symptomatic cholelithiasis in pregnancy is associated with frequent hospitalizations. J Gastrointest Surg. 2015;19(4):598–603.
86. Gilo NB, Amini D, Landy HJ. Appendicitis and cholecystitis in pregnancy. Clin Obstet Gynecol. 2009;52(4):586–96.
87. Kammerer WS. Nonobstetric surgery during pregnancy. Med Clin North Am. 1979;63(6):1157–64.
88. Mazze RI, Källén B. Appendectomy during pregnancy: a Swedish registry study of 778 cases. Obstet Gynecol. 1991;77(6):835–40.
89. Buch KE, Tabrizian P, Divino CM. Management of hernias in pregnancy. J Am Coll Surg. 2008;207(4):539–42.
90. Oma E, Jensen KK, Jorgensen LN. Recurrent umbilical or epigastric hernia during and after pregnancy: a nationwide cohort study. Surgery. 2016;159(6):1677–83.
91. Haskins IN, Rosen MJ, Prabhu AS, Amdur RL, Rosenblatt S, Brody F, Krpata DM. Umbilical hernia repair in pregnant patients: review of the American College of Surgeons National Surgical Quality Improvement Program. Hernia. 2017;21(5):767–70.
92. Rottenstreich A, Elchalal U, Kleinstern G, Beglaibter N, Khalaileh A, Elazary R. Maternal and perinatal outcomes after laparoscopic sleeve gastrectomy. Obstet Gynecol. 2018;131(3):451–6.
93. Mahawar KK. Pregnancy and bariatric surgery. Minerva Chir. 2017;72(6):538–45.
94. Carter S, Depasquale S, Stallings S. Robotic-assisted laparoscopic ovarian cystectomy during pregnancy. AJP Rep. 2011;1(1):21–4.

Neurosurgical Crises and Brain Surgery

36

Chiara Robba, Valeria Spennati, Henry Shapiro, Nechama Kaufman, Federico Bilotta, and Sharon Einav

Bullet Points

- Pregnant and postpartum women have the same incidence of intracranial neoplasms as the general population.
- During pregnancy, the risk for aneurysmal rupture is highest in late pregnancy, but there is little evidence supporting an increased likelihood of rupture during pregnancy, labor, or puerperium.
- Abnormal intracranial pressure and cerebral perfusion pressure thresholds are similar in pregnant women and in the general population.
- The physiological changes of pregnancy can lead to a diproportional increase in pressure as a result of a pathological increase in intracranial volume.
- The clinical signs and symptoms of increased intracranial pressure in pregnant women are similar to those of the general population and include headache, vomiting, and papilledema.
- Neurosurgical procedures (spine and brain) should be considered despite the presence of pregnancy whenever radicular pain and progressive neurological deficits do not respond to medical management.
- Maternal benefit must be prioritized over that of the fetus, particularly in neurosurgical emergencies.
- Diagnostic imaging should be performed as required to advance both diagnosis and management.
- Clinical decisions should be made by a multidisciplinary team that includes an obstetrician, neurosurgeon, anesthesiologist, critical care physician, and neonatologist.
- The hemodynamic responses to intubation and extubation must be blunted if general anesthesia is used.

C. Robba · V. Spennati · F. Bilotta
Neurocritical Care Unit, Addenbrookes Hospital, Cambridge, UK

Department of Neuroanaesthesia, University La Sapienza, Rome, Italy
e-mail: bilotta@tiscali.it

H. Shapiro
Department of Neurosurgery, Shaare Zedek Medical Center, Jerusalem, Israel

N. Kaufman
Department of Emergency Medicine, Shaare Zedek Medical Center, Jerusalem, Israel

S. Einav (✉)
Intensive Care Unit, Shaare Zedek Medical Center and Hebrew University Faculty of Medicine, Jerusalem, Israel
e-mail: einav_s@szmc.org.il

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_36

- Neuraxial anesthesia may be performed in specific cases. Whether this anesthetic approach is possible should be determined on an individual basis according to the specific pathology involved.
- Pregnancy and the puerperium are prothrombotic states. This, combined with the increased likelihood of thrombosis with intracranial pathology, puts all women with neurosurgical problems at increased risk of thromboembolic disease during pregnancy.

36.1 Introduction

Several neurological pathologies may be encountered during pregnancy. Some occur coincidentally with pregnancy, and others may be exacerbated by the presence of pregnancy. The anatomical and physiological adaptations of the central nervous system to pregnancy and their relevance to emergency treatment are discussed elsewhere in this book (Chap. 24). The principles that should guide neuro-anesthesia neuro surgery, and delivery in association with these situations are presented in this chapter. In all of these situations, determining the right choice of action and balancing the needs of the mother with those of the fetus is undoubtedly challenging [1, 2]. However, pregnancy is not a major contraindication to neurosurgery. Delaying surgery in many of these cases may result in maternal deterioration and the need for urgent intervention [3–6]. Maternal deterioration may inevitably damage the fetus; thus, emphasis must always be placed on treatment of the mother. Regardless of the pathology, treatment priorities should always be discussed by a multidisciplinary team (i.e., obstetrician, neurosurgeon, anesthesiologist, critical care physician, and neonatologist). Treatment algorithms which have improved outcomes in the non-pregnant population should be used (e.g., advanced trauma life support protocols). Medications and procedures which may determine maternal outcome should not be withheld (e.g., treatment of vasospasm, antihypertensives, embolization). Diagnostic procedures should be performed as necessary. Delivery should not be performed unless it is intended for maternal benefit. Since there is little evidence regarding the management of many of these emergencies in pregnancy, common sense should always be applied as well.

36.2 Initial Workup

A major setback for diagnosis of intracranial pathology during pregnancy is the prevalence of the alternative diagnosis of eclampsia. Preeclampsia is typically accompanied by hypertension and peripheral edema, and eclampsia will present as generalized tonic-clonic convulsions. Brain tumors are more likely to present with headache and focal signs rather than convulsions. Simple fundoscopy may be useful to identify increased intracranial pressure (ICP). Some pathophysiological effects on the central nervous system may be investigated by transcranial doppler during pregnancy, e.g., aneurysm-associated vasospasm. Preeclampsia may also be accompanied by impairment of autoregulatory mechanisms that manifest as cerebral arteriolar dysfunction; these can be detected using transcranial doppler [7]. Ultrasound measurement of the optic nerve sheath diameter may also assist in this diagnosis [8]. The pulsatility index of the middle cerebral artery increases between 8 and 29 weeks of gestation and peaks in mid-pregnancy. The cerebral perfusion pressure decreases in mid-pregnancy (lowest at 15th week) and after delivery, but it rises significantly during late pregnancy and peaks toward its end [9]. Impaired cerebral flow velocities are common in women with eclampsia and may be involved in the development of eclamptic encephalopathy [10]. Unfortunately, this finding has only been reported anecdotally, making it unreliable for differentiating between potential causes of maternal neurological conditions. Neuro-monitoring is further discussed in Chap. 24.

Once the presence of an intracranial pathology is suspected in a pregnant woman, diagnostic

imaging is inevitable. Ultrasound is the ideal imaging modality for use in pregnancy due to its fetal safety profile. However, it is unlikely to provide sufficient information regarding central nervous system pathologies [11]. Computed tomography (CT) and magnetic resonance imaging (MRI) therefore remain the mainstay of diagnosis when questions arise regarding intracranial and spinal pathological processes. The use of these imaging modalities during pregnancy is typically accompanied by concerns regarding their effect on fetal well-being. However, in the balance of things, the risk of fetal damage from radiation remains lower than the risk of maternal decompensation. Computed tomograpy (CT) and magnetic resonance imaging (MRI), as well as other radiological techniques and clinical assessments (such as Glasgow Coma Scale and neurological assessment) and laboratory tests (full blood count, liver function, clotting, renal function) and their accompanying considerations in pregnancy are discussed in Chaps. 34 and 35. This chapter will not discuss neurosurgical trauma; however Fig. 36.1 presents a decision tree regarding the potential management pathways for pregnant women with traumatic brain injury.

36.3 Intensive Care Considerations

36.3.1 Management of Increased Intracranial Pressure (ICP)

The normal range of ICP varies with age and ranges between 6 and 25 cm H_2O (95% confidence intervals) with a population mean of about 18 cm H_2O for adults [12]. The thresholds of abnormal ICP and cerebral perfusion pressure are similar in pregnant women as in the general population [8]. However, in the presence of intracranial pathology, the physiologic changes of pregnancy (i.e., shifts in hemodynamics, blood volume, and water balance) accompanied by even a small increase in intracranial volume may increase ICP [13]. The clinical signs and symptoms of increased ICP include headache, vomiting, and papilledema. Diagnosis of increased ICP should ideally occur before neurological deterioration begins, as this is an ominous sign in terms of patient prognosis.

Timely management of increased maternal ICP may determine maternal neurological and mortality outcome but will probably not affect

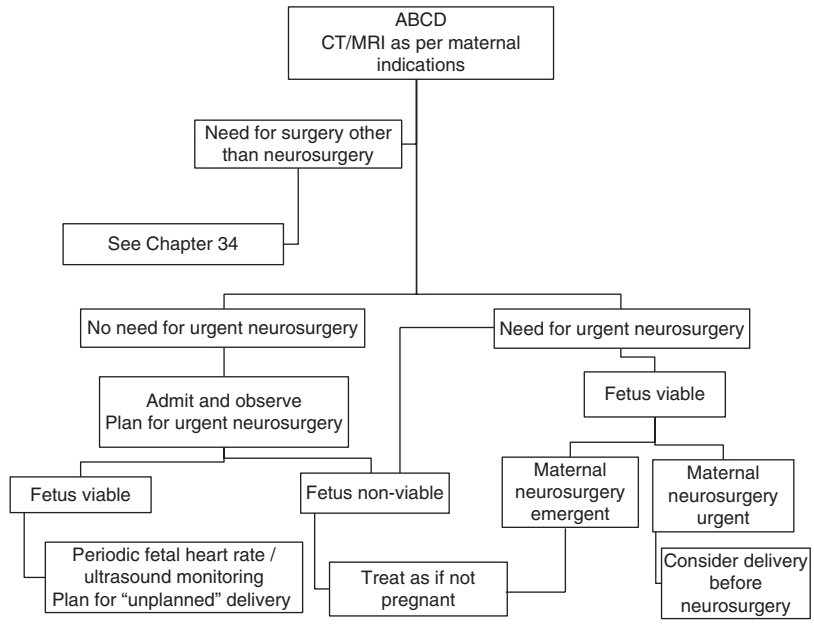


Fig. 36.1 A decision tree regarding the potential management pathways for a pregnant women with traumatic brain injury

the course of pregnancy other than indirectly through the mother. Management of increased ICP includes correct positioning, sedation, drainage of cerebrospinal fluid, and osmotherapy with either mannitol or hypertonic saline. Modest short-term hyperventilation may temporarily be used to reduce dangerously raised ICP or to improve surgical exposure during craniotomy. Ongoing hyperventilation ($PaCO_2$ < 35 mmHg) should be avoided, as it has been shown to adversely affect cerebral metabolism and patient outcomes [14–16]. Extreme hyperventilation may also decrease placental O_2 transfer and resultantly fetal cerebral tissue oxygenation [13, 17].

If time constraints allow, perioperative cerebral edema is best treated with dexamethasone. Intravenous dexamethasone 4 mg every 6 h is the usual initial dose. Corticosteroids are indicated for promoting fetal lung maturity anyway and may therefore improve maternal outcome while causing no fetal harm [18]. In women who receive less than 14 days of dexamethasone therapy, treatment may be abruptly discontinued. However, typical doses of dexamethasone used in patients with brain tumors are supra-physiological and may therefore suppress the hypothalamic-pituitary-adrenocortical axis if administered for longer periods. If such treatment is indeed prolonged, the dose must be slowly tapered prior to cessation.

Mannitol is an osmotic diuretic used to reduce ICP in emergencies. It is usually administered intravenously as a one-time or repetitive bolus dose of 0.25–1 g/kg. Mannitol crosses the placenta and may alter utero-placental perfusion [19], but this physiological effect does not constitute a contraindication to treatment. The relationship between strategies to reduce ICP (e.g., diuretics, mannitol) and uterine blood flow is not well established. Fetal cardiac activity may be monitored and maternal blood pressure maintained within 15% of baseline to ensure adequate uteroplacental circulation during mannitol administration, but neither have actually been shown to make a difference [20] (see also Chap. 38).

36.3.2 Glucose Control

The blood glucose levels of critically ill pregnant women should be targeted to 110–180 mg/dL similarly to other critically ill patients. Three meta-analyses of randomised controlled trials comparing intensive versus conventional insulin therapy in traumatic brain injury have shown that intensive insulin therapy did not improve short- or long-term mortality in patients with traumatic brain injury [21–23]. One of these meta-analyses also sought, yet reported no differences in neurological outcomes [22]. However, two studies have suggested that intensive insulin therapy was associated with increased risk of hypoglycemia [22, 23]. Consequently, although care should be taken to avoid hyperglycemia, a similar degree of effort should be invested in ensuring that hypoglycemia is avoided as well. While none of these studies have looked specifically at pregnant women, there is no evidence to direct practice differently in this population. In addition, maternal hyperglycemia in the pre-delivery period increases fetal insulin secretion and may result in neonatal hypoglycemia [24].

36.3.3 Timing of Neurosurgery Versus Delivery

When a pregnant woman with a viable fetus presents with new intracranial pathology, one of three treatment strategies may be chosen: neurosurgery without delivery, neurosurgery followed by delivery, or delivery followed by neurosurgery. Some of the considerations for these three strategies for the pregnant woman and her fetus are presented in Table 36.1. The sequence of actions selected should be considered case by case in a multidisciplinary discussion. Fetal viability and well-being is never a standalone consideration [6] and should never be prioritized over maternal well-being.

- *Urgent neurosurgery prior to delivery:* If performance of neurosurgery is urgent (i.e., life-saving or function-preserving for the mother), it should be performed without delay regardless

Table 36.1 Considerations regarding the timing of neurosurgery in relation to delivery in pregnant women with an intracranial pathology

	Antepartum neurosurgery	Neurosurgery + cesarean delivery	Postpartum neurosurgery
Fetus	Requires monitoring either pre and post surgery or intraoperatively	Risk of intraoperative uterine atony and uterine hemorrhage	Maternal risks during labor
Intracranial pressure	Managed during surgery	Managed during surgery	Avoid maneuvers to raise intracranial pressure during labor
Seizure risk	Minimized	Minimized	Potential for intrapartum seizures depending on pathology
Pre-surgical deterioration risk	Minimized	Minimized	Concern
Surgical timing	May be delayed if surgical condition permits to allow fetal maturity (surgery may provoke preterm labor)	May be required if neurosurgical deterioration in term/mature fetus	May become urgent if maternal situation deteriorates. Stable patient may undergo vaginal delivery prior to neurosurgery (recommended shortened second stage with epidural). Some advocate cesarean delivery is essential
Fetal corticosteroids for lung maturation	May be required	May be required	May be required
Anesthesia considerations	Potential difficult obstetric airway, aspiration risk, antacid prophylaxis required	Potential difficult obstetric airway, aspiration risk, antacid prophylaxis required	After 2–6 weeks, physiological changes of pregnancy expected to dissipate
Intraoperative obstetric related risks	Urgent cesarean delivery	Risk of postpartum hemorrhage; need for careful uterotonic management	Dependent on timing of surgery
Angiographic procedure	Possible, potential fetal radiation risks and fetal protection required	Not relevant	Not relevant
Patient positioning	Aortocaval compression must be alleviated	Aortocaval compression must be alleviated prior to delivery	Not relevant
Hyperventilation	Risk of compromised fetal oxygenation as oxyhemoglobin dissociation curve shifted left	Not relevant	Not relevant
Mannitol	May be administered in normal clinical doses	May be administered in normal clinical doses	May be administered in normal clinical doses

of pregnancy. Shortening the interim between brain injury and normalization of maternal physiology will likely improve maternal and fetal outcomes. The patient's family should be informed that there may be an increased risk of fetal exposure to anesthetic and analgesic drugs, maternal hyperventilation, hypotension, or hyperglycemia, but these risks are easily offset by the major benefit of optimizing the environment that is ultimately ideal for fetal development. If maternal blood pressure allows, higher minimal alveolar concentrations of volatile anesthetics may be used to ensure uterine relaxation and a parallel decrease in ICP.

In potentially viable pregnancies, fetal monitoring is best performed in this situation after the surgical procedure has been completed and the mother has been stabilized. In other clinical

circumstances, monitoring the fetus has been shown to distract attention away from the mother [25]; this same principle very likely holds true during brain surgery. As the condition of the fetus should not drive treatment decisions for the mother in any case, intraoperative fetal monitoring is not recommended [25]. Furthermore, intraoperative monitoring of the fetus during prolonged neurosurgery requires the availability of a trained clinician to interpret changes, as well as an intervention plan. Simultaneous cesarean delivery is not an option regardless of patient positioning because the hemodynamic shifts accompanying uterine surgery may further endanger the already compromised maternal brain. The only exception to this rule is a situation where the mother is not likely to survive, in which case perimortem cesarean delivery is indicated. Experience with brain dead mothers in the intensive care unit suggests that the fetus can survive significant maternal injury and is more likely to benefit from remaining in utero, but this situation raises important ethical issues (see also Chap. 29).

- *Expedited neurosurgery prior to delivery:* If surgery is recommended but there is still a brief hiatus for decision making, treatment priorities should be discussed. In such cases, fetal age and/or well-being may contribute to the decision-making process. The plan should optimize maternal outcomes while minimizing fetal harm and discussion should include the possibility of unplanned vaginal delivery after recent neurosurgery. This situation is challenging, given the risks of increased ICP and cerebral blood flow due to uterine contractions and labor pain [26, 27].
- *Delivery prior to neurosurgery*: If maternal condition is stable, the intracranial pathology does not require urgent intervention but may worsen with ongoing pregnancy and the fetus is viable, consideration may be given to delivery before neurosurgery. Neuraxial anesthesia, which is generally the preferred technique for cesarean delivery, may be contraindicated in women with an intracranial lesion.

If delivery is to be performed under general anesthesia, the anesthesia plan should include strategies to blunt the hemodynamic and ICP response to intubation. Uterotonic drugs will be needed for prevention of bleeding [28]. The effects of uterotonic drugs on ICP and cerebral blood flow are not well studied. Syntocinon, carbetocin, and misoprostol (prostaglandin E1) have all been used after delivery in women with a variety of neurological diseases with no complications [29]. However, ergometrine may cause hypertension [30, 31]; it has also been reported to be associated with cerebral vasospasm precipitating postpartum cerebral angiopathy, a form of reversible cerebral vasoconstriction syndrome [32, 33]. Therefore, ergometrine is probably best avoided in the presence of increased ICP [34]. Care should also be taken to avoid delivery of high minimal alveolar concentrations of volatile anesthetics, as these induce uterine relaxation and may increase the risk of atony. Prostaglandins F2 alpha, E1, and E2 have a wide range of cardiovascular and smooth muscle effects, but their effect on ICP has not been studied. Regardless of the initial decision, maternal neurosurgery should not be delayed if neurological deterioration occurs.

36.4 Approach to Anesthesia for Surgery

36.4.1 Awake Craniotomy

Locoregional anesthesia is often indicated for procedures requiring intraoperative monitoring of speech/motor function in order to minimize the risk of compromising neurologic function during tumor resection. During awake craniotomy, the patient must be cooperative and capable of reporting the occurrence of sensory and/or motor deficiencies.

In the general population, awake craniotomy has been associated with shorter hospital stay, improved survival, and better neurological outcome [35]. Awake craniotomy has also been described as safe in selected cases of pregnant women with central nervous system tumors [36, 37] or sequelae of traumatic injuries such as pseudoaneurysms [38].

As no large studies are forthcoming on awake craniotomy in pregnant women, data from the

general population should be extrapolated to this special population at this time. A recent meta-analysis of awake craniotomy for neurosurgical procedures [35] included 47 studies that described different techniques: 18 articles that studied the asleep-awake-asleep technique, 27 that studied monitored anesthesia care, one article that studied both above-mentioned techniques, and one article that studied the awake-awake-awake technique. Maternal complications included awake craniotomy failure (2%), intraoperative seizures (8%), new neurological dysfunction (17%), and conversion into general anesthesia (2%). The estimated odds ratio when comparing the asleep-awake-asleep technique to monitored anesthesia care was 1.66 [95%CI:1.35–3.70] for new neurological dysfunction and 2.17 [95%CI:1.22–3.85] for conversion into general anesthesia [35].

Propofol, used alone or in combination with a short-acting opioid, is commonly used for sedation during awake craniotomy [39]. Dexmedetomidine, a highly selective alpha-2 agonist with sedative, analgesic, and anxiolytic properties, is also rapidly gaining popularity for this indication due to its minimal effects on ventilation. Dexmedetomidine has been successfully used as an adjunct to general anesthesia for non-obstetric surgery during pregnancy [40]; it provides excellent hemodynamic stability when used as a sedative in preeclamptic women in the intensive care unit [41] and has been shown to be safe for the neonate when used for cesarean delivery [42]. In animal studies, dexmedetomidine modified uterine contraction [43]. Dexmedetomidine has been shown to reduce opioid requirements by 30–50% [44] and can also substantially decrease the requirement for propofol [45].

36.4.2 General Anesthesia

When performing general anesthesia for cesarean delivery in women without central nervous systems pathology, the patient is first scrubbed, the urinary catheter is inserted, and then general anesthesia is induced. Since the mother is stable and mostly healthy, induction of anesthesia is deferred to the last moment in order to minimize fetal exposure to anesthesia drugs. Conversely, in neurosurgical cases with a raised ICP, the patient is first carefully anesthetized and only then are surgical procedures initiated. The latter option is more appropriate for the pregnant critically ill woman who must undergo a neurosurgical procedure, as physiological stabilization is the first treatment priority.

Patient Positioning: Neurosurgery often entails unique patient positioning. A semi-sitting position may be used for posterior fossa lesions. The authors of this chapter searched the literature and found only one case report of maternal positioning in a semi-sitting position for this type of surgery [46]. However, during pregnancy, the semi-sitting position may actually provide better respiratory function and less risk of aorto-caval compression by the gravid uterus.

Prone positioning may also be required in some pregnant women and has been reported to be possible [47, 48]. Other than the standard left lateral decubitus position, there is little evidence to show which position (i.e., full prone, three-quarters prone or full lateral position) is preferable for uteroplacental perfusion and for relieving compression of large vessels in such cases.

Induction of anesthesia: If general anesthesia is unavoidable, the most important anesthesia consideration to take into account is the need to balance the risk of a difficult airway with the need for rapid intubation in order to prevent increases in ICP. Pregnancy is accompanied by an increased risk of difficulty in airway management (see also Chap. 21). Hypoxia, hypercarbia, and increases in blood pressure must be minimized during tracheal intubation in order to blunt the attendant rise in ICP [49]. Induction of anesthesia must therefore be rapid, albeit smooth. In order to achieve these aims, the airway should ideally be managed by an expert in airway management. If time and maternal condition allow, aspiration prophylaxis should be administered (e.g., oral or intravenous ranitidine 50 mg, sodium bicitrate 0.3 M 20–30 mL) [50]. Cricoid pressure may be used during endotracheal intubation to reduce the risk of regurgitation [51] although care must be taken to ensure that this manuevre does not limit airway visualization.

Propofol may be used as the induction agent. Propofol provides excellent anesthesia, decreases ICP [52], has a relaxing effect on the gravid

uterus [53, 54], and has been associated with no neonatal adverse effects after emergency cesarean delivery [55].

Muscle relaxants should be used in order to facilitate intubation, but the literature remains divided regarding the ideal muscle relaxant in the presence of neurological pathologies. Succinylcholine has traditionally been considered a better option than rocuronium to facilitate intubation; it was believed to provide better muscle relaxation (and therefore better conditions for visualizing and managing the airway) and does not cross the placenta [56–58]. However, Stourac et al. [59] recently compared the two drugs head to head during induction of anesthesia for cesarean delivery and reported no advantage in intubating conditions with either drug. While this finding did not lead the authors to conclude that rocuronium is preferred for intubation, they did note other maternal advantages with the use of this drug (including less postoperative muscle pain) [59].

Adjuvant short-acting drugs may be administered concomitantly to blunt the systemic response to laryngoscopy and intubation. Examples include short-acting opioids (e.g., remifentanyl), lidocaine, and esmolol. Remifentanil can safely be used in pregnant patients, as it is metabolized by non-specific esterases and therefore has an elimination half-life of no more than 5 min [60–62]. Remifentanil also enables performance of rapid wake-up tests which may be invaluable for maternal neurological assessment. For additional literature regarding the use of beta-blocking agents and opioids in pregnancy, refer to Chap. 38.

Throughout induction, medications should be administered in titrated doses despite the need for rapid airway management as maternal cerebral perfusion and fetal systemic perfusion may be compromised by low blood pressures. Uteroplacental perfusion is directly related to maternal blood pressure [63, 64], and cerebral autoregulatory mechanisms are often impaired in the presence of intracranial pathology. Therefore, maternal hypotension (systolic blood pressure less than 100 mmHg) should generally be avoided [65]. At the same time, care must be taken to avoid maternal hypertension, as it may induce or increase intracranial hemorrhage [58]. Additional details regarding airway management and drug safety profiles during pregnancy may be found elsewhere in this book (see Chaps. 21 and 38).

Maintenance of anesthesia: Following endotracheal intubation, controlled mechanical ventilation should generally be used to maintain normocapnea ($PaCO_2$ 35–38 mmHg), unless control of acutely increased intracranial pressure is required [65]. Prolonged prophylactic hyperventilation [14, 15, 65, 66] should be avoided. Maintenance of maternal oxygenation and hydration status are likely conducive to both improved maternal neurological outcome and fetal outcome. Efforts should therefore be made to avoid both hypoxia (O_2 saturation lower than 92–94%) [67] and hyperoxia [68, 69]. Systolic blood pressure is best kept at 100 mmHg or somewhat higher [65]. Anesthesia targets should be similar to those of the general population.

Desflurane and sevoflurane are commonly used during pregnancy to maintain anesthesia [70, 71]. Both have a significant tocolytic effect, but questions remain regarding potential neurotoxicity [60].

Extubation considerations: There are no data regarding the use of neostigmine to reverse the effect of muscle relaxants in pregnancy. However, attempting to balance between minimal dosing of acetylcholine esterase inhibitors and prevention of residual muscle weakness may be redundant; pregnant women undergoing neurosurgery and those who have undergone any other treatment of a neurological crisis that required intubation are best extubated in the intensive care unit. Balancing the risk of aspiration in pregnancy and the peripartum period versus extubation under sedation, pain management during pregnancy with a risk of increased ICP, and preservation of the cough reflex while preventing sharp increases in ICP due to cough are all difficult challenges. It is generally recommeded that such cases be treated clinicians with the relevant expertise and the patience to conduct weaning from mechanical ventilation that may extend hours after the end of surgery.

36.5 Brain Tumors

Pregnant and postpartum women have the same incidence of intracranial neoplasms as the general population [72]. The most common types of brain tumors include gliomas, meningiomas, pituitary

adenomas, acoustic neuromas, and metastatic lesions. The following section will discuss the unique characteristics of three of the more common types of cerebral tumors seen during pregnancy (gliomas, meningiomas, and pituitary adenomas).

36.5.1 Management of Intracranial Tumors in Pregnant Women

Once an intracranial tumor has been discovered during pregnancy, clinical management priorities should be determined by the severity of maternal neurological signs and symptoms and fetal gestational age. If the mother is clinically stable, fetal development is normal, and the pregnant woman wishes to wait, pregnancy may be continued. However, the delivery plan should be clarified a priori; in specific cases it may be recommended to avoid vaginal delivery, as discussed previously [59, 73].

Any "watch-and-wait" strategy must be accompanied by close neurological follow-up with repeated clinical examinations by an expert, repeat MRIs, and a plan for tumor resection shortly after delivery. Whether observation should be conducted in a monitored environment depends on the severity of the findings. Criteria for proceeding immediately to neurosurgery during pregnancy include:

1. Removal of tumors that are malignant, rapidly growing (e.g., high grade glioma), very large, or located in a critical location (posterior fossa or eloquent areas).
2. New onset or worsening of neurological symptoms, including appearance of hydrocephalus (which requires urgent shunting).
3. Compromised or abnormal fetal development, which may direct a decision to proceed with surgery due to the low likelihood of good pregnancy outcome.
4. Maternal preference to receive treatment despite potential fetal harm (if legally allowed).

36.5.1.1 Gliomas

The term "glioma" is currently used to cover a large spectrum of tumors. The relationship between glioma behavior and pregnancy remains to be clarified. Several studies have suggested that the velocity of expansion of low grade gliomas increases during pregnancy, but this claim is based on relatively small cohorts. Therefore, with close follow-up, postponement of neurosurgery to after delivery is an option with some low grade gliomas. In one series of patients [74], the five patients with grade I tumors had stable disease during and after pregnancy, but among the 18 women with grade II or III gliomas, 8 (44%) had clear tumor progression during pregnancy or within eight weeks of delivery [74]. A retrospective study of 281 women who did not undergo delivery immediately after being diagnosed with a low grade glioma showed a median survival of 14.3 years (95% CI 11.7–20.6 years); the effect of pregnancy on survival was insignificant [75].

A systematic review of publications on glioma and pregnancy [76] found only 27 relevant observational studies and articles describing expert opinions on clinical management. Taken all together, these publications included 316 women with either newly diagnosed (n = 202) or known (n = 114) gliomas during pregnancy. Observational studies of adequate quality supported the lack of effect of pregnancy on survival in low grade glioma patients but also suggested that pregnancy can provoke clinical deterioration and tumor growth on MRI [76].

If glioma resection is required during pregnancy, surgery may be extensive and should ideally be accompanied by functional monitoring. Awake craniotomy provides the concomitant advantages of constant assessment of patient neurological condition and reduction in fetal exposure to anesthetics. Delivery considerations should be based on the existing observational findings that in stable women at term, cesarean delivery provides no advantage over vaginal delivery with respect to either maternal or fetal adverse events [76].

Only 12 papers have described the management of brainstem gliomas during pregnancy (16 women); these are summarized in a systematic review [77]. The women presented at a median gestational age of 23 weeks and all but one had already suffered neurologic deficit at the time of

presentation. MRI conclusively diagnosed all the cases. Although the summary noted that "surgical tumor resection (n = 4) and radiation therapy (n = 3) were successfully undertaken during pregnancy", half of the women died either during (n = 5) or within a month (n = 3) of pregnancy. There were 12 live-born babies. One pregnancy was terminated, and four were miscarried in association with maternal critical illness and eventual death. Three babies underwent induced premature delivery to facilitate glioma management, and two were spontaneously delivered preterm. There was one case of fetal growth restriction.

36.5.1.2 Meningioma

Mengiomas, and particularly benign meningiomas, are more common in women than in men (Fig. 36.2). The 5-year relative survival estimates for benign meningiomas in the general population is 85.6%; both young age and female sex predict better survival [78]. A strong association has been observed between female sex hormone levels and the diagnosis of meningiomas [79–81]. There is probably no absolute increase in the incidence of meningiomas during pregnancy [82], but previously asymptomatic tumors may become symptomatic during pregnancy due to tumor expansion [83, 84]. Pregnancy is accompanied by hormonally induced salt and water retention [85]. This increase may exacerbate peri-tumoral edema [86]. Progesterone has traditionally been considered the main contributor to this effect [87–89], but epidemiological studies [90] suggest that this is related to tumor expression rather than development. Prolactin-modulated pathogenesis has also been suggested for this phenomenon [82, 91]. Fortunately, tumor shrinkage has also been reported after delivery [92–94].

Recurrence is possible in additional pregnancies; poor perinatal outcomes and maternal deaths have been associated with unplanned pregnancy in the presence of known brain tumors and with tumors diagnosed during pregnancy.

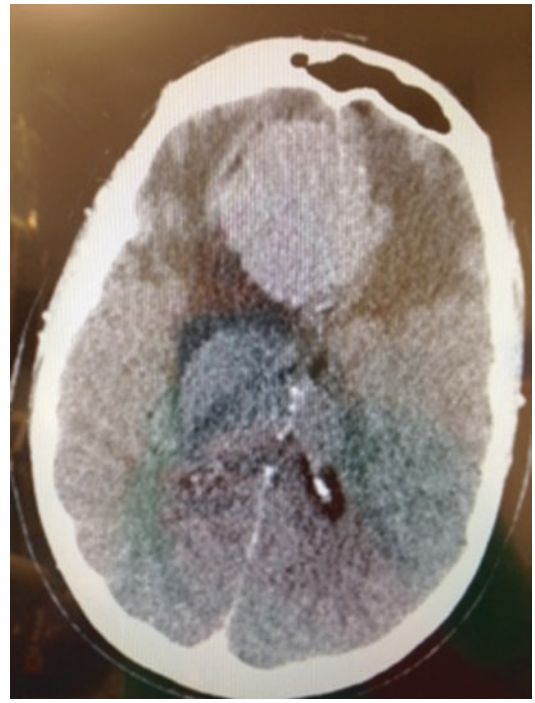


Fig. 36.2 Computed tomography (CT) of a 37-year-old, 18-week pregnant patient admitted for sudden blindness. Unenhanced axial CT scan images of the head show a midline parasagital meningioma of the cerebral falx

Nonetheless, most meningioma survivors of childbearing age report a desire for children despite concerns regarding possible recurrence [95]. Therefore, referral of the post-partum woman to expert counseling is important at the time of hospital discharge [57].

36.5.1.3 Pituitary Adenomas

The normal pituitary gland enlarges during pregnancy, predominantly due to estrogen-stimulated hyperplasia and hypertrophy of lactotrophic cells. Hyperplasia begins within weeks of gestation and peaks postpartum [96–98]. Increased estrogen levels induce the mitotic activity of lactotrophic cells, and tumor cells in patients with prolactinomas express estrogen receptors [99]. In women with a pituitary tumor, this raises concern regarding the possibility of patient deterioration

due to tumor enlargement during pregnancy. The degree of concern should hinge, however, on the size of the tumor.

Microadenomas are generally more common than macroadenomas. However, untreated macroadenomas are 10 times more likely to grow during pregnancy than microadenomas (approximately 1–3% vs. approximately 25–30%, dependent on the case series) [100]. Macroadenoma growth can be prevented by either pre-pregnancy tumor debulking or by chemotherapy [100]. Macroadenomas also reduce in size significantly when treated with dopamine or dopamine agonists [101] such as bromocriptine or cabergoline [100, 102, 103]. These points should therefore be considered before surgery in a pregnant symptomatic woman. In a crisis, a dopamine drip may be administered. Oral therapy with bromocryptine is preferred to cabergoline as there is more experience with this drug during pregnancy. Bromocriptine therapy during pregnancy has been associated with a similar incidence of abortion and congenital anomalies as that observed in the general pregnant population [100].

In a woman diagnosed with a pituitary adenoma who is currently deteriorating (i.e., worsening visual field defects and/or deteriorating level of consciousness), the option of insufficient steroids should also be considered and replacement should be administered if indicated.

If medical treatment fails and there is progressive neurological worsening (clinically or in imaging studies), surgery should be considered [104–108]. Surgery should also be considered in women who develop pituitary apoplexy. The trans-sphenoidal route is most commonly used.

36.6 Cerebrovascular Disease

Cerebrovascular disease is the most common intracranial pathology encountered during pregnancy. The most prevalent conditions include arterio-venous malformations (AVMs), aneurysms, and intracranial bleeding due to pre-eclampsia or eclampsia [109]. Treatment of vascular pathologies during pregnancy usually requires immediate or even emergency treatment.

36.6.1 Arterio-venous Malformation (AVM)

AVMs are congenital anomalous vascular structures comprised of a pathological web of vessels through which arteriovenous shunting occurs. The decisions regarding optimal timing of delivery and type of anesthesia for delivery are discussed in Chap. 25. The pathological process underlying creation of an AVM is believed to be dysregulation of vascular endothelium growth factor. Most AVMs are solitary (95%), but some rare syndromes are associated with multiple AVMs (e.g., Osler-Weber-Rendu, Wyburn Mason). The majority of AVMs are supratentorial (about 85%).

All AVMs have a nidus (Latin for "nest") which includes the shunting arterioles and the venous loops with which they are interconnected. AVMs are classified according to the composition of their nidus into either (1) **compact (or glomerular),** comprised of abnormal vessels only, or (2) **diffuse (or proliferative),** comprised of a poorly formed nidus with functional neuronal tissue interspersed in between the anomalous vessels.

In the general population, about one in ten cerebral AVMs is symptomatic, rendering AVMs the most common symptomatic vascular malformation. Because they worsen over time, diagnosis is more common after puberty. However, almost one-third of AVMs diagnosed due to hemorrhage are identified at ages <20 years. Hemorrhage is by far the most common presenting symptom, representing 65% of clinically symptomatic cases. But clinical presentation may also include headaches, seizures, or ischemic stroke secondary to vascular steal.

In pregnant and peripartum women: There is some controversy with regard to whether pregnancy influences the progression of AVMs.

A study conducted in 1990 (n = 451 pregnant women with cerebral AVM) reported that the hemorrhagic risk of cerebral AVM during pregnancy was 3.5%, which is similar to that observed in the non-pregnant population (3.1%) [110]. More recent studies have concluded that there is an increase in the annual rate of cerebral AVM hemorrhage during pregnancy and puerperium [111, 112]. However, there is no evidence to suggest any relationship between the mode of delivery (vaginal/cesarean) and the risk of AVM hemorrhage [113]. Pregnancy should be allowed to continue if (1) the AVM was an incidental finding and it has not ruptured or (2) the AVM has ruptured but there are no new focal deficits and the neurological course is stable. However, in such women, a plan should be prepared not only for postpartum definitive neurosurgical or endovascular intervention but also for the occurrence of rapid neurological deterioration at any point. More than half of cerebral AVM hemorrhages occur in the first and second trimesters of pregnancy [114], coinciding with maternal hemodynamic changes. Most AVMs are detectable before the 32 week of gestation [115]. The intervention required, whether radiological or surgical, should hinge upon the type of AVM identified, the expertise available, and the severity of maternal condition.

36.6.2 Aneurysm

Cerebral aneurysms are created by the shear stress placed on blood vessel walls by the blood flowing through the vessel. The inner diameter and structure of the arterial walls are regulated by blood flow. Increased arterial blood flow leads to a chronic rise of wall shear stress, with subsequent stretching of the endothelial cells aligned in the direction of the flow. If the wall shear stress increases focally, it can potentially cause a focal enlargement and damage to the arterial wall. This pathological dilatation of the arterial walls frequently occurs near the arterial bifurcations in the circle of Willis [116]. Aneurysms typically develop after age 40. Predisposing factors include hypertension, prior brain injury, infection, drug abuse (e.g., cocaine), and, more rarely, blood vessel disorders (e.g., cerebral arteritis, fibromuscular dysplasia).

Cerebral aneurysms differ in size (small <5 mm diameter, medium 6–15 mm, large 16–24 mm, giant >25 mm) and in shape (saccular to fusiform). An unruptured aneurysm could be small and completely asymptomatic or large and accompanied by symptoms stemming from increased intracranial pressure or compromise of nearby cerebral regions (e.g., headache, coma, visual field disturbance, paresthesia/hyperalgesia, plegia/paresis, dysphasia, amnesia, seizures). Diagnosis requires CT with contrast angiography, MRI, or (rarely) cerebral angiography. A single aneurysm is 15–20% likely to be associated with the presence of additional aneurysm(s) [34].

36.6.2.1 Management of a Pregnant Women with an Aneurysm

Management of pregnant women with an unruptured aneurysm. When an unruptured intracranial aneurysm is incidentally discovered during pregnancy, if there is no neurosurgical emergency and the fetus is viable, neurosurgical or endovascular treatment may be postponed until after the delivery [113]. In this scenario, the primary goal during pregnancy is to maintain maternal cardiovascular stability, as hemodynamic changes (both hypo- and hypertension) may shift the forces acting across the wall of the aneurysm and potentially precipitate aneurysmal rupture [117].

Management of a pregnant woman with a ruptured aneurysm (Fig. 36.3). If the aneurysm has already ruptured and the woman presents with subarachnoid hemorrhage, treating the aneurysm (clipping or coil embolization) should be prioritized. In general, the timing of treatment hinges on the urgency of the required intervention. In emergency cases (life or brain saving), the interest of the fetus must be put aside, and the procedure should not be delayed. In less urgent cases, if endovascular radiological or surgical intervention is indicated, the timing of delivery in relation to the procedure should be discussed. Two obstetric issues require addressing: (1) Endovascular intervention requires systemic anticoagulation. Administration of heparin

together with antiplatelet agents during embolization may lead to increased obstetric hemorrhage during spontaneous labor or cesarean delivery [118]. (2) Endovascular treatment of aneurysms entails exposure to a significant amount of radiation, raising the issue of radiation effects on the fetus [119]. Lead aprons should be always used to cover the abdomen if possible. Regardless of the degree of urgency, the family must clearly understand the situation and the duty to prioritize the mother over the fetus. If time allows and the fetus is viable, the pros and cons of a surgical delivery concurrent or prior to endovascular or surgical treatment versus the option of ongoing pregnancy should also be presented to the family.

In a paper pooling cases of pregnant women with aneurysmal subarachnoid hemorrhage from the literature [120] (n = 52), univariate analysis suggested that maternal outcome hinges on patient age, Hunt and Hess scale score, Glasgow Coma Scale at arrival, treatment modality for the aneurysm, mode, and timing of delivery. However, in multivariate analysis, only the presence of general complications resulted in a significant impact on maternal outcome [120]. Reactive vasospasm complicates approximately 20% of cerebral aneurysm cases, potentially exacerbating cerebral damage. Secondary obstructive hydrocephalus occurs in 20–30% of cases. The onset of this potentially devastating complication can be either acute (within 48 h of hemorrhage) or chronic (a week to months later). Both of these situations may require admission to an intensive care unit. In such cases, the staff of the intensive care unit should be informed of the delivery plan and be prepared for obstetric emergencies.

Aneurysm rupture during pregnancy is no more frequent than rupture of aneurysms in the general population [121]. Despite this, there are potential predisposing factors in pregnancy for rupture of the aneurysm. The maternal physiologic rise in cardiac output can lead to an increase in the hemodynamic shear stress forces exerted over the aneurysmal sac. At the same time, hormones (estrogen, progesterone, human chorionic gonadotropin) affect remodeling of the arterial and venous intima and media [122], thereby weakening the arterial wall. The risk of rupture is highest in late pregnancy (gestational age 30–40 weeks), since at this time hemodynamic stress is maximal [120].

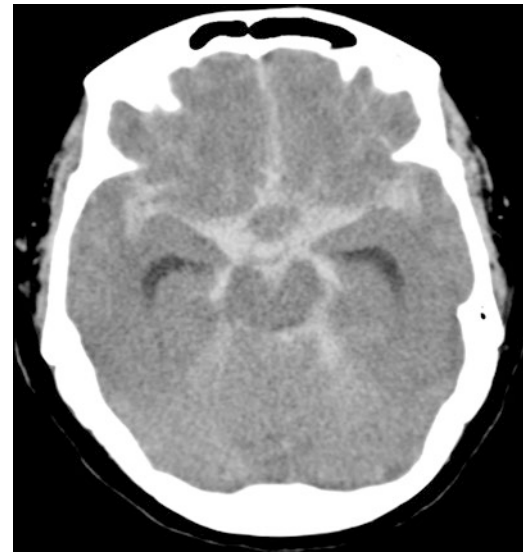


Fig. 36.3 Computed tomography of a 32-year-old patient, who presented with a subarachnoid hemorrhage during her third trimester of pregnancy, shows a large volume of acute subarachnoid hemorrhage blood within the suprasellar and the basal cisterns. The patient underwent surgical clipping of the aneurysm and concurrent cesarean delivery

Anesthesia considerations for surgical delivery. General anesthesia with opioids, propofol, and volatile anesthetics is often described for emergency delivery for pregnant women with aneurysms) [13]. However, neuraxial anesthesia with control of intracranial pressure is also a viable option [123]. In terms of hemodynamic stability, neuraxial anesthesia may actually provide some advantages compared to general anesthesia [13, 124].

36.6.3 Cavernous Malformation

Cerebral cavernous (or capillary venous) malformations (CCMs) are vascular abnormalities comprised of closely clustered, abnormal, partly thrombosed capillaries. These capillaries are typically dilated with hyalinized walls and are surrounded by deposits of hemosiderin. Since

they exhibit vascular proliferation and neoangiogenesis, CCMs are often described as vascular neoplasms. CCMs may be either sporadic (incidence of 0.1–0.5% in the general population) [125] or familial (incidence 20%, autosomal dominant with varied expression and incomplete penetrance) [126].

CCMs are low pressure and low flow lesions and are therefore rarely associated with dramatic hemorrhage due to simple trans-vessel pressure shifts. Rather, blood slowly leaks through the vessel walls into the angioma, changing its shape and/or size. Stagnating blood thromboses, thus re-routing these leaks. Unless the CCM has enlarged sufficiently to encroach upon the surrounding brain tissue, these events remain mostly asymptomatic. Gross hemorrhage, which is most commonly associated with clinical symptoms, occurs only when blood begins to escape the confines of the vascular lesion. Most CCMs are supratentorial and therefore manifest with headaches or new-onset seizures.

In pregnant and postpartum women. There are so few cases that the natural history and treatment of CCMs remains anecdotal. CCMs may modify their morphological and clinical features as a result of physiological changes occurring during pregnancy [127, 128]. Some authors have claimed that pregnancy and the puerperium are associated with an increased risk of hemorrhage and, based on this claim, promote aggressive treatment of CCMs in pregnant women; however, data to support this assumption are scarce [129, 130]. Conversely, the guidelines published in 2017 by the Angio Alliance [131] state that the risk of neurological symptoms during pregnancy is likely no different than in the non-pregnant state. If hemorrhage does occur, factors that need to be taken into account in treating the patient are the severity of symptoms, the risk of recurrent hemorrhage, and the risk of surgical intervention at that point in the pregnancy. It was generally agreed that vaginal delivery is appropriate unless there is a precluding neurological deficit or recent hemorrhage.

36.7 Spinal Surgery

Back pain and specifically low back pain are very common during pregnancy, affecting about 56% of women typically between the 5th and the 7th month of gestation [132]. However, only about one in 10,000 pregnant women actually shows symptoms from a lumbar disc herniation [133]. There are no treatment guidelines for spinal surgery in pregnant women; therefore the indications for surgery should reflect those of non-pregnant patients [134]. Spinal surgery should only be considered during pregnancy if radicular pain and progressive neurological deficits do not respond to medical management. Cauda equina syndrome is a neurosurgical emergency. It is caused by compression of the lumbosacral nerve roots. The clinical signs and symptoms include radiating pain or numbness in the lower limbs, paralysis, sexual dysfunction, and bladder or bowel impairment (ranging from painless retention to full incontinence). MRI should be performed as soon as possible if cauda equina syndrome is suspected, since this neurological crisis is potentially reversible if managed in a timely manner [135]. If imaging demonstrates a causative lesion, urgent surgical intervention is indicated regardless of pregnancy.

Patient positioning for lumbar spine surgery may be challenging during pregnancy. Most surgeons are familiar with the prone position. This position may be used during the first trimester of pregnancy and at the beginning of the second [136]. In the third trimester, surgery in the prone position may be problematic, particularly if pressure is to be placed on the area above the gravid uterus. Therefore, in the late stages of pregnancy, the left lateral decubitus position is usually chosen [137], although even the right lateral decubitus position has been described [138]. Alternatively, surgery can be performed on the Relton–Hall laminectomy frame, an equivalent four-poster or bow frame [136]. There is no literature supporting a specific choice of anesthesia.

36.8 Conclusion

This chapter summarizes much of the literature with regard to management of the pregnant and peripartum woman with space occupying intracranial and spinal pathologies. The challenges presented by this population are unique, as both the direct hormonal and indirect effects of pregnancy may affect the delicate balance of the neuroanatomical milieu. Much of our knowledge today is still based on case reports and epidemiological studies. Hence, data collection with regard to this population is imperative to enable improvements in patient care.

References

1. Santi BW, Sulistyono A, Dachlan EG. P48. Brain injury on pregnancy. Pregnancy Hypertens. 2011;1(3–4):295–6.
2. Hopkins AN, Alshaeri T, Akst SA, Berger JS. Neurologic disease with pregnancy and considerations for the obstetric anesthesiologist. Semin Perinatol. 2014;38(6):359–69.
3. Block HS, Biller J. Neurology of pregnancy. Handb Clin Neurol. 2014;121:1595–622.
4. Johnson AC, Cipolla MJ. The cerebral circulation during pregnancy: adapting to preserve normalcy. Physiology (Bethesda). 2015;30(2):139–47.
5. Mohan AR, Nelson-Piercy C. Neurological disease in pregnancy. Obstet Gynaecol Reprod Med. 2014;24(10):303–8.
6. Nossek E, Ekstein M, Rimon E, Kupferminc MJ, Ram Z. Neurosurgery and pregnancy. Acta Neurochir. 2011;153(9):1727–35.
7. Oehm E, Reinhard M, Keck C, Els T, Spreer J, Hetzel A. Impaired dynamic cerebral autoregulation in eclampsia. Ultrasound Obstet Gynecol. 2003;22(4):395–8.
8. Robba C, Santori G, Czosnyka M, et al. Optic nerve sheath diameter measured sonographically as non-invasive estimator of intracranial pressure: a systematic review and meta-analysis. Intensive Care Med. 2018;44(8):1284–94.
9. Lindqvist PG, Marsál K, Pirhonen JP. Maternal cerebral Doppler velocimetry before, during, and after a normal pregnancy: a longitudinal study. Acta Obstet Gynecol Scand. 2006;85(11):1299–303.
10. Belfort M, Van Veen T, White GL, et al. Low maternal middle cerebral artery Doppler resistance indices can predict future development of pre-eclampsia. Ultrasound Obstet Gynecol. 2012;40(4):406–11.
11. Harrison BP, Crystal CS. Imaging modalities in obstetrics and gynecology. Emerg Med Clin North Am. 2003;21(3):711–35.
12. Lee SC, Lueck CJ. Cerebrospinal fluid pressure in adults. J Neuroophthalmol. 2014;34(3):278–83.
13. Anson JA, Vaida S, Giampetro DM, McQuillan PM. Anesthetic management of labor and delivery in patients with elevated intracranial pressure. Int J Obstet Anesth. 2015;24(2):147–60.
14. Coles JP, Fryer TD, Coleman MR, et al. Hyperventilation following head injury: effect on ischemic burden and cerebral oxidative metabolism. Crit Care Med. 2007;35(2):568–78.
15. Carrera E, Schmidt JM, Fernandez L, et al. Spontaneous hyperventilation and brain tissue hypoxia in patients with severe brain injury. J Neurol Neurosurg Psychiatry. 2010;81(7):793–7.
16. Muizelaar JP, Marmarou A, Ward JD, et al. Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial. J Neurosurg. 1991;75(5):731–9.
17. Tomimatsu T, Kakigano A, Mimura K, et al. Maternal carbon dioxide level during labor and its possible effect on fetal cerebral oxygenation: mini review. J Obstet Gynaecol Res. 2013;39:1–6.
18. Kasper EM, Hess PE, Silasi M, et al. A pregnant female with a large intracranial mass: reviewing the evidence to obtain management guidelines for intracranial meningiomas during pregnancy. Surg Neurol Int. 2010;1:95.
19. Balki M, Manninen PH. Craniotomy for suprasellar meningioma in a 28-week pregnant woman without fetal heart rate monitoring. Can J Anaesth. 2004;51:573–6.
20. Handlogten KS, Sharpe EE, Brost BC, Parney IF, Pasternak JJ. Dexmedetomidine and mannitol for awake craniotomy in a pregnant patient. Anesth Analg. 2015;120(5):1099–103.
21. Zafar SN, Iqbal A, Farez MF, Kamatkar S, de Moya MA. Intensive insulin therapy in brain injury: a meta-analysis. J Neurotrauma. 2011;28(7):1307–17.
22. Núñez-Patiño RA, Zorrilla-Vaca A, Rivera-Lara L. Comparison of intensive versus conventional insulin therapy in traumatic brain injury: a meta-analysis of randomized controlled trials. Brain Inj. 2018;32(6):693–703.
23. Hermanides J, Plummer MP, Finnis M, Deane AM, Coles JP, Menon DK. Glycaemic control targets after traumatic brain injury: a systematic review and meta-analysis. Crit Care. 2018;22(1):11.
24. Sumikura H. Neonatal hypoglycemia after cesarean section. J Anesth. 2013;27:167–8.
25. Sela HY, Weiniger CF, Hersch M, Smueloff A, Laufer N, Einav S. The pregnant motor vehicle accident casualty: adherence to basic workup and admission guidelines. Ann Surg. 2011;254(2):346–52.
26. Roy KK, Baruah J, Kumar S, Deorari AK, Sharma JB, Karmakar D. Cesarean section for suspected fetal distress, continuous fetal heart monitoring and decision to delivery time. Indian J Pediatr. 2008;75(12):1249–52.

27. Smith IF, Skelton V. An unusual intracranial tumour presenting in pregnancy. Int J Obstet Anesth. 2007;16:82–5.
28. Yoo KY, Lee JC, Yoon MH, et al. The effects of volatile anesthetics on spontaneous contractility of isolated human pregnant uterine muscle: a comparison among sevoflurane, desflurane, isoflurane, and halothane. Anesth Analg. 2006;103:443–7.
29. Dyer RA, van Dyk D, Dresner A. The use of uterotonic drugs during caesarean section. Int J Obstet Anesth. 2010;19:313–9.
30. Secher NJ, Arnsbo P, Wallin L. Haemodynamic effects of oxytocin (syntocinon) and methyl ergometrine (methergin) on the systemic and pulmonary circulations of pregnant anaesthetized women. Acta Obstet Gynecol Scand. 1978;57(2):97–103.
31. Jago AA, Ezechi OC, Achinge GI, Okunlola MA. Effect of oxytocics on the blood pressure of normotensive Nigerian parturients. J Matern Fetal Neonatal Med. 2007;20(9):703–5.
32. Sato S, Shimizu M, Endo K, Homma M, Yamamoto T. Postpartum cerebral angiopathy—a case report the vasculopathy associated with co-administration of two vasoconstrictives, methylergometrine maleate and sumatriptan. [Article in Japanese]. Rinsho Shinkeigaku. 2004;44(2):96–101.
33. Granier I, Garcia E, Geissler A, Boespflug MD, Durand-Gasselin J. Postpartum cerebral angiopathy associated with the administration of sumatriptan and dihydroergotamine—a case report. Intensive Care Med. 1999;25(5):532–4.
34. Bacigaluppi S, Piccinelli M, Antiga L, et al. Factors affecting formation and rupture of intracranial saccular aneurysms. Neurosurg Rev. 2014;37:1–14.
35. Stevanovic A, Rossaint R, Veldeman M, Bilotta F, Coburn M. Anaesthesia management for awake craniotomy: systematic review and meta-analysis. PLoS One. 2016;11(5):e0156448.
36. Kamata K, Fukushima R, Nomura M, Ozaki M. A case of left frontal high-grade glioma diagnosed during pregnancy. JA Clin Rep. 2017;3:18.
37. Meng L, Han SJ, Rollins MD, Gelb AW, Chang EF. Awake brain tumor resection during pregnancy: decision making and technical nuances. J Clin Neurosci. 2016;24:160–2.
38. Hedayat H, Felbaum DR, Reynolds JE, Janjua RM. Awake craniotomy for the treatment of a cortical pseudoaneurysm in a pregnant patient. Cureus. 2017;9(12):e1921.
39. Kulikov A, Lubnin A. Anesthesia for awake craniotomy. Curr Opin Anaesthesiol. 2018;31(5):506–10.
40. Godlewski CA, Castellanos PF. Pre-emptive awake airway management under dexmedetomidine sedation in a parturient with spinal muscular atrophy type-2. Int J Obstet Anesth. 2018;33:81–4.
41. Rashid MR, Najeeb R, Mushtaq S, Habib R. Comparative evaluation of midazolam, dexmedetomidine, and propofol as intensive care unit sedatives in postoperative electively ventilated eclamptic patients. J Anaesthesiol Clin Pharmacol. 2017;33(3):331–6.
42. Zhang J, Zhou H, Sheng K, Tian T, Wu A. Foetal responses to dexmedetomidine in parturients undergoing caesarean section: a systematic review and meta-analysis. J Int Med Res. 2017;45(5):1613–25.
43. Öcal I, Güneş Y, Mert T, Özcengiz D, Günay I. Dexmedetomidine modifies uterine contractions in pregnancy terms of rats. Indian J Pharmacol. 2013;45(2):168–73.
44. Liu Y, Liang F, Liu X, Shao X, Jiang N, Gan X. Dexmedetomidine reduces perioperative opioid consumption and postoperative pain intensity in neurosurgery: a meta-analysis. J Neurosurg Anesthesiol. 2018;30(2):146–55.
45. Le Guen M, Liu N, Tounou F, et al. Dexmedetomidine reduces propofol and remifentanil requirements during bispectral index-guided closed-loop anesthesia: a double-blind, placebo-controlled trial. Anesth Analg. 2014;118(5):946–55.
46. Giannini A, Bricchi M. Posterior fossa surgery in the sitting position in a pregnant patient with cerebellopontine angle meningioma. Br J Anaesth. 1999;82(6):941–4.
47. Casabella AM, Urakov TM, Basil G, Morcos JJ. Management of foramen magnum meningioma during pregnancy: literature review and case report. World Neurosurg. 2017;97:752.e15–8.
48. Priddy BH, Otto BA, Carrau RL, Prevedello DM. Management of skull base tumors in the obstetric population: a case series. World Neurosurg. 2018;113:e373–82.
49. Sharma D, Vavilala MS. Perioperative management of adult traumatic brain injury. Anesthesiol Clin. 2012;30:333–46.
50. Calthorpe N, Lewis M. Acid aspiration prophylaxis in labour: a survey of UK obstetric units. Int J Obstet Anesth. 2005;14(4):300–4.
51. Desai N, Wicker J, Sajayan A, Mendonca C. A survey of practice of rapid sequence induction for caesarean section in England. Int J Obstet Anesth. 2018;36:3–10.
52. Kazemi P, Villar G, Flexman AM. Anesthetic management of neurosurgical procedures during pregnancy: a case series. J Neurosurg Anesthesiol. 2014;26:234–40.
53. Thind AS, Turner RJ. In vitro effects of propofol on gravid human myometrium. Anaesth Intensive Care. 2008;36(6):802–6.
54. Lesage S. Cesarean delivery under general anesthesia: continuing professional development. Can J Anaesth. 2014;61(5):489–503.
55. Yu D, Sun G. Propofol retards fetal neurodevelopment: does propofol have neurotoxic effects? Neurotoxicol Teratol. 2014;46:77.
56. Johnson EG, Meier A, Shirakbari A, Weant K, Baker JS. Impact of rocuronium and succinylcholine on sedation initiation after rapid sequence intubation. J Emerg Med. 2015;49(1):43–9.

57. Girault A, Dommergues M, Nizard J. Impact of maternal brain tumours on perinatal and maternal management and outcome: a single referral centre retrospective study. Eur J Obstet Gynecol Reprod Biol. 2014;183:132–6.
58. Wang LP, Paech MJ. Neuroanesthesia for the pregnant woman. Anesth Analg. 2008;107:193–200.
59. Stourac P, Adamus M, Seidlova D, et al. Low-dose or high-dose rocuronium reversed with neostigmine or sugammadex for cesarean delivery anesthesia: a randomized controlled noninferiority trial of time to tracheal intubation and extubation. Anesth Analg. 2016;122(5):1536–45.
60. Jevtovic-Todorovic V. General anesthetics and the developing brain: friends or foes? J Neurosurg Anesthesiol. 2005;17(4):204–6.
61. Loop T, Priebe HJ. Recovery after anesthesia with remifentanil combined with propofol, desflurane, or sevoflurane for otorhinolaryngeal surgery. Anesth Analg. 2000;91(1):123–9.
62. Manullang TR, Chun K, Egan TD. The use of remifentanil for cesarean section in a parturient with recurrent aortic coarctation. Can J Anaesth. 2000;47(5):454–9.
63. Lato K, Bekes I, Widschwendter P, et al. Hypotension due to spinal anesthesia influences fetal circulation in primary caesarean sections. Arch Gynecol Obstet. 2018;297(3):667–74.
64. Ventura W, De Paco C, Delgado JL, Blanco JE, Peñalver C, Parrilla JJ. Reliability of examining the external iliac artery with Doppler ultrasound in the first trimester and its relationship with maternal blood pressure and uterine artery blood flow. Eur J Obstet Gynecol Reprod Biol. 2012;165(1):42–6.
65. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. Neurosurgery. 2017;80(1):6–15.
66. Schierhout G, Roberts I. Hyperventilation therapy for acute traumatic brain injury. Cochrane Database Syst Rev. 2000;1997(2):CD000566. https://doi.org/10.1002/14651858.CD000566
67. Oddo M, Levine JM, Mackenzie L, et al. Brain hypoxia is associated with short-term outcome after severe traumatic brain injury independently of intracranial hypertension and low cerebral perfusion pressure. Neurosurgery. 2011;69(5):1037–45. https://doi.org/10.1227/NEU.0b013e3182287ca7
68. Quintard H, Patet C, Suys T, Marques-Vidal P, Oddo M. Normobaric hyperoxia is associated with increased cerebral excitotoxicity after severe traumatic brain injury. Neurocrit Care. 2015;22(2):243–50.
69. Damiani E, Adrario E, Girardis M, et al. Arterial hyperoxia and mortality in critically ill patients: a systematic review and meta-analysis. Crit Care. 2014;18(6):711.
70. Yalcin S, Aydoğan H, Yuce HH, et al. Effects of sevoflurane and desflurane on oxidative stress during general anesthesia for elective cesarean section. Wien Klin Wochenschr. 2013;125(15–16):467–73.
71. Murdoch H, Scrutton M, Laxton CH. Choice of anaesthetic agents for caesarean section: a UK survey of current practice. Int J Obstet Anesth. 2013;22(1):31–5.
72. Haas JF, Jänisch W, Staneczek W. Newly diagnosed primary intracranial neoplasms in pregnant women: a population-based assessment. J Neurol Neurosurg Psychiatry. 1986;49:874–80.
73. Verheecke M, Halaska MJ, Lok CA, et al. Primary brain tumours, meningiomas and brain metastases in pregnancy: report on 27 cases and review of literature. Eur J Cancer. 2014;50(8):1462–71.
74. Yust-Katz S, de Groot JF, Liu D, et al. Pregnancy and glial brain tumors. Neuro-Oncology. 2014;16(9):1289–94.
75. Rønning PA, Helseth E, Meling TR, Johannesen TB. The effect of pregnancy on survival in a low-grade glioma cohort. J Neurosurg. 2016;125(2):393–400.
76. van Westrhenen A, Senders JT, Martin E, DiRisio AC, Broekman MLD. Clinical challenges of glioma and pregnancy: a systematic review. J Neurooncol. 2018;139(1):1–11.
77. Rosen A, Anderson V, Bercovici E, Laperriere N, Rohan D'Souza. Brainstem gliomas in pregnancy: a systematic review. J Matern Fetal Neonatal Med. 2018:1–311.
78. Dressler EV, Thakkar JP, Liu M, Al-Qaisi A, Villano JL. Epidemiology of meningiomas post-public law 107-206: the benign brain tumor cancer registries amendment act. Cancer. 2015;121(14):2400–10.
79. Claus EB, Black PM, Bondy ML, et al. Exogenous hormone use and meningioma risk: what do we tell our patients? Cancer. 2007;110(3):471–6.
80. Wigertz A, Lönn S, Mathiesen T, et al. Risk of brain tumors associated with exposure to exogenous female sex hormones. Am J Epidemiol. 2006;164(7):629–36.
81. Wrensch M, Minn Y, Chew T, Bondy M, Berger MS. Epidemiology of primary brain tumors: current concepts and review of the literature. Neuro-Oncology. 2002;4(4):278–99.
82. Laviv Y, Bayoumi A, Mahadevan A, Young B, Boone M, Kasper EM. Meningiomas in pregnancy: timing of surgery and clinical outcomes as observed in 104 cases and establishment of a best management strategy. Acta Neurochir. 2018;160(8):1521–9.
83. Kanaan I, Jallu A, Kanaan H. Management strategy for meningioma in pregnancy: a clinical study. Skull Base. 2003;13(4):197–203.
84. Moscovici S, Fraifeld S, Cohen JE, et al. Parasellar meningiomas in pregnancy: surgical results and visual outcomes. World Neurosurg. 2014;82(3–4):e503–12.
85. Stachenfeld NS. Sex hormone effects on body fluid regulation. Exerc Sport Sci Rev. 2008;36(3):152–9.
86. Hortobágyi T, Bencze J, Murnyák B, Kouhsari MC, Bognár L, Marko-Varga G. Pathophysiology of meningioma growth in pregnancy. Open Med (Wars). 2017;12:195–200.

87. Smith JS, Quinones-Hinojosa A, Harmon-Smith M, Bollen AW, McDermott MW. Sex steroid and growth factor profile of a meningioma associated with pregnancy. Can J Neurol Sci. 2005;32:122–7.
88. Gazzeri R, Galarza M, Gazzeri G. Growth of a meningioma in a transsexual patient after estrogen-progestin therapy. N Engl J Med. 2007;357:2411–2.
89. Cahill DW, Bashirelahi N, Solomon LW, Dalton T, Salcman M, Ducker TB. Estrogen and progesterone receptors in meningiomas. J Neurosurg. 1984;60:985–93.
90. Custer B, Longstreth WT Jr, Phillips LE, Koepsell TD, Van Belle G. Hormonal exposures and the risk of intracranial meningioma in women: a population-based case-control study. BMC Cancer. 2006;6:152.
91. Laviv Y, Ohla V, Kasper EM. Unique features of pregnancy-related meningiomas: lessons learned from 148 reported cases and theoretical implications of a prolactin modulated pathogenesis. Neurosurg Rev. 2018;41(1):95–108.
92. Kerschbaumer J, Freyschlag CF, Stockhammer G, et al. Hormone-dependent shrinkage of a sphenoid wing meningioma after pregnancy: case report. J Neurosurg. 2016;124(1):137–40.
93. Chakravarthy V, Kaplan B, Gospodarev V, Myers H, De Los RK, Achiriloaie A. Houdini tumor: case report and literature review of pregnancy-associated meningioma. World Neurosurg. 2018;114:e1261–5.
94. Chacko JG, Miller JL, Angtuaco EJ. Spontaneous postpartum resolution of vision loss caused by a progesterone receptor-positive tuberculum sellae meningioma. J Neuroophthalmol. 2010;30(2):132–4.
95. Owens MA, Craig BM, Egan KM, Reed DR. Birth desires and intentions of women diagnosed with a meningioma. J Neurosurg. 2015;122(5):1151–6.
96. Elster AD, Sanders TG, Vines FS, Chen MY. Size and shape of the pituitary gland during pregnancy and post partum: measurement with MR imaging. Radiology. 1991;181:531–5.
97. Miki Y, Asato R, Okumura R, et al. Anterior pituitary gland in pregnancy: hyperintensity at MR. Radiology. 1993;187:229–31.
98. Dinc H, Esen F, Demirci A, Sari A, Resit GH. Pituitary dimensions and volume measurements in pregnancy and post partum. MR assessment. Acta Radiol. 1998;39:64–9.
99. Pichon MF, Bression D, Peillon F, Milgrom E. Estrogen receptors in human pituitary adenomas. J Clin Endocrinol Metab. 1980;51:897–902.
100. Gillam MP, Molitch ME, Lombardi G, Colao A. Advances in the treatment of prolactinomas. Endocr Rev. 2006;27(5):485–534.
101. Serri O, Kuchel O, Buu NT, Somma M. Differential effects of a low dose dopamine infusion on prolactin secretion in normal and hyperprolactinemic subjects. J Clin Endocrinol Metab. 1983;56:255–9.
102. Almalki MH, Alzahrani S, Alshahrani F, et al. Managing prolactinomas during pregnancy. Front Endocrinol (Lausanne). 2015;6:85.
103. Erroi A, Bassetti M, Spada A, Giannattasio G. Microvasculature of human micro- and macroprolactinomas. A morphological study. Neuroendocrinology. 1986;43:159–65.
104. Gemzell C, Wang CF. Outcome of pregnancy in women with pituitary adenoma. Fertil Steril. 1979;31(4):363–72.
105. Kupersmith MJ, Rosenberg C, Kleinberg D. Visual loss in pregnant women with pituitary adenomas. Ann Intern Med. 1994;121(7):473–7.
106. Molitch ME. Pregnancy and the hyperprolactinemic woman. N Engl J Med. 1985;312(21):1364–70.
107. Rossi AM, Vilska S, Heinonen PK. Outcome of pregnancies in women with treated or untreated hyperprolactinemia. Eur J Obstet Gynecol Reprod Biol. 1995;63(2):143–6.
108. de Castro Musolino NR, Bronstein MD. Prolactinomas and pregnancy. In: Bronstein MD, editor. Pituitary tumors in pregnancy. Endocrine updates, vol. 15. Boston: Springer; 2001. p. 91–108.
109. Dias MS, Sekhar LN. Intracranial hemorrhage from aneurysms and arteriovenous malformations during pregnancy and the puerperium. Neurosurgery. 1990;27:855–65.
110. Horton JC, Chambers WA, Lyons SL, Adams RD, Kjellberg RN. Pregnancy and the risk of hemorrhage from cerebral arteriovenous malformations. Neurosurgery. 1990;27(6):867–71. discussion 871–2.
111. Zhu D, Zhao P, Lv N, et al. Rupture risk of cerebral arteriovenous malformations during pregnancy and puerperium: a single-center experience and pooled data analysis. World Neurosurg. 2018;111:e308–15.
112. Porras JL, Yang W, Philadelphia E, et al. Hemorrhage risk of brain arteriovenous malformations during pregnancy and puerperium in a North American Cohort. Stroke. 2017;48(6):1507–13.
113. Lv X, Li Y. The clinical characteristics and treatment of cerebral AVM in pregnancy. Neuroradiol J. 2018;28(4):385–8.
114. Lv X, Liu P, Li Y. Pre-existing, incidental and hemorrhagic AVMs in pregnancy and postpartum: gestational age, morbidity and mortality, management and risk to the fetus. Interv Neuroradiol. 2016;22(2):206–11.
115. Takahashi JC, Iihara K, Ishii A, Watanabe E, Ikeda T, Miyamoto S. Pregnancy-associated intracranial hemorrhage: results of a survey of neurosurgical institutes across Japan. J Stroke Cerebrovasc Dis. 2014;23(2):e65–71.
116. Chalouhi N, Hoh BL, Hasan D. Review of cerebral aneurysm formation, growth, and rupture. Stroke. 2013;44(12):3613–22.
117. Marshman LA, Rai MS, Aspoas AR. Comment to "endovascular treatment of ruptured intracranial aneurysms during pregnancy: report of three cases". Arch Gynecol Obstet. 2005;272(1):93.
118. Carvalho CS, Resende F, Centeno MJ, Ribeiro I, Moreira J. Anesthetic approach of pregnant woman

with cerebral arteriovenous malformation and subarachnoid hemorrhage during pregnancy: case report. Braz J Anesthesiol. 2013;63(2):223–6.
119. Marshman LA, Aspoas AR, Rai MS, Chawda SJ. The implications of ISAT and ISUIA for the management of cerebral aneurysms during pregnancy. Neurosurg Rev. 2007;30(3):177–80. discussion 180.
120. Robba C, Bacigaluppi S, Bragazzi NL, et al. Aneurysmal subarachnoid hemorrhage in pregnancy-case series, review, and pooled data analysis. World Neurosurg. 2016;88:383–98.
121. Kim YW, Neal D, Hoh BL. Cerebral aneurysms in pregnancy and delivery: pregnancy and delivery do not increase the risk of aneurysm rupture. Neurosurgery. 2013;72(2):143–9. discussion 150.
122. Chen JZ, Sheehan PM, Brennecke SP, Keogh RJ. Vessel remodelling, pregnancy hormones and extravillous trophoblast function. Mol Cell Endocrinol. 2012;349(2):138–44.
123. Reschke M, Sweeney JM, Wong N. Spinal anesthesia performed for cesarean delivery after external ventricular drain placement in a parturient with symptomatology from an intracranial mass. Int J Obstet Anesth. 2019;37:122–5.
124. Parikh N, Parikh N. Management of anesthesia for cesarean delivery in a patient with an unruptured intracranial aneurysm. Int J Obstet Anesth. 2018;36:118–21.
125. Kondziolka D, Lunsford LD, Kestle JR. The natural history of cerebral cavernous malformations. J Neurosurg. 1995;83:820–4.
126. Brouillard P, Vikkula M. Genetic causes of vascular malformations. Hum Mol Genet. 2007;16 (Spec No. 2):R140–9.
127. Di Tommaso L, Scarpellini F, Salvi F, Ragazzini T, Foschini MP. Progesterone receptor expression in orbital cavernous hemangiomas. Virchows Arch. 2000;436(3):284–8.
128. Zauberman H, Feinsod M. Orbital hemangioma growth during pregnancy. Acta Ophthalmol. 1970;48(5):929–33.
129. Pozzati E, Acciarri N, Tognetti F, Marliani F, Giangaspero F. Growth, subsequent bleeding, and de novo appearance of cerebral cavernous angiomas. Neurosurgery. 1996;38(4):662–9. discussion 669–70.
130. Porter RW, Detwiler PW, Spetzler RF, et al. Cavernous malformations of the brainstem: experience with 100 patients. J Neurosurg. 1999;90(1):50–8.
131. Akers A, Al-Shahi Salman R, Awad IA, et al. Synopsis of guidelines for the clinical management of cerebral cavernous malformations: consensus recommendations based on systematic literature review by the angioma alliance scientific advisory board clinical experts panel. Neurosurgery. 2017;80(5):665–80.
132. Mousavi SJ, Parnianpour M, Vleeming A. Pregnancy related pelvic girdle pain and low back pain in an Iranian population. Spine (Phila Pa 1976). 2007;32:E100–4.
133. O'Laoire SA, Crockard HA, Thomas DG. Prognosis for sphincter recovery after operation for cauda equina compression owing to lumbar disc prolapse. Br Med J (Clin Res Ed). 1981;282:1852–4.
134. Iyilikçi L, Erbayraktar S, Tural AN, Celik M, Sannav S. Anesthetic management of lumbar discectomy in a pregnant patient. J Anesth. 2004;18:45–7.
135. Di Martino A, Russo F, Denaro L, Denaro V. How to treat lumbar disc herniation in pregnancy? A systematic review on current standards. Eur Spine J. 2017;26(Suppl 4):496–504.
136. Ansari NN, Hasson S, Naghdi S, Keyhani S, Jalaie S. Low back pain during pregnancy in Iranian women: prevalence and risk factors. Physiother Theory Pract. 2010;26:40–8.
137. Hayakawa K, Mizutani J, Suzuki N, et al. Surgical management of the pregnant patient with lumbar disc herniation in the latter stage of the second trimester. Spine (Phila Pa 1976). 2017;42(3):E186–9.
138. Kovari VZ, Horvath L. Surgical management of cauda syndrome in third trimester of pregnancy focusing on spinal anesthesia and right lateral positioning during surgery as possible practices. Eur Spine J. 2018;27(Suppl 3):483–8.

Maternal Critical Care in a Disaster

37

Gillian Abir and Kay Daniels

Bullet Points

- Disaster planning requires unique considerations for pregnant and peripartum women.
- Providers of obstetric care and facilities that deliver maternity services must be able to render appropriate care to their patients in a disaster.
- Pregnant women and their unborn infants are more vulnerable to short- and long-term effects from disasters.
- Introduction of an obstetric-specific triage tool and hospital levels of maternal care is offered as a means to facilitate rapid evacuation and transfer.
- Obstetric-specific tools that are readily available to be utilized in a disaster are vital for the well-being and safety of obstetric patients.
- Disaster preparedness and training of staff should be ongoing with regular updates for maintenance of knowledge to enable a seamless process.

37.1 Introduction

37.1.1 Historical Disaster Preparedness

The World Health Organization defines a disaster as "an occurrence disrupting the normal condition of existence and causing a level of suffering that exceeds the capacity of adjustment of the affected community" and an emergency as "a state in which normal procedures are suspended and extra-ordinary measures are taken in order to avert a disaster" [1]. The key to a successful outcome in a disaster situation is good preparation, fast response, rehabilitation, reconstruction, and when possible, prevention of future events [1]. The etiology of a disaster can be natural, human, technological, or from hazardous material (HAZMAT) (Table 37.1).

Disasters differ in terms of speed, spread, and impact. Epidemics or pandemics (e.g., H1N1 influenza, Ebola virus disease, and severe acute respiratory syndrome) may originate in one geographical area and spread globally because of international travel. Natural disasters may be geographically limited and unique to specific locations (e.g., earthquakes, floods, tornados) or less limited but still dependent on location (e.g., major volcano eruptions, hurricanes). Man-made disasters are typically not geographically limited and result from an unwanted impact of modern

G. Abir (✉)
Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, CA, USA
e-mail: gabir@stanford.edu

K. Daniels
Department of Obstetrics and Gynecology, Stanford University School of Medicine, Stanford, CA, USA
e-mail: kdaniels@stanford.edu

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_37

Table 37.1 Disaster types

Natural	Human	Technological	Hazardous materials (HAZMAT)
Geophysical – Earthquake – Landslide – Tsunami – Volcano Hydrological – Flood – Avalanche Climatological – Extreme temperature – Drought – Wildfires Meteorological – Cyclones – Storms/wave surges Biological – Disease epidemics – Insect/animal plagues	Power outage Electrical fire Internal flood Structural defect Terrorism Bombs Shooting Violence Transport accidents Industrial accidents	Communication failure IT system outage Cyberattack	Chemical spill Gas leak Radioactive leak Toxic biological leak

http://www.ifrc.org/en/what-we-do/disaster-management/about-disasters/definition-of-hazard/

society (e.g., nuclear plant breakdowns, oil spills, global warming).

Hazard vulnerability analysis is a method used by healthcare organizations and public health departments to identify hazards and risks that are most likely to impact the facility and/or surrounding community, thereby directing planning efforts [2]. Community disaster preparedness (i.e., the ability of a community to withstand and recover from disasters) mainly focuses on disasters that occur in society as a whole and assume that hospitals will exist to treat the potential mass of injured victims. Hazard vulnerability analysis and community disaster preparedness are therefore complementary.

Hospitals are required to have their own disaster plans in place and to ensure that staff are familiar and trained in their use. However, within the framework of a hospital, disaster plans are usually generic. Consequently, they may not encompass the needs of specific medical disciplines, especially when a wide spectrum of requirements exists, ranging from neonatal care to geriatric care.

If the hospital itself is directly or indirectly affected by the disaster, and can no longer function as a receiving facility for casualties or provide routine care to existing patients, finding an alternative location to care for these patients may also be particularly challenging.

37.1.2 Why Disaster Preparedness for Pregnant and Peripartum Women Is Unique

Pregnant women, laboring women, and newborn infants are vulnerable populations whose unique needs are often overlooked in disaster planning. A simple generic disaster plan will not cover the large spectrum of needs seen on every obstetric unit, ranging from providing a disaster plan for a healthy woman after a normal vaginal delivery to a patient who is undergoing emergency surgery with regional/general anesthesia (Table 37.2) [3]. In addition to the varied acuity of the mother, there is also the challenge of caring for more than one patient at a time: the mother and her fetus. When consideration must be given to evacuation of a pregnant woman, the best location for the mother may not be optimal for the fetus or vice versa. Careful thought and preplanning are needed to assure the best care for both patients.

Furthermore, in a disaster, the obstetric and neonatal populations are likely to be disproportionally more affected by social and environmental changes

Table 37.2 Obstetric patient subgroups

Patient type
Pregnant patient hospitalized for non-obstetric reasons
Antepartum patient requiring observation and/or monitoring
Laboring patient
Intraoperative and postoperative patient
Postpartum patient—uncomplicated, healthy newborn(s)
Postpartum patient—complicated, requiring observation and/or treatment

such as disruption of housing, lack of routine medical care, and food and water supply shortages and may be particularly vulnerable to the effects of both violence and toxins [4]. Hence, mitigating the immediate physical effects of a disaster for both the mother and fetus is of great importance.

Finally, indirect exposure to stress may also endanger both the mother and the fetus. Pregnant women exposed to a disaster seem prone to a higher incidence of pregnancy-associated diseases (e.g., stress perception significantly predisposes to maternal hypertension and gestational diabetes); the mental health of the mother is thought to affect fetal growth and timing of delivery [5]. A higher incidence of premature delivery and low birth weight babies have been observed after major stress. Exposure to major stress at an earlier gestational age has been associated with shorter gestation [6–9]. While a clear delineation of all the effects on the neonate remain controversial, those on the mother remain largely unstudied [10]. Therefore, at this point, preparedness should include plans to alleviate maternal stress in order to minimize the chances of an untimely or complicated delivery that could endanger both the mother and neonate.

37.2 Organization and Resources

37.2.1 Organizational Support of Disaster Readiness

The American Medical Association's code of medical ethics notes that physicians have an ethical obligation to provide urgent medical care in a disaster, even in the face of greater than usual risks to their safety, health, or life [11]. It is also the responsibility of physicians to keep up to date with knowledge in this field to ensure their ability to provide appropriate medical care in a disaster. However, the last two decades of experience with major disasters have made it evident that hospital disaster preparedness should also include the needs of special populations, including patients who differ from general medical patients, such as pregnant or peripartum women. The 2013 American College of Obstetricians and Gynecologists (ACOG) document addressing disaster preparedness states: "Providers of obstetric care and facilities that provide maternity services offer services to a population that has many unique features warranting additional consideration" [12]. The ACOG statement highlights that disaster planning for trauma and medical patients requires a special skill set needed to be able to deliver a pregnant woman or to care for a newborn infant in austere environments.

Disasters may have a major impact on staffing, which can affect patient care if no pre-planning has been organized by the hospital. Institutional policies detailing contractual obligations of mandatory disaster duty requirements should be clearly stated ahead of time [13]. The ability and willingness of healthcare providers to respond during an event may also be dependent on a staff member's mental and physical fitness and stamina in extreme heat or cold temperatures, especially with limited food or water [14]. Other considerations include the personal needs of some staff members, such as chronic illness requiring medications (e.g., diabetes or hypertension), and their out-of-hospital responsibilities, such as dependent family members and pets. The hospital must find a way to accommodate family members and pets in order to ensure that these staff members remain available to perform their work duties.

37.2.2 Framework of an Obstetric Disaster Plan

A comprehensive obstetric disaster plan must include several organizational aspects of care:

1. Understanding of a standard disaster language
2. A commonly used obstetric-specific triage system
3. An agreed upon stratification of maternity hospitals' levels of care
4. A preexisting collaborative network of regional and national obstetric hospitals
5. An effective patient tracking system

37.3 Terminology

For clear communication, there must be a common language when describing disaster concepts and processes.

Evacuation refers to vacating the current location. The decision to evacuate patients may be time-dependent and directly or indirectly related to the disaster that occurred (i.e., fire rendering the unit unusable). This decision may also be determined by the number of casualties, availability of resources for mobilizing patients, and availability of an alternative location.

Shelter-in-place refers to the decision to remain in the current location rather than evacuate. The decision to shelter-in-place is guided by the need to maximize patient care. There are a variety of reasons that shelter-in-place may be chosen: evacuating patients may be hazardous, staff and supplies remain available on-site, or the situation is considered temporary.

Surge refers to the capability of managing a sudden, unexpected influx of patients and consists of three subsets (Table 37.3) [15].

Hospital staff should be educated and adept with this terminology to allow ease of communication in a disaster incident.

Table 37.3 Surge subsets

Capacity type	Definition
Conventional capacity	Spaces, staff, and supplies used are consistent with daily practices within the institution
Contingency capacity	Spaces, staff, and supplies used are not consistent with daily practices but maintain or have minimal effect on usual patient care practices
Crisis capacity	Adaptive spaces, staff, and supplies are not consistent with usual standards of care but provide sufficiency of care in the setting of a catastrophic disaster

37.4 Tools

Throughout the United States, the hospital incident command system (HICS) has been adopted as the system for managing medical facilities during a disaster [11]. HICS is a flexible management method designed to adapt to the needs of different facilities. The idea underlying the establishment of this system was that it should be useful for managing all types of disasters by (a) establishing a clear chain of command, (b) integrating staff members from different departments into a team capable of effectively addressing problems and delegating responsibilities, (c) providing logistical and administrative support that operational personnel may require, and (d) ensuring key elements of the hospital response function while eliminating duplication.

The HICS must include an outline of the incident management team, including the hospital command functions that have been identified, who has been assigned to these roles, and how authority and responsibility are distributed. Among other command functions, HICS requires designation of an incident commander and establishment of a hospital command center (HCC) situated in a predetermined area in the hospital (dependent on local preferences) and unit leaders who are responsible for staff with specific roles. The HCC manages the hospital's response to an incident and establishes priorities. If resources are limited, the HCC is responsible for allocation and obtainment of additional items, allowing clinical units to concentrate on patient care.

The only line of communication from the HCC to/from the unit/ward should be through the unit leaders. Each medical unit or floor in the hospital has a unit leader (UL). The UL will generally be a nurse or physician who is familiar with the needs of those specific patients. Throughout the disaster, the HCC must communicate and update the ULs as to the status of

events. At the same time, the ULs must provide the HCC with real-time information regarding staff and patients, safety, hazards encountered, and resources needed. An order to evacuate can only be authorized by the HCC, which will also dictate the evacuation plan and time line.

Online tools specifically developed to guide hospital-based evacuation or shelter-in-place for labor and delivery/antepartum and postpartum units are available at https://obgyn.stanford.edu/community/disaster-planning.html. These documents can be edited to be institution-specific.

37.4.1 Hospital Stratification

In 2015, the ACOG published an obstetric care consensus that distinguishes levels of maternal care [16]. There are five levels of maternal care centers; these are dependent on facility capabilities and availability of healthcare providers. The definitions provided for levels of maternity care are distinct but complimentary to the long-standing stratification of neonatal care [16]. Each facility should create a list of their local and regional hospitals based on maternity and neonatal levels of care to ensure that the mother and infant are sent to the most appropriate hospital in an evacuation event.

37.4.2 Availability of a Disaster Plan

Units that provide care to pregnant and peripartum women during a disaster should collate all relevant information and tools in paper format and place these in a designated binder. This "disaster plan binder" should be stored in an easily accessible and known location. The binder should contain such items as a disaster roles poster, job action sheets, census sheets, department damage map, triage forms, grab-and-go lists, transfer forms, transfer order forms, maternal discharge forms, neonatal discharge checklists, generic prescription forms, useful contacts, and other pertinent information (see below for more details). It is prudent to also have paper medical record options available in the binder as the electronic medical record (EMR) may not be available in an emergency (e.g., during a power failure or cyber attack) [17–19].

Equipment specifically designated for use in a disaster should be stored in designated, labeled boxes in an easily accessible location in each unit. The box should contain such items as paper forms, flashlights, headlamps, non-rechargeable batteries, handheld Doppler probes (that obstetricians likely use daily and are familiar with), lanyards, grab-and-go bags (empty), and vests for designated leadership roles. To ensure inventory maintenance, the box should only be retrieved in a disaster situation.

The purpose of the binder and the box is to provide the necessary information and vital equipment when needed urgently, allowing for seamless patient care. Each institution should have a department, in some institutions called the Office of Emergency Management (OEM), responsible for routine maintenance of both binder and box.

Leadership—As in any emergency situation, in order to achieve optimal patient outcomes, all staff members should work as a team with a clear leadership hierarchy. Within the unit, the main leadership roles should be titled using nomenclature used by HICS. Using these common terms will avoid confusion between units. The assigned positions should begin with the ULs who should be the most knowledgeable individuals on the unit. For example, in the delivery suite this would be the obstetric attending and/or charge nurse. Further roles are the assistant unit leaders (e.g. obstetric resident and/or team leader nurse), anesthesiologist, triage physician or nurse, bedside nurses, nursing assistants, technicians, and clerk/administrator. Of note, the designation of medical case managers for specific patients based on the patients' conditions may expedite care [20]. The disaster roles poster found in the disaster plan binder should be displayed with each team member's name and designated role. This will ensure that all the staff understand their own and other team members' responsibilities on the unit.

Job Action Sheet—An example of a job action sheet (JAS) is presented in Fig. 37.1. The purpose of JASs is to ensure that all mandatory tasks are completed and pre-assigned to specific roles. The

JAS should include role-specific task lists divided into predetermined time frames. The time frames are immediate (operational period 0–2 h), intermediate (operational period 2–12 h), and extended (operational period >12 h or as otherwise determined by the HCC). However, the list of tasks on the JASs is not exhaustive; they provide only an initial framework.

Obstetric Triage—A major step in planning evacuation is patient triage, i.e., determining who should be evacuated, in what order, by whom, and by what means. Whether the need is to evacuate

OB Anesthesiology Job Action Sheet:

• L&D: OB Anesthesiology Attending +/- Anesthesiology Fellows & Residents

Date: _____ Start: _____ End: _____Position Assigned to: _____

Position Reports to: OB Unit Leader **(UL)** & Assistant Unit Leader **(AUL)**, Hospital Command Center **(HCC)** H3210 Tel:

****Equipment needed: ID Badge, Stethoscope, Pen, Flashlight *****

Immediate (Operational Period 0-2 Hours)	**Done?**	**Initial**
Getting Started: 1. **Attending to check-in at Main OR front desk** - if attending pulled to Main OR, designate OB anesthesiology role on L&D to a fellow or appropriate resident 2. Allocate anesthesiology staff (fellows/residents/tech) to check machines & equipment 3. Meet with UL at nurses station or other safe area as designated by the UL 4. Identify which patients have necessary epidurals or procedures running to triage anesthesia care 5. Meet with all available on-site MDs and nursing staff at nursing station 6. Provide the UL with your best form of communication (phone, text, pager)		
PATIENT CARE 1. Ensure only life sustaining equipment is plugged into RED EMERGENCY PLUGS 2. Communicate with AUL & OB Tech after TRAIN Triage to identify high-risk/injured patients 3. Report emergent/life-threatening conditions to AUL, who reports to Hospital Command		
DAMAGES 1. Familiarize self with general condition and needs of the unit 2. Discuss status of O_2 & N_2O gas valves with AUL and Tech (only Engineering can turn on)		
SUPPLIES 1. Gather supplies for anesthesiology GRAB & GO Bag: Keep bag with you to be prepared for rapid evacuation 2. Assess anesthesiology medication, equipment, and supply needs for the next 24 - 48 hours		
Intermediate (Operational Period 2-12 Hours)	**Done?**	**Initial**
STAFF 1. Meet with UL on the time intervals designated by UL		
PATIENT CARE 1. Ensure only life sustaining equipment is plugged into RED EMERGENCY PLUGS 2. Assist with TRAIN triage: Identify high-risk patients and injured patients 3. Report emergent/life-threatening conditions to UL, who reports to Hospital Command		
COMMUNICATION 1. Communicate with AUL regarding medical status change of any patients 2. Communicate anesthesiology-related updates to patients and family members		
SUPPLIES 1. Communicate needs to AUL 2. Keep anesthesiology GRAB and GO bag with you and be prepared for rapid evacuation		
Extended (>12 Hours or as determined by Command Center)	**Done?**	**Initial**
Continue to provide care as directed in the Immediate & Intermediate Plan (see above)		

Fig. 37.1 Obstetric anesthesiology job action sheet. Reprinted with permission from the Obstetric Disaster Planning Committee at the Johnson Center for Pregnancy and Newborn Services, Stanford, USA

the facility or to prepare for increased surge capacity, a triage method is required to quickly and accurately assess patients [21]. The most effective triage tool is one that is clearly defined, with consistent and understood categories, and has a method of recording and displaying the information [22]. Urgent transportation of pregnant and laboring women can be very challenging and poses significant risk to both the mother and the fetus. Factors to consider when initiating an evacuation that are related to transportation include the lack of training in obstetric and neonatal resuscitation by general transport staff, space limitations in terms of pelvic access to deliver urgent care during transport, inadequate monitoring, and lack of specialized medications such as tocolytics [23]. During a mass disaster, the number of available (and appropriate) vehicles will most likely be limited, and road conditions may vary considerably. To optimize management of high-risk pregnant and peripartum patients during transportation, it is recommended to have a specialized obstetric transport nurse or obstetrician to escort these patients during the transfer process.

Neonatologists at Lucile Packard Children's Hospital at Stanford developed a pre-event triage tool, the "Triage by Resource Allocation for Inpatient" (TRAIN), which is used in daily practice to rapidly categorize patients depending on what clinical resources are needed in case of evacuation [24]. The OB TRAIN was adapted from TRAIN specifically for triage of antepartum and laboring women (Fig. 37.2a) and postpartum women (Fig. 37.2b) [21]. The antepartum/labor OB TRAIN is comprised of four maternal parameters (labor status, mobility, epidural status, and maternal or fetal risk status), with each component color graded according to the mode of transportation. Women are designated to a final mode of transportation dependent on their highest risk identified in the OB TRAIN (Fig. 37.2a, b). Transportation options include (with increasing level of care) car, emergency medical technician-staffed ambulance, paramedic-staffed ambulance, and a specialized ambulance with a specifically trained obstetric transport nurse or physician escort. There is also the option to shelter-in-place if delivery is imminent. Due to the rapidly changing status of laboring women, categorizing patients using OB TRAIN must be repeated shortly before evacuation. Incorporating OB TRAIN into daily practice on the unit or placing it in the EMR is optimal, so providers can become familiar with the terminology facilitating its use during a disaster. Setting up a triage system with a language specific to obstetric patients in a disaster is vital to allow a rapid evacuation and transfer of patients between facilities.

Hospital policy should state that in the event of a disaster, only urgent and emergent antepartum, labor, and postpartum care should be provided. All scheduled surgical cases (including scheduled cesarean deliveries) should be postponed, as well as other scheduled procedures such as induction of labor.

Grab-and-Go bag—Grab-and-go bags are intended for individualized patient care at the time of either shelter-in-place off the unit or during patient evacuation. Creating a list of essential items with details of the exact locations of where the items are stored on the unit will allow for ease of use. An empty backpack is retrieved from the disaster box; the patient's nurse then fills the bag with medications and essential supplies neede for that patient (e.g., for a vaginal delivery in a non-medical area). The bags stay with the individual patients during evacuation and transportation. The bags are not pre-filled due to perishable items. An example of a grab-and-go bag for the anesthesiologist is presented in Fig. 37.3.

Communication—Clear and effective communication is vital within a team, between teams, within a facility, and between facilities. As the usual lines of communication (telephone, text message, e-mail, facsimile, and media) may not be functional during a disaster, alternative methods of communication (e.g., satellite phones) should be readily available. Communication may be required for coordination of patient transfers and/or for patient treatment. Specialists may not be able to reach facilities by regular transportation, so in such a situation, telemedicine (videophones) may be used for communicating expert advice from a specialized center to a remote and/or isolated facility [25].

a

Transport	CAR (Discharge)	BLS	ALS	SPC	SHELTER IN PLACE
Labor Status	None	Early	Active	At risk for en route delivery	If delivery is imminent, 'Shelter-in-place' and TRAIN after delivery
Mobility	Ambulatory*	Ambulatory or Non-ambulatory	Non-ambulatory	Non-ambulatory	
Epidural Status	None	Placement >1 hr**	Placement <1 hr**	N/A	
Maternal Risk	Low	Low/Moderate	Moderate/High	High	

b

Transport	CAR (Discharge)	BLS	ALS	SPC
Delivery	VD >6 hr or CD >48 hr	VD<6 hr or CD <48 hr	Complicated VD or CD	Medically complicated
Mobility	Ambulatory*	Ambulatory or Non-ambulatory	Ambulatory or Non-ambulatory	Non-ambulatory
Post Op	Non CD surgery >2 hr**	>2 hr from CD	<2 hr from CD	Medically complicated
Maternal Risk	Low	Low/Moderate	Moderate/High	High

Fig. 37.2 (**a**) OB TRAIN for antepartum and labor and delivery. (*BLS* Basic Life support [Emergency Medical Technician-staffed ambulance], *ALS* Advanced Life Support [Paramedic-staffed ambulance], *SPC* Specialized [must be accompanied by MD or Transport Nurse], * Able to rise from a standing squat, ** Epidural catheter capped off). (**b**) OB TRAIN for postpartum. (*BLS* Basic Life support [Emergency Medical Technician-staffed ambulance], *ALS* Advanced Life Support [Paramedic-staffed ambulance], *SPC* Specialized [must be accompanied by MD or Transport Nurse], *VD* Vaginal delivery, *CD* Cesarean delivery, * Able to rise from a standing squat, ** If adult supervision is available for 24 h). Reprinted with permission from the Obstetric Disaster Planning Committee at the Johnson Center for Pregnancy and Newborn Services, Stanford, USA

37.4.3 Specifics for Evacuation

The evacuation process should only begin with an order from the HCC, at which time an updated patient, staff, and equipment census data, as well as information regarding structural damage and specific requests, are transferred from the ULs to the HCC. Review of the patients' triage status should be ongoing, so the correct information is up-to-date at the time of evacuation. Those who meet discharge criteria (which may be more lenient in a disaster) will need a discharge form. Those who are being evacuated to another location within the facility or to another facility will need a grab-and-go bag, a patient transfer form, unit-specific transfer orders, and a completed neonatal discharge checklist if applicable (for examples of these forms, see website in "Tools"). Complete and correct transmission of patient information to the receiving facility is of utmost importance during a rapid evacuation. The patient transfer form should stay with the patient at all times (preferably attached to the patient) and contains maternal and neonatal identifiable data, as well as laboratory results, and information regarding ongoing medical issues.

OB Anesthesiology Grab & Go Bag List:

	Airway:	Location/Notes:
☐	Ambu bag x 2	From epidural cart or on wall in LDR hallway
☐	O2 tank x 2 + wrenches	Dirty utility room across from LDR 8
☐	Laryngoscope & Blade x 2	
☐	ETT x 2	
☐	NRB mask x 3	
☐	Oral airways	
☐	Proseal LMA #3, #4, #5	
☐	Bougie	
	Suction:	
☐	Portable Suction machine	Top of code cart (across from LDR8)
	Monitors:	
☐	Propaq + power and monitor cables	Anesthesia Tech Rm
☐	Portable SpO2	Top of OR C Anesthesia machine
	IV:	
☐	IV start equipment	
☐	NS or LR 1000ml bag x 4	
☐	IV blood tubing x 2	
	Meds:	
☐	Omnicell Keys 1. Pick up key packet from Main Pharmacy for anesthesia cabinets and/or nursing cabinets 2. Insert appropriately labelled keys into top + bottom locks on front panel	3. Retrieve needed drugs 4. Keep track of drugs administered and associated MRNs 5. Give key to Pharmacist or RN Manager (not Resource RN)
☐	Propofol & Succinylcholine	
☐	Labetalol	
☐	Pitocin	
☐	PPH Kit x 2	Med room + PACU Omnicells only
☐	Emergency meds: Epinephrine/ Atropine / Phenylephrine/ Ephedrine	
☐	SL NTG	
☐	2% lidocaine/epi/bicarbonate 10ml syringes x2	
	Other:	
☐	10cc syringe x 20	
☐	18g needle x 20	
☐	25g needle x 10	

Gas Shut-Off Valves: Turn off if smoke or fire present, once off, only Engineering can turn back on	
PACU/11A, 11B, 11C/US room:	Just outside PACU
LDR rooms:	Between break room and double doors to OR
OR A:	Just outside OR A
OR B:	Just outside OR B
OR C:	Just outside OR C

Fig. 37.3 Obstetric anesthesiology grab-and-go bag list. Reprinted with permission from the Obstetric Disaster Planning Committee at the Johnson Center for Pregnancy and Newborn Services, Stanford, USA

37.4.4 Specifics for Surge

The surge capacity of a medical facility refers to its ability to accommodate a sudden surge (increase) in the number of patients requiring treatment. A situation requiring surge capacity requires deviation from the normal workflow. In other words, when there is a sudden influx of patients, there needs to be a new understanding of what level of medical care can be achieved. Surge capacity is divided into three strata: conventional, contingency and crisis (Table 37.3) [15, 26]. In a conventional surge level, service expansion generally remains in line with existing licensing and regulatory requirements. Once a maximum conventional surge level has been reached, contingency capacity begun. Contingency capacity requires preplanning by the facility with a plan that delineates where overflow patients can be safely accommodated and how to call for additional staff. Contingency plans should also include a method to transfer patients to local facilities, so the hospital can return to normal or conventional surge plans as quickly as possible. Having a preexisting list of hospital levels of maternity and neonatal care will ensure that the patient and her infant are sent to the right location. For example, a bed may be appropriate for use for general patient care but not for specialized care for pregnant or postpartum women.

Beyond contingency planning, at crisis surge, the level of medical care may be significantly compromised. Difficult choices will have to be made during a crisis surge level. This would likely include expanding the scope of practice of healthcare providers. During a state of emergency, it may be necessary to practice outside specialty expertise (e.g., performance of a cesarean delivery by a general surgeon) to provide better care for a greater number of patients, rather than optimal care to a few. Providers must still practice within their skill set; a nurse will still function as a nurse and a physician as a physician. For example, a floor nurse may be tasked with working in the intensive care unit (ICU) as a nurse with direct supervision by an ICU nurse. It is recommended that the OEM of each hospital maintains an inventory of skills/experiences beyond the normal licensing scope for each staff member. Examples of extra licensing skills include a respiratory therapist who has suturing skills from the military or a laboratory technician with experience in grief counseling [27]. Much discussion has been dedicated to the degree of leniency in standards of care allowed during crises [28, 29]. It is imperative that practitioners are aware of local regulations that mandate adherence to local laws. For example, in some places, staff members from neighboring areas/facilities may only be allowed to assist (even voluntarily) if they are already credentialed locally [27]. In others, there may be an emergency credentialing system.

In terms of supplies and equipment, the main considerations for critically ill patients have been outlined elsewhere [30]. While these may generically include critically ill pregnant or peripartum women, the special needs of this population were not taken into consideration when compiling this resource. At this time, there is no consensus list for pregnant and peripartum women for medications and fluids, equipment, food and water, and waste disposal or sanitation requirements.

37.5 Disaster Training

Disaster training consists of educating healthcare providers on anticipation and planning, disaster concepts and language, local protocols, action plans, and familiarity with available tools and aids. Within the hospital, training to treat pregnant or peripartum women during and immediately after a disaster should be led by a local champion who is familiar with the unit and understands the unique needs of this population. Neonatology services also need to be incorporated in training programs as they play a fundamental role in ensuring a safe environment for the neonate.

Disaster training is relevant not only for healthcare providers but also for community members. All communities, not only those in high-risk geographical areas, should be prepared for disasters, since man-made or infectious disasters may occur in any location. Disaster plans

therefore should include a coordinated community response (e.g., how to provide care to a pregnant woman delivering at home because of damage to infrastructure that prevents her from traveling to hospital or how to ensure that pregnant women who require medications have access to needed medications), along with the facility response (outlined in this chapter).

One possible training modality is the use of multidisciplinary simulation. Simulation training has proven effective in the management of trauma and resuscitation and other emergency situations and is currently being used for obstetrical emergencies; the leap to include disaster training is not large [31]. Training through simulation compels the participants to "experience" an actual disaster setup and to "use" the same tools and aids they will use in a genuine event, thereby hopefully improving recall. Including all healthcare team members (obstetricians, anesthesiologists, intensivists, pediatricians, nurses, technicians, and clerks) during a simulation will ensure that all staff will be effective during an actual event. Involvment of intensive care is important since in a disaster scenario, treatment may be suboptimal. Suboptimal treatment has been associated with complications and poorer maternal outcomes.

Inter-agency simulations provide the most realistic experience. Inter-agency simulations involve collaboration between emergency services/departments and disaster organizations and the hospital to replicate a catastrophic event for the purpose of training. Most inter-agency simulations are planned annually or biannually and provide the best basis for observing how an actual event may unfold, thereby allowing identification of system errors.

For healthcare providers to invest time and effort in preparing and training for disasters, they need to be aware of the potential benefits it will provide them, their patients, and their families. Some of the training received though hospital-based training schemes is transferrable to the community or home. Several useful websites provide an abundance of information for community disaster preparedness [32, 33].

Regular updates are required to keep healthcare providers apprised of new/revised protocols and guidelines. To this end, there are several useful training resources online [34–36]. Updates can also be led by a local point person (i.e. champion) through refresher courses and/or bulletins. The HICS should reach out (using the local point person) to neighboring facilities and regional leadership to establish a collaborative training environment.

In summary, disaster preparedness is relevant and necessary for all institutions. Particular attention needs to be given to the vulnerable and overlooked populations of obstetrical and neonatal patients. Disaster planning, including incorporation of an obstetric-specific triage tool, understanding levels of care for maternity hospitals both locally and regionally, training staff to be ready for these events, and understanding local resources will optimize patient care throughout the whole spectrum of disaster situations.

References

1. Disasters & Emergencies. World Health Organization; 2002. http://apps.who.int/disasters/repo/7656.pdf. Accessed Jul 2017.
2. Gawande AA, Arriaga AF. A simulation-based trial of surgical-crisis checklists. N Engl J Med. 2013;368(15):1460.
3. Mathews TJ, Curtin S. When are babies born: morning, noon, or night? Birth certificate data for 2013. NCHS Data Brief. 2015;200:200.
4. Pfeiffer J, Avery MD, Benbenek M, Prepas R, Summers L, Wachdorf CM, O'Boyle C. Maternal and newborn care during disasters: thinking outside the hospital paradigm. Nurs Clin North Am. 2008;43(3):449–67. x
5. Oni O, Harville E, Xiong X, Buekens P. Relationships among stress coping styles and pregnancy complications among women exposed to Hurricane Katrina. J Obstet Gynecol Neonatal Nurs. 2015;44(2):256–67.
6. Maslow CB, Caramanica K, Li J, Stellman SD, Brackbill RM. Reproductive outcomes following maternal exposure to the events of september 11, 2001, at the world trade center, in New York City. Am J Public Health. 2016;106(10):1796–803.
7. Glynn LM, Wadhwa PD, Dunkel-Schetter C, Chicz-Demet A, Sandman CA. When stress happens matters: effects of earthquake timing on stress responsivity in pregnancy. Am J Obstet Gynecol. 2001;184(4):637–42.
8. Harville EW, Giarratano G, Savage J, Barcelona de Mendoza V, Zotkiewicz T. Birth outcomes in a disas-

ter recovery environment: New Orleans women after Katrina. Matern Child Health J. 2015;19(11):2512–22.
9. Harville E, Xiong X, Buekens P. Disasters and perinatal health: a systematic review. Obstet Gynecol Surv. 2010;65(11):713–28.
10. Saulnier DD, Brolin K. A systematic review of the health effects of prenatal exposure to disaster. Int J Public Health. 2015;60(7):781–7.
11. AMA Council on Ethical and Judicial Affairs. AMA Code of Medical Ethics' Opinion on Physician Duty to Treat. Virtual Mentor. 2010;12(6):459. https://doi.org/10.1001/virtualmentor.2010.12.6.coet1-100.
12. American College of Obstetricians and Gynecologists Committee on Obstetric Practice. Committee opinion no. 555: hospital disaster preparedness for obstetricians and facilities providing maternity care. Obstet Gynecol. 2013;121(3):696–9.
13. Gray BH, Hebert K. Hospitals in hurricane Katrina: challenges facing custodial institutions in a disaster. J Health Care Poor Underserved. 2007;18(2):283–98.
14. Orlando S, Bernard ML, Mathews P. Neonatal nursing care issues following a natural disaster: lessons learned from the Katrina experience. J Perinat Neonatal Nurs. 2008;22(2):147–53.
15. Hick JL, Barbera JA, Kelen GD. Refining surge capacity: conventional, contingency, and crisis capacity. Disaster Med Public Health Prep. 2009;3(Suppl 2):S59–67.
16. Levels of maternal care. Obstetric Care Consensus No. 2. American College of Obstetricians and Gynecologists. Obstet Gynecol 2015;125:502–15.
17. O'Dowd A. Major global cyber-attack hits NHS and delays treatment. BMJ. 2017;357:j2357.
18. Angantyr LG, Häggström E, Kulling P. KAMEDO report no. 93-the power failure at Karolinska University Hospital, Huddinge, 07 April 2007. Prehosp Disaster Med. 2009;24(5):468–70.
19. Lee C, Robinson KM, Wendt K, Williamson D. The preparedness of hospital health information services for system failures due to internal disasters. Health Inf Manag. 2009;38(2):18–25.
20. Einav S, Schecter WP, Matot I, Horn JK, Hersch M, Reissman P, Spira RM. Case managers in mass casualty incidents. Ann Surg. 2009;249(3):496–501.
21. Daniels K, Oakeson AM, Hilton G. Steps toward a national disaster plan for obstetrics. Obstet Gynecol. 2014;124(1):154–8.
22. Aitken P, FitzGerald G. Disaster triage: evidence, consistency and standard practice. Emerg Med Australas. 2012;24(3):222–4.
23. Jones AE, Summers RL, Deschamp C, Galli RL. A national survey of the air medical transport of high-risk obstetric patients. Air Med J. 2001;20(2):17–20.
24. Cohen RSMB, Ahern T, Hackel A. Disaster planning—triaging resource allocation in neonatology. J Investig Med. 2010;58(1):188.
25. Latifi R, Tilley E. Telemedicine for disaster management: can it transform chaos into an organized, structured care from the distance? Am J Disaster Med. 2014;9(1):25–39.
26. Hick JL, Einav S, Hanfling D, Kissoon N, Dichter JR, Devereaux AV, Christian MD, Task Force for Mass Critical Care; Task Force for Mass Critical Care. Surge capacity principles: care of the critically ill and injured during pandemics and disasters: CHEST consensus statement. Chest. 2014;146(Suppl 4):e1S–e16S.
27. California Department of Public Health Standards and Guidelines for Healthcare Surge During Emergencies. California Department of Public Health. http://www.bepreparedcalifornia.ca.gov/CDPHPrograms/PublicHealthPrograms/EmergencyPreparednessOffice/EPOProgramsandServices/Surge/SurgeStandardsandGuidelines/Documents/volume1_hospital_FINAL.pdf. Accessed Jul 2017.
28. Biddison LD, Berkowitz KA, Courtney B, De Jong CM, Devereaux AV, Kissoon N, Roxland BE, Sprung CL, Dichter JR, Christian MD, Powell T, Task Force for Mass Critical Care, Task Force for Mass Critical Care. Ethical considerations: care of the critically ill and injured during pandemics and disasters: CHEST consensus statement. Chest. 2014;146(Suppl 4):e145S–55S.
29. Leider JP, DeBruin D, Reynolds N, Koch A, Seaberg J. Ethical guidance for disaster response, specifically around crisis standards of care: a systematic review. Am J Public Health. 2017;107(9):e1–9.
30. Einav S, Hick JL, Hanfling D, Erstad BL, Toner ES, Branson RD, Kanter RK, Kissoon N, Dichter JR, Devereaux AV, Christian MD, Task Force for Mass Critical Care, Task Force for Mass Critical Care. Surge capacity logistics: care of the critically ill and injured during pandemics and disasters: CHEST consensus statement. Chest. 2014;146(Suppl 4):e17S–43S.
31. Merien AE, van de Ven J, Mol BW, Houterman S, Oei SG. Multidisciplinary team training in a simulation setting for acute obstetric emergencies: a systematic review. Obstet Gynecol. 2010;115(5):1021–31.
32. The Department of Homeland Security. https://www.ready.gov/. Accessed Jul 2017.
33. How to Prepare for Emergencies. American Red Cross. http://www.redcross.org/get-help/how-to-prepare-for-emergencies. Accessed Jul 2017.
34. Disaster Management and Emergency Preparedness. American College of Surgeons. https://www.facs.org/quality-programs/trauma/education/dmep. Accessed Jul 2017.
35. Center for Domestic Preparedness. Federal Emergency Management Agency. https://cdp.dhs.gov/. Accessed Jul 2017.
36. National Incident Management System (NIMS). Federal Emergency https://training.fema.gov/nims/. Accessed Jul 2017.

Part XI

Medications and Complications

Medication Use During Pregnancy in the Intensive Care Unit

38

Asher Ornoy

Bullet Points

- While treating a pregnant woman, it is important to remember that most drugs cross the placenta and reach the embryo or fetus.
- Although most drugs are relatively safe for the developing embryo and fetus, efforts should be made to avoid drugs that might adversely affect pregnancy if possible.
- Since there are usually several drugs with similar action, it is often possible to change a teratogenic drug to a less or non-teratogenic one.
- The effects of an agent on the fetus are also dose and duration dependent, therefore some drugs may be used for short periods of time even if they may have adverse effects on the pregnancy.
- Teratogen information services can be consulted regarding the safety of drug use in pregnancy.

Supported by the Harris Fund, Chicago, USA

A. Ornoy (✉)
Laboratory of Teratology, Department of Medical Neurobiology, Canada-Israel Medical Research Institute, Hebrew University Hadassah Medical School, Jerusalem, Israel
e-mail: ornoy@cc.huji.ac.il

38.1 Introduction

Of the thousands of drugs used in medicine, there are relatively few drug groups that are completely safe in pregnancy, as most drugs cross the placental barriers and reach the fetus. On the other hand, relatively few drugs are highly teratogenic. As, for most drugs there is no proof of teratogenicity, pregnant women who require medications during pregnancy should receive the required treatment. However, since there are likely several alternative drugs, it is generally possible to avoid treatment with the more teratogenic drugs. An example of such considerations is treatment with antiepileptic drugs in pregnancy. There are many antiepileptic drugs, with several that are teratogenic and some that are not. Among these, valproic acid, which is the most teratogenic antiepileptic drug, can be replaced by less teratogenic (i.e., carbamazepine) or non-teratogenic (i.e., lamotrigine, levetiracetam) antiepileptic drugs. Teratogen information services and appropriate medical literature [1–4] can be consulted to find the least harmful drug. Sometimes, a teratogenic drug is the single choice—a problem which is often encountered in intensive care. In such cases it is for the physician and patient or their family to weigh the potential risk to the fetus against the potential benefit of saving the mother.

This chapter summarizes the data on the possible effects on the embryo and fetus of most drugs used in intensive care units (ICUs). The

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_38

Appendix presents pregnancy and breastfeeding drug classifications.

The major groups of drugs covered in this chapter are:

1. Drugs for control of cardiac rhythm: lidocaine, alpha and beta blockers, calcium channel blockers (verapamil), amiodarone, digoxin
2. Vasopressors: noradrenaline and adrenaline, ephedrine, milrinone, vasopressin, and phenylephrine
3. Antibiotics
4. Antifungals
5. Antiviral (antiretroviral) drugs
6. Drugs for decreasing intracerebral pressure: pentothal, propofol, and mannitol
7. Anticonvulsants (phenytoin, sodium valproate, levetiracetam)
8. Nitric oxide
9. Peptic ulcer prophylaxis
10. Sedatives
11. Analgesics
12. Anesthetics

For some drugs we will give a brief discussion related to the entire group of drugs, and for some the discussion will deal with individual drugs. There will be no attempt to cover the entire literature, and we will summarize only the more important points. Additional drugs are discussed elsewhere in this book when relevant.

38.2 Drugs That Control Cardiac Rhythm (Anti-arrhythmic Drugs)

These are classified according to their mechanism of action. Class I, IA, to class IC are drugs that affect the sodium channel, thereby generally affecting the action potential and slowing conduction in the heart; class II are beta adrenergic blocking agents; class III drugs affect the potassium channel (k-channel blockers); and class IV are calcium channel blocking agents [5].

Lidocaine: Lidocaine, in addition to its use as a local anesthetic, is also a class I B anti-arrhythmic agent used for the treatment of ventricular arrhythmias, generally with other anti-arrhythmic agents (e.g., verapamil). Lidocaine is also used for epidural anesthesia during labor. Its main mechanism of action is blocking of sodium channels.

Lidocaine does not produce congenital anomalies in rodents even when administered systemically in high doses. However, in high doses/prolonged use, it may induce adverse behavioral effects in rats [6] and even fetal convulsions in sheep [7]. In humans, lidocaine crosses the placental barrier. There is insufficient data on the use of systemic lidocaine during pregnancy; however, prospective and retrospective investigations on more than 1000 pregnancies following systemic administration of lidocaine did not find any increase in the rate of major congenital malformations or of neurodevelopmental problems [8, 9]. Hence, lidocaine can be safely administered systemically in pregnant women at any stage of pregnancy.

Procainamide: Procainamide, which is a class IA antiarrhythmic agent, can be used in pregnancy as no teratogenicity was reported in animals or human [8].

Amiodarone (Procor): This class III, potassium channel blocking agent is generally administered intravenously in intensive care settings and has a very long duration of action. It may be important in pregnancy to use drugs of shorter duration of action if possible. Amiodarone has not been found to be teratogenic in rats and rabbits [9, 10]. However, amiodarone contains a high proportion of iodine, and adverse effects on fetal thyroid function were reported by several investigators [11–13]. Due to these possible complications, it is advisable to use amiodarone in pregnant women only in cases where other anti-arrhythmic agents are ineffective [13, 14].

Verapamil (Ikacor): This class IV calcium channel blocker is the preferred calcium channel blocker in pregnancy as there is more data regarding its use that any other drug of this group. Verapamil does not produce congenital anomalies in rats in relatively low doses but may be teratogenic in vivo and in vitro in high doses, generally affecting the central nervous system and the heart [15]. In human pregnancies, several large population studies have shown that verapamil is not a human teratogen [16–18]. Although there are no controlled data in human pregnancy,

there have been reports of fetal harm while using verapamil for treatment of arrhythmia. The hypothesis is that relatively large doses of verapamil may produce maternal hypotension [19], decreasing placental perfusion and potentially leading to fetal growth retardation and in rare cases even fetal death [20]. Hence, verapamil should be used with caution in pregnancy, and during its use, maternal blood pressure should be constantly monitored. Verapamil may be helpful in preventing premature delivery but may also delay delivery, causing post-maturity. Other calcium channel blockers can also be used in pregnancy, but there is little data on their safety for the developing embryo and fetus, except for nifedipine, where data are relatively sufficient.

38.3 Adrenergic Blockers

Alpha and beta adrenergic blockers generally act as antagonists to epinephrine and norepinephrine, used for the control of cardiac rhythm and as hypotensive agents. There are relatively few alpha adrenergic blockers (i.e., phentolamine) and a large number of beta blockers (i.e., propranolol, atenolol, metoprolol). Labetalol and carvedilol are both alpha and beta blockers [1–4, 21–25]. All these drugs seem to cross the human placenta.

38.3.1 Alpha adrenergic blockers

There is very little data on the possible effects of phentolamine in pregnant women other than some animal data reported by the manufacturer showing that even high doses did not induce congenital malformations in mice rats and rabbits [22]. There is very little data also on the possible perinatal effects of prenatal phentolamine treatment.

38.3.2 Beta adrenergic blockers

Propranolol [23] and metoprolol [24] seem to be the drugs in this group with most data on pregnancy outcome with associated use. These drugs may induce a higher rate of perinatal hypoglycemia and a decrease in the pulse rate of the newborn if administered close to term [23, 24, 26]. Recent evidence suggests that any adverse effects on the developing embryo and fetus caused by beta blockers are extremely rare [27].

Propranolol: While most studies did not report on human or animal teratogenicity, there seems to be sufficient data demonstrating an association between propranolol use in pregnancy and intrauterine fetal growth restriction (FGR). For example, the reports by Pruyn et al. [28] and by Redmond [29] on over 30 pregnancies, show an increased rate of FGR not associated with maternal hypertension.

A plausible mechanism for impairment of fetal growth by beta blockers is the reduction of placental perfusion due to the inhibitory effects on maternal cardiac rate and output. This has been observed in animals, especially in rats where it was also associated with intrauterine growth restriction [30].

Metoprolol: There seems to be sufficient data on metoprolol in pregnancy to demonstrate that metoprolol, similar to other beta blockers, is not a human teratogen [24]. Animal studies found no teratogenicity in rats and rabbits, but fetal growth restriction and death were observed with very high doses [31]. Decreased birth weight but no increase in malformations was also reported in humans [32]. A possible increase in cardiac malformations following prenatal exposure to beta blockers was reported [33], but this was not verified by other studies [24]. No increase in other malformations was described. A higher rate of hypoglycemia was reported in several studies [24].

There is little data on other beta adrenergic blockers, but there is no reason to believe that any of these drugs are teratogenic.

38.3.3 Combined Alpha and Beta Adrenergic Blockers

Labetalol: The animal data from rats and rabbits is reassuring as no increase in congenital anomalies has been observed even following treatment with high doses of labetalol. However, decreased fetal weight was described in rats. Several reports

on perinatal effects of prenatal exposure to labetalol have described an increased rate of hypoglycemia, transient hypotension, respiratory distress, and FGR [25, 26]. Evidence from two large international cohorts suggests this drug is relatively safe for administration during pregnancy [27].

It can be summarized that alpha or beta adrenergic blockers can be used safely in critically ill pregnant women. As they are generally used for short-term periods, there is only a remote possibility that they will affect fetal growth. However, if used near term, the possible perinatal adverse effects should be kept in mind.

38.4 Digoxin

Digitalis glycoside is used in the treatment of cardiac arrhythmia and heart failure. It does not belong to any anti-arrhythmia classes. It inhibits the action of sodium potassium adenosine triphosphatase (Na+/K+ ATPase), mainly in the myocardium, causing increased intracellular sodium, thereby reducing the heart rate and improving cardiac output [34].

Animal studies did not show any teratogenicity in mice and in rats, despite transplacental transfer of digitalis [35]. Although digoxin crosses the human placenta as well, [36] it has been broadly used during pregnancy and is considered a safe antiarrhythmic during pregnancy, as human data is also generally negative in relation to teratogenicity [37]. However, maternal overdose that results in fetal overdose may be lethal to the fetus [38]. Hence, digoxin can be used safely in pregnancy for maternal or fetal needs, but special care should be given to the dose administered and to monitoring of drug levels.

38.5 Vasopressors and Inotropes

Phenylephrine: This sympathomimetic drug is a selective α_1-adrenergic receptor agonist that potentiates the release of norepinephrine. It is a potent vasoconstrictor used in spinal anesthesia to treat the possible accompanying hypotension. Phenylephrine is recommended to prevent hypotension induced by spinal anesthesia during cesarean deliveries [39]. Phenylephrine caused fetal growth restriction in rabbits and may have fetal adverse effects in sheep [40]. Phenylephrine as a decongestant is even sold over the counter without need for a prescription. However, several case control and population studies have been published demonstrating an increase in various malformations in offspring of women treated during pregnancy. In the Collaborative Perinatal Project, a study of 1249 pregnancies with first trimester use of phenylephrine found an increase in the rate of neonatal ear, eye, and limb defects [8]. Other studies [41–43] found an increase in several types of cardiac malformations (endocardial cushion defect, ventricular septal defects) as well as in anomalies of the gut (pyloric stenosis), abdominal wall (umbilical hernia), and feet. These malformations may be related to the vasoconstrictive effects of phenylephrine. Hence, it may be advisable not to use phenylephrine in the first trimester of pregnancy and even thereafter.

Ephedrine (and pseudoephedrine): This sympathomimetic amine has similar action and indications to phenylephrine, being a vasoconstrictor and decongestant. Animal data exist for chick embryos demonstrating an increase in cardiovascular malformations. In humans, there are several case reports associating the use of ephedrine in pregnancy with several malformations [44–46]. However, studies on the effects of ephedrine taken in pregnancy did not find any adverse effects on the developing embryo and fetus [8]. Ephedrine is used for the same indications as phenylephrine with similar clinical benefits for possible hypotension during spinal anesthesia [47]. It can be concluded that ephedrine for use during spinal anesthesia is preferable over phenylephrine in the first trimester of pregnancy, while in the second half of pregnancy, there seems to be no such preference.

Noradrenaline (norepinephrine): This α_1 and α_2 adrenergic agonist is a naturally occurring neurotransmitter and hormone. Due to its vasoconstrictive effects, it is mainly used for the elevation of blood pressure. In rodents, high doses of norepinephrine may produce fetal ischemia and

hence delayed ossification, cataract, and intrauterine growth retardation [48, 49]. Intra-amniotic injection of norepinephrine and epinephrine to 15- or 16-day-old mouse fetuses produced arterial constrictions and hemorrhage in the limbs [50]. Recently norepinephrine has been used for short periods during cesarean delivery to prevent spinal hypotension, without untoward fetal effects reported [39]. There seem to be no large studies on the possible effects of norepinephrine in human pregnancies, but it is reasonable to assume that it is not teratogenic [8]. However, due to the paucity of data in pregnancy, norepinephrine should be used in pregnancy only for life saving indications and mainly if there are no other alternatives.

Adrenaline (epinephrine): This naturally occurring hormone was found to be teratogenic in high doses in rodents. Administration of high adrenaline doses to rabbit fetuses on days 18–22 produced peripheral edema and necrosis of the distal extremities [51, 52]. In pregnant mice, epinephrine administration produced a 14% frequency of cleft palate, and in rats, direct fetal injection on day 17 produced limb malformations [51, 52].

Regarding human pregnancies, the Collaborative Perinatal Project found a significant association between first trimester exposure to epinephrine and an increased risk of malformations, especially inguinal hernias [8]. However, inguinal hernias may also be related to other factors. Schatz et al. [53] studied the pregnancy outcomes of 180 women who used inhaled beta sympathomimetics in the first trimester of pregnancy and did not find any increase in the rate of congenital malformations or other adverse fetal effects. However, only few used adrenaline. Moreover, as anaphylactic shock is rare in pregnancy, the few cases of treatment with adrenaline generally occurred during the second half of pregnancy [54]. Hence, adrenaline can be used in pregnancy if needed for life-saving procedures.

Vasopressin (antidiuretic hormone): This hormone is a potent vasoconstrictor used for the treatment of diabetes insipidus and for the elevation of blood pressure. Lysine vasopressin has similar effects to the native, arginine vasopressin hormone. Its use in pregnancy is very rare, and most data is from description of pregnant women treated for diabetes insipidus. Most cases describe treatment in the second half of pregnancy, generally with favorable outcomes for the mother and fetus. Experimental data from mice and rats shows that intra-amniotic injections of vasopressin (as well as adrenaline and noradrenaline)-induced hemorrhage in the fetal limbs due to constriction of the main limb arteries [50, 55]. There is practically no data on the possible effects of vasopressin on the developing embryo and fetus if administered to the mother in the first trimester of pregnancy. Due to the possible effects of vasopressin on uterine contractions, it is advisable, if possible, to avoid the use of vasopressin in pregnant women. In pregnant women with diabetes insipidus, it is advised to use the synthetic analogue, desmopressin (DDAVP) which acts more specifically on the kidney [56–58].

Milrinone (Primacor): This vasodilator and inotropic agent is a phosphodiesterase-3 inhibitor that increases cardiac contractility and decreases pulmonary vascular resistance. It is used for the treatment of pulmonary hypertension in infants and in elder patients with cardiac failure and/or pulmonary hypertension undergoing cardiac surgery [59]. It is generally given intravenously but can also be given by inhalation [60]. There are no data on the possible of milrinone in human pregnancies. In animals, the data in rats and rabbits show that milrinone is not teratogenic or embryotoxic even at high doses, unless maternal toxicity occurs [61]. Hence, if needed, milrinone can be used in pregnant women.

38.6 Antibiotics

Generally, antibiotic drugs used for the treatment of acute infections in the ICU are not teratogenic, despite crossing the placental barrier. In animals too, most antibiotic agents are not teratogenic unless used in very high doses. Quinolones are an exception as they may affect the cartilage of fetuses and young offspring. Similarly, several aminoglycosides may be nephrotoxic in exposed fetuses when used in large doses. We will discuss briefly each one of the more commonly used antibiotics in the ICU.

38.6.1 Aminoglycoside Antibiotics

This is a group of bactericidal antibiotics that inhibit protein synthesis and contain, as a portion of the molecule, an amino-modified glycoside (sugar). They are mainly effective against aerobic Gram-negative bacteria but not against Gram-positive or anaerobic bacteria. They specifically inhibit bacterial protein synthesis by binding to ribosomes [62]. The first antibiotic of this group was streptomycin, but the more commonly used drugs of this group are gentamycin (garamycin), kanamycin, tobramycin, amikacin, neomycin, streptomycin, and dehydrostreptomycin. All drugs belonging to this group might be toxic in high doses and may exert a nephrotoxic and ototoxic effect. They generally cross the placental barrier but are not considered human teratogens [63]. In pregnant animals, some of these antibiotics induced congenital malformations, especially ototoxicity, but there are very few human reports on fetal ototoxicity.

Gentamycin: Fetal renal damage was demonstrated in rats and guinea pigs following prenatal exposures to high doses [64, 65]. In humans, neither fetal nephropathy nor ototoxicity has been demonstrated, although in neonates treated with gentamycin, nephrotoxicity is a known complication. Hence, maternal treatment with gentamycin near term should be given with caution and drug levels should be monitored [66]. In human population studies, gentamycin was not found to increase the rate of congenital anomalies [63]. Hence, gentamycin can be administered to pregnant women whenever clinically indicated.

Kanamycin: Experimental animal studies have demonstrated a low rate of ototoxicity in the offspring of pregnant rats and other rodents [67]. No other anomalies were reported in pregnant animals. In human, there are no reports of congenital malformations except a few cases of fetal ototoxicity, generally following high maternal doses that also caused maternal ototoxicity [68, 69]. The risk for fetal ototoxicity is apparently very low. Hence, kanamycin can be administered during pregnancy whenever clinically indicated.

Tobramycin: Experimental studies in pregnant rodents did not find any increase in major anomalies in the offspring. High doses that were nephrotoxic to the dams also induced nephrotoxicity in the offspring of rats [70]. Similar data were found in guinea pigs [71]. In humans, despite some individual case reports, larger population studies did not find an increased rate of congenital malformations [63]. However, nephrotoxicity and possibly ototoxicity in human pregnancies cannot be completely ruled out due to a relatively small number of cases reported. Hence, tobramycin may be used during pregnancy, but if other aminoglycosides are similarly effective, they should be preferred.

Neomycin: This aminoglycoside is generally used topically, with no reported teratogenic effects in humans or animals. It is often used in combination with other antibiotics. The studies on systemic use in animals have demonstrated only ototoxicity with the administration of very high doses [72]. There is very little data on the use of systemic neomycin in pregnant women, but these showed no increase in the rate of congenital anomalies. Hence systemic neomycin may be administered if required.

Amikacin: Studies in pregnant animals have not shown fetal damage [73], unless maternal toxicity was induced. However, there are no studies on the possible effects of amikacin in pregnant women. Hence it seems reasonable to avoid using amikacin in pregnant women if possible.

38.6.2 Cephalosporins

The first, second, and third generation of these beta lactam antibiotics comprise over 20 different antibiotics (e.g., cephalexin, cefuroxime, ceftriaxone). These drugs exert a bactericidal effect through disruption of the peptidoglycan layer of the bacterial wall. Generally these drugs do not increase the rate of congenital anomalies when administered to pregnant rodents [74, 75]. Human data in pregnancy did not demonstrate any damaging effects on the developing embryo and fetus, as demonstrated in a large population-based, case-control study and in several cohort studies [74]. Hence, it can be concluded that cephalosporins can be used safely in pregnancy. It should also be noted that treating pregnant women with different penicillins (penicillin V, G, amoxicillin ext) has been found to be safe [74].

38.6.3 Fluoroquinolones

This group of broad-spectrum antibiotic agents is bactericidal to many Gram-positive and Gram-negative microorganisms and thus is used extensively in various infections. Their main mechanism of action is by inhibition of bacterial DNA gyrase, thus preventing DNA synthesis and replication [76]. The commonly used drugs in this category are ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin, norfloxacin, and nalidixic acid.

In animals, quinolones were not teratogenic, but large doses, especially ciprofloxacin, administered to very young dogs, rats, and mice produced arthropathic changes [77]. In humans, there is now data on over 2000 women treated during various phases of pregnancy with different quinolones, demonstrating the safety of these drugs. The largest study was published by Padberg et al. [76] on 949 pregnancies prospectively following first trimester exposure to different fluoroquinolones, and there was no reported increase in the rate of major congenital anomalies, prematurity, or spontaneous abortions. No cases of arthropathy were observed in human studies. Hence, quinolones during pregnancy do not increase the general rate of congenital anomalies or other pregnancy complications [76, 78, 79] and can be safely administered whenever needed.

38.6.4 Metronidazole (Flagyl)

Metronidazole is a wide-spectrum antibiotic and antiprotozoal drug that is used in the treatment of amoebiasis, trichomonas, giardia, and several bacteria causing pelvic inflammation. In critical care settings, it is often used in combination with other antibiotic or antifungal drugs for coverage of anaerobic infections. Metronidazole inhibits nucleic acid synthesis by disrupting the DNA of microbial cells but has little effects on mammalian cells. Metronidazole is also administered to pregnant women for the prevention of preterm birth in bacterial vaginosis [80].

Animal studies in pregnancy generally did not show any teratogenicity of metronidazole [81, 82]. However, a single high dose of metronidazole with miconazole induced axial skeletal malformations in mice offspring [83].

Prospective and retrospective studies have reported the outcome of almost 3000 human pregnancies treated with metronidazole. There was no indication that metronidazole is a human teratogen as there was no increase in the rate of major congenital anomalies, of premature deliveries, or of spontaneous abortions [84, 85]. On the contrary, treatment prevented premature deliveries [80]. Hence, if indicated, metronidazole can be administered during pregnancy.

With the worldwide increase in the prevalence of multidrug-resistant pathogens, critically ill women are more likely to require treatment with additional antibiotics. There is little to no information regarding the short- and long-term effects of most antibiotics on the fetus, a situation exacerbated by the near-exclusion of pregnant women from drug trials. Given the lack of data, if a clinical situation arises that requires consideration of such treatment during pregnancy, treatment should not be withheld from the mother due to concerns regarding the fetus.

38.7 Antifungal Drugs

Amphotericin B (liposomal): There is very little data on the possible effects of liposomal amphotericin B in pregnant animals or in human. The few animal experiments did not reveal teratogenicity, although the doses administered did not exceed those used in human treatment [86]. The data on human pregnancies are also very limited but so far negative. Due to the clinical benefits of this drug in severe cases of *Cryptococcus* infections (and possibly leishmaniasis), it is recommended to use this drug in pregnancy when clinically indicated [87, 88].

Imidazole fungicides (fluconazole, miconazole itraconazole variconazole, oxiconazole): These antifungal drugs have been tested in pregnant animals and often produced maternal toxicity with adverse effects on the developing embryo and fetus (i.e., increased spontaneous abortions and fetal death) or skeletal, nervous system, and other malformations. These anomalies were especially pronounced with itraconazole. In some studies

skeletal axial malformations or other adverse effects were produced in rodents even without signs of maternal toxicity. These were mostly attributed to the anti-estrogenic or other endocrine effects of these drugs. However, in the absence of maternal toxicity, there were generally no teratogenic or embryotoxic effects [89, 90].

Human studies in pregnancy have reported on a large number of infants and are generally negative. However, there are large differences in the amount of data for each one of these drugs. For example, there is sufficient data for fluconazole and miconazole, demonstrating that these drugs are safe for use in pregnancy, but there is much less data for itraconazole [91–93], and no human data for voriconazole or oxiconazole. Hence, if clinically possible, fluconazole and miconazole are the preferred options for pregnant women.

38.8 Antiviral Drugs

38.8.1 Antiretroviral Drugs

There are about 30 drugs that help to control HIV infections that minimize the presence of the virus, effectively preventing the disease progression. These drugs can be classified according to their mechanism of action and resistance profiles into six groups: (1) nucleoside-analog reverse transcriptase inhibitors (NNRTIs), (2) non-nucleoside reverse transcriptase inhibitors (NNRTIs), (3) integrase inhibitors, (4) protease inhibitors (PIs), (5) fusion inhibitors, and (6) co-receptor antagonists [94]. Many of these drugs have been and continue to be used in pregnancy with promising data as to their clinical effectiveness in preventing the transplacental transmission of the virus to the fetus and the fact that they seem to be harmless for the embryo and fetus.

Animal studies were generally negative for teratogenicity. Even drug combinations in concentrations similar to those used in humans were not teratogenic. However, very high doses generally induced maternal toxicity in a rat model, with a high frequency of fetal death and other adverse effects [95].

When assessing the possible effects of these drugs on human pregnancy outcomes, the possible adverse effects of the underlying disease should also be considered. There are now many studies on thousands of pregnancies, most of them showing no teratogenicity. Conversely, most also demonstrate the protective effects of these drugs on the developing fetus [96–98]. Hence, antiretroviral therapy should be administered in pregnancy when indicated.

38.8.2 Other Antiviral Drugs

These can be administered as well during pregnancy, and for most there is sufficient evidence that they have no adverse effects on the developing embryo and fetus.

38.9 Drugs for Decreasing Intracerebral Pressure (ICP)

Mannitol: This hypertonic alcohol is used for the alleviation of increased ICP due to its high osmolarity and rarely as a diuretic substance [99]. Rarely, mannitol may cross the blood-brain barrier and therefore increase intracranial pressure. Although it might be superior to pentothal, it is not as effective as hypertonic saline for decreasing ICP [99]. Animal studies in pregnancy in rats and rabbits were generally negative regarding teratogenicity with mannitol. Human data is relatively scant, and most data are from second and third trimester pregnancies. So far, there seem to be no adverse effects on the fetus following maternal mannitol administration [100, 101]. Hence, mannitol can be used during pregnancy if needed.

Pentothal (thiopental): This rapidly acting barbiturate, affecting several ion channels in the brain, was previously used for induction of anesthesia. Today it has generally been replaced by other sedative/anesthesia drugs such as propofol. Pentothal decreases neuronal activity and is nowadays used mainly to reduce acute brain edema in the ICU setting because it decreases the production of osmotically active metabolites, which in

turn decreases brain swelling. It is also used for the induction of "barbiturate coma" for the treatment of severe brain edema, although the benefit of such treatment is questionable [102, 103]. Pentothal may also have some general neuroprotective effects.

In rats and mice, pentothal is not teratogenic, but high doses may cause fetal death and abortion [104]. There are little human data regarding the use of pentothal in pregnancy. The Perinatal Collaborative Study [8] described data on 152 pregnant women anesthetized with thiopental in the first trimester of pregnancy, and did not find any increase in major congenital malformations. In several other studies and reviews, anesthetic agents including pentothal, were not teratogenic in human [105]. Hence, if needed, pregnant women can be treated with pentothal.

Propofol: Propofol is an anesthetic agent sometimes used for the induction of anesthesia and for the treatment of increased intracranial pressure [102]. It is a well-tolerated agent with relatively few side effects. Administration to pregnant rats and rabbits was not teratogenic, but if administered early or late in pregnancy to rats, it induced neurobehavioral changes in the offspring, impairing learning and memory [106, 107]. In pregnant women propofol crosses the mature placenta, leading to fetal blood concentrations very close to those of the mother. However, most existing data on the possible effects of propofol on the fetus are from term pregnancies. Hence, its possible teratogenicity was not studied, although studies evaluating effects of anesthesia in general suggest no connection [8, 105]. When used in the third trimester of pregnancy, no adverse effects on the offspring were noticed, including no effects on the Apgar score or other neonatal assessment scores. Although there is very little data, if needed, propofol may be used in pregnancy.

38.10 Anticonvulsant Therapy

Many antiepileptic drugs are teratogenic. Since anticonvulsive treatment is sometimes mandatory, these drugs are used in pregnancy. It is, however, important to use the most effective but least teratogenic among them. It is generally accepted that antiepileptic drugs should not be changed during pregnancy as such change may increase the risk of seizure activity in a previously balanced patient, and this might endanger the mother and fetus. The exception to this rule is valproic acid (VPA) that could be switched to an alternative due to its neurodevelopmental adverse effects. In a recent review and meta-analysis on a large number of pregnant women treated with antiepileptic drugs [108], the following drugs significantly increased the rate of major congenital malformations: ethosuximide, valproate, topiramate, phenobarbital (odds ratio of 2 or above), and phenytoin and carbamazepine (odds ratio below 2). Only gabapentine (OR, 1.0; 95% CI 0.47–1.82), lamotrigine (OR, 0.96; 95% CI, 0.72–1.25), and levetiracetam (OR, 0.72; 95% CI, 0.43–1.16) did not increase the rate of major malformations. We will discuss only the antiepileptic drugs used in the ICU to control acute seizures: VPA, levetiracetam (Keppra), and phenytoin.

Valproic acid: VPA seems to be the most teratogenic antiepileptic drug; hence, whenever possible, its use in pregnancy should be avoided [109–113]. It is teratogenic in most animals in doses that are not much higher than the human dose [95]. VPA in humans has been associated with a 1–2% incidence of lumbar meningomyelocele (neural tube defects). Other congenital anomalies that are increased following the use of VPA in pregnancy are cardiac anomalies, facial clefts, dental agenesis, hypospadias, craniosynostosis, and limb defects, particularly radial aplasia. A typical "valproic acid facial dysmorphic features" (VPA syndrome) has been described, manifested by small nose, depressed nasal bridge, abnormal ears, a flat and long philtrum, and a thin upper lip. These features are similar to those described as the "antiepileptic drug syndrome." VPA syndrome is often accompanied with neurodevelopmental delay and an increased rate of Autism Spectrum Disorder [109–114]. The rate of congenital malformations among offspring prenatally exposed to VPA generally ranges between 6.7% [110] to over 16% and is dose dependent [111, 112]. When VPA is administered

together with other antiepileptic drugs, the rate of congenital malformations increases and is generally above the rate induced by VPA alone [99, 100]. However, multiple studies have shown that there is a threshold for VPA-induced teratogenicity; daily doses below 800 mg are apparently not teratogenic [109, 110]. If possible, VPA treatment should be avoided in pregnancy.

Phenytoin: Phenytoin has been used for many years to control seizures. It mainly acts by blocking sodium channels, thus interfering with synaptic impulse propagation [115]. Levetiracetam and phenytoin are both used in the intensive care unit (ICU) for prevention of convulsions following head trauma or brain occupying lesions. Phenytoin is a known teratogenic drug that induces various congenital malformations in rodents. It is also teratogenic in man [94, 97, 98] and, if possible, should not be used in pregnancy. However, it is preferred over VPA.

Levetiracetam (Keppra): Keppra is the preferred drug in pregnant patients at high risk for convulsions for prevention of seizures. This relatively new drug has not been found to be teratogenic in pregnant rats or rabbits even in relatively high doses, but it often interfered with fetal growth [116]. The drug inhibits presynaptic calcium channels, reducing neurotransmitter release, thereby decreasing impulse conduction across synapses. As noted above, it is used to prevent seizures after head trauma or brain tumors [117]). There are several relatively large human cohort studies with more than 1000 pregnancies exposed to keppra monotherapy in the first trimester. Generally there was no increase in the rate of congenital malformations, spontaneous abortions, or stillbirths. In several studies, evaluating the neurodevelopmental effects of keppra, there were no also differences between the children prenatally exposed to keppra and controls [118]. It seems, therefore, that keppra can be used in pregnancy whenever needed.

38.11 Nitric Oxide

Nitric oxide (NO) is a reactive nitrogen species that serves as a signalling molecule in several biological systems. It dilates blood vessels, lowering blood pressure as it also causes smooth muscle relaxation. Nitric oxide plays an important role in pregnancy; trophoblastic cells produce nitrous oxide which plays an important role in trophoblastic invasion [118]. Inhaled NO is used in mechanically ventilated adult critical care patients with severe V-Q mismatch and in severe pulmonary hypertension. Nitric oxide is very important in the control of placental blood flow, explaining the effects of nitric oxide manipulations in pregnancy in mice [119] and in human [120]. In experimental animals, increased production of nitric oxide was not teratogenic. There is very little data on the effects of inhaled nitric oxide in human pregnancies. Transdermal nitroglycerin that produces vasodilation by the formation of nitric oxide does not interfere with pregnancy and does not seem to affect fetal cardiac function or fetal growth [108]. L-arginine, a precursor of nitric oxide, is often used for the treatment of preeclampsia and does not affect the fetus either [121]. Hence, it can be concluded that nitric oxide treatment in pregnancy seems safe.

38.12 Peptic Ulcer Prophylaxis

The main drugs used for stress ulcer prophylaxis are proton pump inhibitors (omeprazole, pantoprazole, esomeprazole) or H_2 receptor antagonists (ranitidine, cimetidine, famotidine) [122].

Proton pump inhibitors: Animal studies on drugs of this group did not find teratogenic effects with omeprazole or esomeprazole in rats and rabbits, and as a group, animal teratogenic studies with proton pump inhibitors are negative [123]. Most human data in pregnancy is on omeprazole. So far, more than 2000 human pregnancy outcomes have been described, and the data does not show any increase in the rate of congenital malformations, spontaneous abortions, or effects on fetal growth and gestational age at delivery [124, 125]. It can therefore be summarized that proton pump inhibitors can be used in pregnancy.

H_2 receptor antagonists: Studies on pregnant rats and rabbits did not find any increase in the rate of congenital anomalies or of other adverse effects

in pregnancy. Prospective cohort studies on about 2000 human pregnancies following ranitidine treatment during pregnancy, mostly during the first trimester, did not reveal any increase in the rate of major congenital anomalies or other adverse effects [126–129]. Similar reassuring data exists for famotidine and cimetidine. Hence, H_2 receptor antagonists can be used in pregnancy.

38.13 Anti-histamines and Anti-emetics

Passiflora, valerian, histamine H_1 antagonists (antihistamines -doxylamine, diphenidramine).

Various animal studies in mice, rats, and rabbits did not demonstrate teratogenic effect of any of these agents. There is very little data in human pregnancies for passiflora and valerian obtained from plants but more data on histamine H_1 antagonists. The available human data is generally reassuring [8, 130–132]. Hence, if needed, these drugs can be used in pregnancy. Non-pharmacologic and pharmacologic options are also available for management of nausea and vomiting in pregnancy [133]. Ondansetron administered in the first trimester is not associated with cardiac malformations; however there is a small increased risk of cleft lip [134].

38.14 Analgesics

Generally, the different groups of analgesics may be used in pregnancy for short periods of time (up to several days). However, if prolonged use is needed, it is preferable to avoid treatment with high doses.

38.14.1 Paracetamol

Studies in pregnant mice and rats did not find any increase in the rate of congenital anomalies or other adverse effects on pregnancy. Case control or population-based studies in human pregnancies were also largely negative, except for some increase in the rate of cryptorchidism following paracetamol use during the first and second trimesters of pregnancy. There are some studies pointing to a possible increase in the rate of autism following prenatal exposure to paracetamol, but the data are problematic as many possible confounding factors were not excluded [135–137]. Hence, paracetamol can be used during pregnancy, especially when taken for short periods of time.

38.14.2 Dipyrone

This rapidly reversible inhibitor of cyclooxygenase (metamizole) is not licensed in the USA but is used in other developed and non-developed countries. There are no clear data on the possible effects of dipyrone in pregnant animals, and the data on human pregnancies is also insufficient, but so far no adverse effects on pregnancy were found [138, 139]. There is a single description of a case of premature constriction of the ductus arteriosus apparently produced by high doses of dipyrone administered toward the end of pregnancy [140]. However, since dipyrone is used extensively in Israel, Brazil, and several European countries, and no negative effects were reported, it seems safe to use this drug in pregnancy.

38.14.3 Opioids

There are several opioid-based analgesic drugs: i.e., fentanyl, methadone, codeine, pethidine, morphine, oxycodone, tramadol. These will be addressed as one group differing among themselves as to their indications and effectiveness.

All opioids seem to bind to opioid receptors in the central nervous system. Some adverse pregnancy outcomes described in association with opioid misuse include preterm birth, low birth weight, reduced infant head circumference, increased perinatal mortality, neonatal withdrawal syndrome, and postnatally increased sudden infant death as well as increased rate of learning difficulties and ADHD. It is generally agreed that there is no increase in the rate of congenital malformations [141, 142].

The low cognitive abilities observed in association with opioid use in pregnancy are, to a large extent, attributed to poor home environ-

ment. Children that were born to opiate dependent mothers but were raised in a "good" home environment (i.e., adopted at a young age) have normal or close to normal cognitive abilities but still have a very high rate of ADHD [142, 143]. Hence, many of the pregnancy complications believed to be induced by opioids in the offspring of opioid-dependent mothers can be attributed to factors related to maternal addiction and the impact of the poor home environment on the young child, rather than to the opiates themselves. Opioids used as analgesics for management of acute pain are not necessarily associated with a poor home environment, and therefore the adverse effects observed in the offspring of opioid addicted mothers are not expected in such circumstances. Hence, opioid analgesics can be used in pregnancy if required.

38.14.4 Non-steroidal Anti-inflammatory Drugs (NSAIDs) Including Aspirin

Generally, as a group, NSAIDs are not considered human teratogens although some of the drugs of this group are teratogenic in rodents (i.e., high doses of aspirin in mice and rats) [144, 145]. There are many studies on the possible effects of NSAIDs in human pregnancies. Most studies did not reveal any increase in the rate of congenital malformations following exposure in the first trimester of pregnancy.

Aspirin: Aspirin was not found to increase the rate of congenital anomalies as evidenced from a large meta-analysis [146] and from a prospective study on over 50,000 pregnancies treated with aspirin [8, 147, 148]. However, several smaller studies have demonstrated some adverse effects on the developing embryo/fetus, i.e., increased oral clefts and reduced fetal weight [148, 149]. Rarely, long-term treatment with high doses of aspirin can also cause fetal and maternal bleeding [8]. However, low doses of aspirin do not increase bleeding tendency in the newborn [146].

Indomethacin: Some increase has been reported in the rate of spontaneous abortions following indomethacin treatment in the first trimester of pregnancy, but most large prospective studies have found no evidence of an increase in the rate of congenital anomalies [150]. Treatment with indomethcin in the later stages of pregnancy was reported to cause some adverse effects, especially constriction of the ductus arteriosus which may rarely occur between weeks 28–31 but is more common from 32 weeks of gestation. Some increase in the rate of intracerebral hemorrhage was also reported with prenatal exposure to indomethacin [151].

Ibuprofen: Ibuprofen has been associated in some studies of human pregnancies with an increased rate of cardiac malformations, but the data is inconsistent and cohort studies are generally negative [152].

Naproxen: Regarding naproxen, some studies have demonstrated an increased rate of oral clefts and of cardiac anomalies with naproxen, while others did not [153]. Increased pulmonary hypertension and constriction of the ductus arteriosus have been described with the use of naproxen as well as other NSAIDs late in pregnancy [154].

Diclofenac: Diclofenac was not teratogenic in most studies on pregnant mice and rats. In humans, most studies did not demonstrate any increase in the rate of congenital anomalies among the offspring or of spontaneous abortions [155].

It can be summarized that the use of the different NSAIDs may cause increased early spontaneous abortions, but this might also be related to the underlying disease. The use of NSAIDs in the first 7 months of pregnancy is generally safe with regard to congenital anomalies and other adverse effects, but these drugs should not be used from week 32 of pregnancy and perhaps even from week 28 onwards [156]. Low-dose aspirin is the exception to this rule. No adverse effects have been observed with the long-term use of such low amounts of aspirin, and it can therefore be used throughout pregnancy.

38.15 Anesthetic Agents

It is estimated that 1–2% of pregnant women undergo general anesthesia during pregnancy, generally for reasons unrelated to gestation; see above

for descriptions of thiopentone and propofol. Due to their lipid solubility, general anesthetic agents easily cross the placental barriers, thereby reaching the fetus and affecting the fetal brain. There seems to be sufficient data demonstrating that general anesthesia, even in the first trimester of pregnancy, does not result in adverse effects on the fetus. However, if such an association exists, it may also be due to the underlying cause that necessitated general anesthesia [1, 8, 100, 157, 158]. Exposure to anesthetic agents is usually brief, and it generally occurs no more than once during pregnancy. Experimental animal studies, even with long-term treatment, are generally negative with no proven teratogenic effects. The anesthetic gases or injectable agents are not considered to be human teratogens, and the data on the safety of halogenated inhalation anesthetic agents are quite convincing [8, 100, 157, 159]. The safety for the fetus of non-obstetric surgery and anesthesia in pregnancy is well-documented. These findings suggest no substantial detrimental risk on child fine motor and attention deficit disorder symptoms after prenatal benzodiazepines/hypnotics, whether exposure was to these drugs alone or in combination with opioids or antidepressants [160, 161].

Nitrous oxide: Although nitrous oxide has limited anesthetic abilities, it is used often during delivery because it is well tolerated and has very limited negative effects on the circulation or uterine contractures. This substance seems to have no adverse effects on the developing embryo and fetus and can be used in pregnancy [8, 162].

Local, epidural, and spinal anesthesia are similarly performed for non-obstetric as well as for obstetric procedures, i.e., vaginal delivery and cesarean sections. The drugs used for these procedures also seem to be safe for the embryo and fetus and have no adverse effects on the newborn infant, and the different agents used are not teratogenic in man [8]. Hence, local anesthetics can be used in pregnancy.

38.16 Conclusions

Pharmacological treatment is essential for pregnant women in the ICU, and it often necessitates quick decisions. Maternal safety is the prime consideration in such cases. Fortunately, most drugs used in the ICU are not human teratogens and can be used without endangering the embryo or fetus. In this chapter we have tried to describe in brief the possible adverse effects of the different drugs in use and demonstrate that most drugs are safe, especially if used for short periods of time. However, many drugs that might adversely affect pregnancy can be replaced by other, safer drugs with similar pharmacologic action (Box. 38.1).

Box 38.1 Drugs to be Used with Caution in Pregnancy

Use less teratogenic (carbamazepine) or non-teratogenic (levetiracetam, lamotrigine) drugs

Phenytoin. Avoid if possible but still preferred over VPA

Amiodarone. Use only when other drugs are ineffective

Verapamil. The preferred calcium channel blocker in pregnancy due to most reports of use; However, use with caution and monitor blood pressure. Nifedipine may be an alternative

Adrenaline. Can be used for life saving procedures

Norepinephrine. Can be used for life saving procedures

Vasopressin. Avoid if possible

Phenylephrine. Use ephedrine where possible in first trimester of pregnancy; no preference in second/third trimester.

Tobramycin. Preference for other aminoglycosides if indicated

NSAIDS. Can be used up to week 28–32

38.17 Appendix

38.17.1 Pregnancy and Breastfeeding Drug Classifications

Drugs are labelled with a narrative according to the recommendations for stages of pregnancy and breastfeeding. For most drugs there is no definitive answer, and clinical judgment is required. Information taken from https://www.drugs.com/pregnancy-categories.html, accessed 27th September 2019.

Pregnancy (includes Labor and Delivery):
- Pregnancy Exposure Registry
- Risk Summary
- Clinical Considerations
- Data

Lactation (includes Nursing Mothers)
- Risk Summary
- Clinical Considerations
- Data

Females and Males of Reproductive Potential
- Pregnancy Testing
- Contraception
- Infertility

Until 2015, drugs were labelled according to five risk categories that may still be stated on drug package labels:

Category A Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).

Example drugs or substances: **levothyroxine**, **folic acid**, **liothyronine**

Category B Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

Example drugs: **metformin**, **hydrochlorothiazide**, **cyclobenzaprine**, **amoxicillin**

Category C Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Example drugs: **gabapentin**, **amlodipine**, **trazodone**

Category D There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Example drugs: **losartan**

Category X Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

Example drugs: **atorvastatin**, **simvastatin**, **methotrexate**, **finasteride**

References

1. Schaefer C, Peters P, Miller RK, editors. Drugs in pregnancy and lactation: treatment options and risk assessment. 3rd ed. Amsterdam: Elsevier; 2015.
2. Briggs GG, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 8th ed. Alphen aan den Rijn: Wolters Kluwer/Lippincott Williams & Wilkins; 2009. ISBN: 978-0-7817787-6-3.
3. WWW.reprotox.org
4. https://www.teris.co/
5. Ferrero S, Colombo BM, Ragni N. Maternal arrhythmias during pregnancy. Arch Gynecol Obstet. 2004;269:244–53.
6. Smith RF, Wharton GG, Kurtz SL, Mattran KM, Hollenbeck AR. Behavioral effects of mid-pregnancy administration of lidocaine and mepivacaine in the rat. Neurobehav Toxicol Teratol. 1986;8:61–8.
7. Teramo K, Benowitz N, Heymann MA, Kahanpää K, Siimes A, Rudolph AM. Effects of lidocaine on heart rate, blood pressure and electrocorticogram in fetal sheep. Am J Obstet Gynecol. 1974;118:943–9.

8. Heinonen OP, editor. Birth defects and drugs in pregnancy. Littleton, MA: Publishing Science Group; 1977.
9. Hill DA, Reasor MJ. Effects of amiodarone administration during pregnancy in Fischer 344 rats. Toxicology. 1991;65:259–69.
10. Yamada T, Collin A. Reproductive and developmental toxicity studies of amiodarone. Clin Rep. 1992;26:3871–85.
11. Widerhorn J, Bhandari AK, Bughi S, Harimtoola SH, Elkayarn U. Fetal and neonatal adverse effects profile of amiodarone treatment during pregnancy. Am Heart J. 1994;122:1162–6.
12. Ovadia M, Brito M, Hoyer GL, Marcus FL. Human experience with amiodarone in the embryonic period. Am J Cardiol. 1994;73:316–7.
13. Strunge P, Frandsen J, Andreasen F. Amiodarone during pregnancy. Eur Heart J. 1988;9:106–9.
14. Foster CJ, Love HG. Amiodarone in pregnancy. Case report and review of the literature. Int J Cardiol. 1988:307–16.
15. Scott WJ Jr, Resnick E, Hummler H, Clozel J-P, Burgin H. Cardiovascular alterations in rat fetuses exposed to calcium channel blockers. Reprod Toxicol. 1997;11:207–14.
16. Weber-Schoendorfer C, Hannemann D, Meister R, Elfant E, Cuppers-Maarschalkerweerd B, Arnon J, Vial T, Rodriguez-Pinilla E, Clementi M, Robert-Gnansia E, De Santis M, Malm H, Dolivo A, Schaefer C. The safety of calcium channel blockers during pregnancy: a prospective, multicenter, observational study. Reprod Toxicol. 2008;26:24–30.
17. Magee LA, Schick B, Donnenfeld SSR, Conover B, Cook L, McElhatton PR, Schmidt MA, Koren G. The safety of calcium channel blockers in human pregnancy: a prospective, multicenter cohort study. Am J Obstet Gynecol. 1996;174:823–8.
18. Czeizel AE, Rockenbauer M. Population-based case-control study of teratogenic potential of corticosteroids. Teratology. 1997;56:335–40.
19. https://www.drugs.com/pregnancy/diltiazem.html. Accessed 12 Nov 2019.
20. Owen J, Colvin EV, Davis RO. Fetal death after successful conversion of fetal supraventricular tachycardia with digoxin and verapamil. Am J Obstet Gynecol. 1988;158(5):1169–70.
21. Schaefer C, Peters P, Miller RK editors. Drugs in pregnancy and lactation: treatment options and risk assessment. 3rd ed. Amsterdam: Elsevier; 2015. pp. 196–197; 202–203.
22. www.reprotox. Phentolamine. Accessed 14 May 2018.
23. www.reprotox. Propranolol. Accessed 22 Aug 2018.
24. www.reprotox. Metoprolol. Accessed 12 Sep 2018.
25. www.reprotox. Labetalol. Accessed 14 Sep 2018.
26. Bateman BT, Patorno E, Desai RJ, WEely EW, Mogun H, Maeda A, Fischer MA, Hernandez-Diaz S, Huybrechts KF. Late pregnancy beta blocker exposure and risks of neonatal hypoglycemia and bradycardia. Pediatrics. 2016;138(3):e20160731.
27. Bateman BT, Huybrechts KF, Hernandez-Diaz S, Kieler H, Zoega H. β-Blocker use in pregnancy and the risk for congenital malformations. Ann Intern Med. 2019;170(12):909–10.
28. Pruyn SC, Phelan JP, Buchanan GC. Long-term propranolol therapy in pregnancy: maternal and fetal outcome. Am J Obstet Gynecol. 1979;135:485–9.
29. Redmond GP. Propranolol and fetal growth retardation. Semin Perinatol. 1982;6:142–7.
30. Schoenfeld N, et al. Effects of propranolol during pregnancy and development of rats. I. Adverse effects during pregnancy. Pediatr Res. 1978;12:747–50.
31. Bodin NO, Flodh H, Magnusson G, Malmfors T, Nyberg JA. Toxicological studies on metoprolol. Acta Pharmacol Toxicol. 1975;36(Suppl 5):96–103.
32. Czeizel AE, Toth M. Birth weight, gestational age and medications during pregnancy. Int J Gynecol Obstet. 1998;60:245–9.
33. Lennestal R, Otterblad Olausson P, Kallen B. Maternal use of antihypertensive drugs in early pregnancy and delivery outcome, notably the presence of congenital heart defects in the infants. Eur J Clin Pharmacol. 2009;65(6):615–25.
34. Gheorghiade M, Adams KF Jr, Colucci WS. Digoxin in the management of cardiovascular disorders. Circulation. 2004;109(24):2959–64.
35. Hatano M. Reproduction studies of beta-methyldigoxin 1. Teratogenicity study in rats (Japanese). Clin Rep. 1976;10:579–93.
36. Chen V, Tse T, Wong V. Transfer of digoxin across the placenta and into breast milk. Br J Obstet Gynaecol. 1978;85:605–9.
37. Joglar JA, Page RL. Management of arrhythmia syndromes during pregnancy. Curr Opin Cardiol. 2014;29(1):36–44.
38. Martin-Suarez A, Sanchez-Hernandez JG, Medina-Barajas F, Pérez-Blanco JS, Lanao JM, Garcia-Cuenllas Alvarez L, Calvo MV. Pharmacokinetics and dosing requirements of digoxin in pregnant women treated for fetal supraventricular tachycardia. Expert Rev Clin Pharmacol. 2017;10(8):911–7.
39. Kinsella SM, Carvalho B, Dyer RA, Fernando R, McDonnell N, Mercier FJ, Palanisamy A, Sia ATH, Van de Velde M, Vercueil A, Consensus Statement Collaborators. International consensus statement on the management of hypotension with vasopressors during cesarean section under spinal anaesthesia. Anaesthesia. 2018;73(1):71–92.
40. Shabanah EH, Tricomi V, Suarez JR. Effect of epinephrine on fetal growth and the length of gestation. Surg Gynecol Obstet. 1969;129:341–3.
41. Gilbert-Barness E, Drut RM. Association of sympathomimetic drugs with malformations. Vet Hum Toxicol. 2000;42:168–71.
42. Kallen BA, Olausson PO. Use of oral decongestants during pregnancy and delivery outcome. Am J Obstet Gynecol. 2006;194(2):480–5.

43. Yau W-P, Mitchell AA, Lin KJ, Werler MM, Hernandez-Diaz S. Use of decongestants during pregnancy and the risk of birth defects. Am J Epidemiol. 2013;178(2):198–208.
44. www.reprotox. Ephedrine. Accessed 9 Feb 2018.
45. Werler MM, Mitchell AA, Shapiro S. First trimester maternal medication use in relation to gastroschisis. Teratology. 1992;45:361–7.
46. Howards PP, Hertz-Picciotto I, Bech BH, Nohr EA, Andersen A-MN, Poole C, Olsen J. Spontaneous abortion and a diet drug containing caffeine and ephedrine: a study within the Danish national birth cohort. PLoS One. 2012;7(11):e50372.
47. Dusitkasem S, Herndon BH, Somjit M, Stahl DL, Bitticker E, Coffman JC. Comparison of phenylephrine and ephedrine in treatment of spinal-induced hypotension in high-risk pregnancies: a narrative review. Front Med (Lausanne). 2017;4:2. https://doi.org/10.3389/fmed.2017.00002. eCollection.
48. Hirsch KS, Fritz HI. Teratogenic effects of mescaline, epinephrine, and norepinephrine in the hamster. Teratology. 1981;23:287–91.
49. Pitel M, Lerman S. Studies on the fetal rat lens. Effects of intrauterine adrenaline and noradrenaline. Investig Ophthalmol. 1962;1:406–12.
50. Davies J, Robson JM. Effects of vasopressin, adrenaline and noradrenaline on the mouse fetus. Br J Pharmacol. 1970;38:446.
51. Jost A. Degenerescence des extremites du foetus de rat provoquee par l'adrenaline. CR Acad Sci Paris. 1953;236:1510–2.
52. Loevy H, Roth BF. Induced cleft palate development in mice: comparison between the effect of epinephrine and cortisone. Anat Rec. 1968;160:386.
53. Schatz M, Zeiger RS, Harden KM, Hoffman CP, Forsythe AB, Chilingar LM, Prreco RP, Benenson AS, Sperling WL, Saunders BS, Kagnoff MC. The safety of inhaled (beta)-agonist bronchodilators during pregnancy. J Allergy Clin Immunol. 1988;82:686–95.
54. Tsuzuki Y, Narita M, Nawa M, Nakagawa U, Wakai T. Management of maternal anaphylaxis in pregnancy: a case report. Acute Med Surg. 2016;4(2):202–4.
55. Love AM, Vickers TH. Vasopressin induced dysmelia in rats and its relation to amniocentesis dysmelia. Br J Exp Pathol. 1973;54:291–7.
56. Hime MC, Richardson JA. Diabetes insipidus and pregnancy. Obstet Gynecol Surv. 1978;33:375–9.
57. Hadi HA, Mashini IS, Devoe LD. Diabetes insipidus during pregnancy complicated by preeclapmpsia. A case report. J Reprod Med. 1985;30(3):206–8.
58. Refardt J, Christ-Crain M. Diabetes insipidus in pregnancy: how to advice the patient? Minerva Endocrinol. 2018;43(4):458–64.
59. James AT, Bee C, Corcoran JD, McNamara PJ, Franklin O, El-Khuffash AF. Treatment of premature infants with pulmonary hypertension and right ventricular dysfunction with milrinone: a case series. J Perinatol. 2015;35(4):268–73.
60. Wang H, Gong M, Zhou B, Dai A. Comparison of inhaled and intravenous milrinone in patients with pulmonary hypertension undergoing mitral valve surgery. Adv Ther. 2009;26(4):462–8.
61. Baxter Healthcare Corporation. Milrinone lactate injection product label. 2016. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8fd0f93a-6150-4020-b7ee-4b95b520f6ce/ars.
62. Mingeot-Leclercq MP, Glupczynski Y, Tulkens PM. Aminoglycosides: activity and resistance. Antimicrob Agents Chemother. 1999;43(4):727–37.
63. Czeizel AE, Rockenbauer M, Olsen J, Sørensen HT. A teratological study of aminoglycoside antibiotic treatment during pregnancy. Scand J Infect Dis. 2000;32(3):309–13.
64. www.reprotox. Gentamycin. Accessed 30 Sep 2017.
65. Mallié JP, Gerard H, Gerard A. In-utero gentamicin-induced nephrotoxicity in rats. Pediatr Pharmacol. 1986;5(4):229–39.
66. Regev RH, Litmanowitz I, Arnon S, Shiff J, Dolfin T. Gentamicin serum concentrations in neonates born to gentamicin-treated mothers. Pediatr Infect Dis J. 2000;19:890–1.
67. Onejeme AU, Khan KM. Morphologic study of effects of kanamycin on the developing cochlea of the rat. Teratology. 1984;29:57–71.
68. Jones HC. Intrauterine ototoxicity. A case report and review of literature. J Natl Med Assoc. 1973;65:201–3.
69. Nishimura H, Tanimura T. Clinical aspects of the teratogenicity of drugs. Amsterdam: Excerpta Medica; 1976. p. 131.
70. Mantovani A, Macri C, Stazi AV, Ricciardi C, Guastadisegni C, Maranghi F. Tobramycin-induced changes in renal histology of fetal and newborn Sprague-Dawley rats. Teratog Carcinog Mutagen. 1992;12:19–30.
71. Akiyoshi M. Evaluation of ototoxicity of tobramycin in Guinea pigs. J Antimicrob Chemother. 1978;4(Suppl A):69–72.
72. Kameyama T, Nabeshima T, Itoh J. Measurement of an auditory impairment induced by prenatal administration of aminoglycosides using a shuttle box method. Folia Pharmacol Jpn. 1982;80:525–35.
73. Mallie JP, Coulon G, Billery C, Faucourt A, Morin JP. In utero aminoglycoside-induced nephrotoxicity in rat neonates. Kidney Int. 1988;33:36–44.
74. Mylonas I. Antibiotic chemotherapy during pregnancy and lactation period: aspects for consideration. Arch Gynecol Obstet. 2011;283(1):7–18.
75. Baxter Healthcare Corp. Ceftriaxone product labeling. 2010. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f5d7ae2f-5485-42e2-af2b-bd7f06df85d7.
76. Padberg S, Wacker E, Meister R, Panse M, Weber-Schoendorfer C, Oppermann M, Schaefer C. Observational cohort study of pregnancy outcomes after first-trimester exposure to fluoroquinolones. Antimicrob Agents Chemother. 2014;58(8):4392–8.

77. Linseman DA, Hampton LA, Branstetter DG. Quinolone-induced arthropathy in the neonatal mouse. Morphological analysis of articular lesions produced by pipemidic acid and ciprofloxacin. Fundam Appl Toxicol. 1995;28:59–64.
78. Loebstein R, Addis A, Ho E, Andreou R, Sage S, Donnenfeld AE, Schick B, Bonati M, Moretti M, Lalkin A, Pastuszak A, Koren G. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. Antimicrob Agents Chemother. 1998;42:1336–9.
79. Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, Dyer SM, Gideon PS, Hall KS, Kaltenbach LA, Ray WA. Antibiotics potentially used in response to bioterrorism and the risk of major congenital malformations. Paediatr Perinat Epidemiol. 2009;23(1):18–28.
80. Sheehy O, Santos F, Ferreira E, Berard A. The use of metronidazole during pregnancy: a review of evidence. Curr Drug Saf. 2015;10(2):170–9.
81. Cella PL. Experimental studies on the teratology of metronidazole. Rev Patolog Clin. 1969;24:529–37.
82. Bost RG. Metronidazole: toxicology and teratology. In: Finegold SM et al. editors: Metronidazole: proceedings of the International Metronidazole Conference, Montreal, Quebec, Canada; 1977.
83. Tiboni GM, Marotta F, Castigliego AP. Teratogenic effects in mouse fetuses subjected to the concurrent in utero exposures to miconazole and metronidazole. Reprod Toxicol. 2008;26(3–4):254–61.
84. Czeizel AE, Rockenbauer M. A population based case-control teratologic study of oral metronidazole treatment during pregnancy. Br J Obstet Gynaecol. 1998;105:2–7.
85. Diav-Citrin O, Gotteiner T, Shechtman S, Arnon J, Ornoy A. Pregnancy outcome following gestational exposure to metronidazole: a prospective controlled cohort study. Teratology. 2001;63:186–92.
86. Hoberman AM, Foss JA, Martin T. Developmental toxicity studies of amphocil administered intravenously to Sprague-Dawley rats and New Zealand white rabbits. (abstract). Toxicologist. 1994;14:573.
87. Perfect JR, Dismukes WE, Dromer F, Goldman DL, Graybill JR, Hamill RJ, Harrison TS, Larsen RA, Lortholary O, Nguyen MH, Pappas PG, Powderly WG, Singh N, Sobel JD, Sorrell TC. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2010;50(3):291–322.
88. Ali S, Jones GL, Culligan DJ, Marsden PJ, Russell N, Embleton ND, Craddock C. British Committee for Standards in Haematology. Guidelines for the diagnosis and management of acute myeloid leukaemia in pregnancy. Br J Haematol. 2015;170(4):487–95.
89. www.reprotox. Itraconazole. Accessed 17 Jan 2018.
90. DIFLUCAN (Fluconazole Tablets). Package labeling. 2017. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f694c617-3383-416c-91b6-b94fda371204.
91. Bar-Oz B, Moretti ME, Bishai R, Mareels G, Van Tittelboom T, Verspeelt J, Koren G. Pregnancy outcome after in utero exposure to itraconazole: a prospective cohort study. Am J Obstet Gynecol. 2000;183:617–20.
92. De Santis M, Di Gianantonio E, Cesari E, Ambrosini G, Staface G, Clementi M. First-trimester itraconazole exposure and pregnancy outcome. Drug Saf. 2009;32(3):239–44.
93. Molgaard-Nielsen D, Pasternak B, Hviid A. Use of oral fluconazole during pregnancy and the risk of birth defects. N Engl J Med. 2013;369(9):830–9.
94. Arts EJ, Hazuda DJ. HIV-1 antiretroviral drug therapy. Cold Spring Harb Perspect Med. 2012;2(4):a007161.
95. Cunha AM, Hagemann CC, Simoes RS, Oliveira-Filho RM, Simões MJ, Soares JM Jr, Maciel GA, Oliveira FH, Amed AA, Kulay L Jr. Effects of lopinavir-ritonavir combined therapy during the rat pregnancy: morphological and biochemical aspects. Eur J Obstet Gynecol Reprod Biol. 2007;133:60–3.
96. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 January 1989 through 31 July 2017. Wilmington, NC: Registry Coordinating Center; 2017. http://www.apregistry.com/forms/interim_report.pdf.
97. Sibiude J, Mandelbrot L, Bianche S, Le Chenadec J, Boullag-Bonnet N, Faye A, Dolifus C, Tubiana R, Bonnet D, Lelong N, Khoshnood B, Warszawski J. Association between prenatal exposure to antiretroviral therapy and birth defects; and analysis of the French perinatal cohort study (ANRS CO1/C)11. PLoS Med. 2014;11(4):e1001635.
98. Mofenson LM, Baggaley RC, Mameletzis I. Tenofovir disoproxil fumarate safety for women and their infants during pregnancy and breastfeeding. AIDS. 2017;31(2):213–32.
99. Wakai A, McCabe A, Roberts I, Schierhout G. Mannitol for acute traumatic brain injury. Cochrane Database Syst Rev. 2013;(8):CD001049. https://doi.org/10.1002/14651858.CD001049.pub5.
100. Kazemi P, Villar G, Flexman AM. Anesthetic management of neurosurgical procedures during pregnancy: a case series. J Neurosurg Anesthesiol. 2014;26(3):234–40.
101. Roberts I, Sydenham E. Barbiturates for acute traumatic brain injury. Cochrane Database Syst Rev. 2012;12:CD000033. https://doi.org/10.1002/14651858.CD000033.
102. Alnemari AM, Krafcik BM, Mansour TR, Gaudin D. A comparison of pharmacologic therapeutic agents used for the reduction of intracranial pressure after traumatic brain injury. World Neurosurg. 2017;106:509–28.
103. Turner BK, Wakim JH, Secrest J, Zachary R. Neuroprotective effects of thiopental, propofol, and etomidate. AANA J. 2005;73(4):297–302.
104. Friedman JM. Teratogen update: anesthesia agents. Teratology. 1988;37:69–77.

105. Czeizel AE, Pataki T, Rockenbauer M. Reproductive outcome after exposure to surgery under anesthesia during pregnancy. Arch Gynecol Obstet. 1998;261(4):193–9.
106. Li J, Xiong M, Alhashem HM, Zhang Y, Tilak V, Patel A, Siegel A, Ye JH, Bekker A. Effects of prenatal propofol exposure on postnatal development in rats. Neurotoxicol Teratol. 2014;43:51–8.
107. Astra Zeneca. Diprivan prescribing information. 2017. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=fee3bd4a-ade3-41fa-839a-48e9af69bcf4.
108. Veroniki AA, Cogo E, Rios P, Straus SE, Finkelstein Y, Kealey R, Reynen E, Soobiah C, Thavorn K, Hutton B, Hemmelgarn BR, Yazdi F, D'Souza J, MacDonald H, Tricco AC. Comparative safety of anti-epileptic drugs during pregnancy: a systematic review and network meta-analysis of congenital malformations and prenatal outcomes. BMC Med. 2017;15(1):95.
109. Ornoy A. Valproic acid in pregnancy: how much are we endangering the embryo and fetus? A review. Reprod Toxicol. 2009;28:1–10.
110. Diav-Citrin O, Shechtman S, Bar-Oz B, Cantrell D, Arnon J, Ornoy A. Pregnancy outcome after in utero exposure to valproate: evidence of dose relationship in teratogenic effect. CNS Drugs. 2008;22(4):325–34.
111. Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Sabers A. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. Lancet Neurol. 2011;10(7):609–17.
112. Holmes LB, Mittendorf R, Shen A, Smith CR, Hernandez-Diaz S. Fetal effects of anticonvulsant polytherapies: different risks from different drug combinations. Arch Neurol. 2011;68(10):1275–81.
113. Christensen J, Gronborg TK, Sorensen MJ, Schendel D, Parner ET, Pedersen LH, et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. JAMA. 2013;309(16):1696–703.
114. Rithman T, Parush S, Ornoy A. Developmental outcomes at preschool age after fetal exposure to Valproic acid and Lamotrigine: cognitive, motor, sensory and behavioral function. Reprod Toxicol. 2013;41:115–25.
115. Brodie MJ. Sodium channel blockers in the treatment of epilepsy. CNS Drugs. 2017;31(7):527–34.
116. www.reprotox. Keppra. Accessed 19 Feb 2018.
117. Nasr ZG, Paravattil B, Wilby KJ. Levetiracetam for seizure prevention in brain tumor patients: a systematic review. J Neuro-Oncol. 2016;129(1):1–13.
118. Khalil A, Hardman L, O Brien P. The role of arginine, homoarginine and nitric oxide in pregnancy. Amino Acids. 2015;47(9):1715–27.
119. Kulandavelu S, Whiteley KJ, Bainbridge SA, Qu D, Adamson SL. Endothelial NO synthase augments fetoplacental blood flow, placental vascularization, and fetal growth in mice. Hypertension. 2013;61(1):259–66.
120. Myatt L, Brewer A, Brockman DE. The action of nitric oxide in the perfused human fetal-placental circulation. Am J Obstet Gynecol. 1991;164:587–92.
121. Germain AM, Manzur A, Faundez L, Carvajal JA, Valdes G. Chronic oral L-arginine supplementation may improve the reproductive performance of patients with a history of recurrent pregnancy loss or severe preeclampsia. Hypertens Pregnancy. 2000;19(Suppl 1):89.
122. Krag M, Perner A, Wetterslev J, Lange T, Wise MP, Borthwick M, Bendel S, Pelosi P, Keus F, Guttormsen AB, Schefold JC, Meyhoff TS, Marker S, Møller MH. Stress ulcer prophylaxis in the intensive care unit trial: detailed statistical analysis plan. Acta Anaesthesiol Scand. 2017;61(7):859–68.
123. Prilosec. Product labeling. 2014. http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022056s017lbl019810s101lbl.pdf.
124. Diav-Citrin O, Arnon J, Shechtman S, Schaefer C, van Tonningen MR, Clementi M, De Santis M, Robert-Gnansia E, Valti E, Malm H, Ornoy A. The safety of proton pump inhibitors in pregnancy: a multicentre prospective controlled study. Aliment Pharmacol Ther. 2005;21(3):269–75.
125. Pasternak B, Hviid A. Use of proton-pump inhibitors in early pregnancy and the risk of birth defects. N Engl J Med. 2010;363:2114–23.
126. Freeman P, Sturman G, Suhonen AM, Meade HM, Seeley NA. Effects of histamine H2-antagonists on pre- and post-natal development in the rat. Inflamm Res. 1997;46(Suppl 1):S55–6.
127. Magee LA, Inocencion G, Kamboj L, Rosetti F, Koren G. Safety of first trimester exposure to histamine H2 blockers. A prospective cohort study. Dig Dis Sci. 1996;41(6):1145–9.
128. Ruigomez A, Garcia Rodriguez LA, Cattaruzzi C, Troncon MG, Agostinis L, Wallander MA, Johansson S. Use of cimetidine, omeprazole, and ranitidine in pregnant women and pregnancy outcomes. Am J Epidemiol. 1999;150:476–81.
129. Garbis H, Elefant E, Diav-Citrin O, Schaefer C, Vial T, Clementi M, Valti E, McElhatton P, Smorlesi C, Rodriguez EP, Robert-Gnansia E, Merlob P, Peiker G, Pexieder T, Schueler L, Ritvanen A, Mathieu-Nolf M. Pregnancy outcome after exposure to ranitidine and other H2-blockers. A collaborative study of the European Network of Teratology Information Services. Reprod Toxicol. 2005;19:453–8.
130. Koren G, Carey N, Reydman E, Sanjuan E, Farine D, Nulman I. Neurocognitive development of children exposed to doxylamine-pyridoxine combination in utero for morning sickness. Obstet Gynecol. 2014;23(5):151S.
131. Duchesnay Inc. Diclegis prescribing information. 2017. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8bde08f6-e8bd-4e90-baa7-82e01876a86a.
132. Anderka M, Mitchell AA, Louik C, Werler MM, Hernandez-Diaz S, Rasmussen SA, National Birth Defects Prevention Study. Medications used to treat nausea and vomiting of pregnancy and the risk of

selected birth defects. Birth Defects Res A Clin Mol Teratol. 2012;94(1):22–30.
133. Committee on Practice Bulletins-Obstetrics. ACOG practice bulletin no. 189: nausea and vomiting of pregnancy. Obstet Gynecol. 2018;131(1):e15–30.
134. Huybrechts KF, Hernández-Díaz S, Straub L, Gray KJ, Zhu Y, Patorno E, Desai RJ, Mogun H, Bateman BT. Association of maternal first-trimester ondansetron use with cardiac malformations and oral clefts in offspring. JAMA. 2018;320(23):2429–37.
135. Feldkamp ML, Meyer RE, Krikov S, Botto LD. Acetaminophen use in pregnancy and risk of birth defects. Obstet Gynecol. 2010;115:109–15.
136. Jensen MS, Rebordosa C, Thulstrup AM, Toft G, Sorensen HT, Bonde JP, Henriksen TB, Olsen J. Maternal use of acetaminophen, ibuprofen, and acetylsalicylic acid during pregnancy and risk of cryptorchidism. Epidemiology. 2010;21:779–85.
137. Toda K. Is acetaminophen safe in pregnancy? Scand J Pain. 2017;17:445–6.
138. Bar-Oz B, Clementi M, Di Giantonio E, et al. Metamizol (dipyrone, optalgin) in pregnancy, is it safe? A prospective comparative study. Eur J Obstet Gynecol Reprod Biol. 2005;119:176–9.
139. Banhidy F, Acs N, Puh E, Czeizel AE. A population-based case-control teratologic study of oral dipyrone treatment during pregnancy. Drug Saf. 2007;30(1):59–70.
140. Weintraub A, Mankuta D. Dypirone-induced oligohydramnios and ductus arteriosus restriction. Isr Med Assoc J. 2006;8(10):722–3.
141. Lind JN, Interrante JD, Ailes EC, Gilboa SM, Khan S, Frey MT, Lawson AL, Honein MA, Dowling NF, Razzaghi H, Creanda AA, Broussard CS. Maternal use of opioids during pregnancy and congenital malformations: a systematic review. Pediatrics. 2017;139(6):e20164131.
142. Ornoy A, Michailevskaya V, Lukashov I, Bar-Hamburger R, Harel S. The developmental outcome of children born to heroin dependent mothers, raised at home or adopted. Child Abuse Negl. 1996;20:385–96.
143. Ornoy A, Segal J, Bar-Hamburger R; Greenbaum C. The developmental outcome of school age children born to heroin-dependent mothers: importance of environmental factors. Dev Med Child Neurol. 2001;43:668–75.
144. Gupta U, Cook JC, Tassinari MS, Hurtt ME. Comparison of developmental toxicology of aspirin (ASA) in rats using selected dosing paradigms. Birth Defects Res (Part B). 2003;68:27–37.
145. Kusanagi T, et al. Teratogenic effects of non-steroidal anti-inflammatory agents in mice. Cong Anom. 1977;17:177–85.
146. Kozer E, Nikfar S, Costei A, Boskovic R, Nulman I, Koren G. Aspirin consumption during the first trimester of pregnancy and congenital anomalies: a meta-analysis. Am J Obstet Gynecol. 2002;187:1623–30.
147. Slone D, Siskind V, Heinonen OP, Monson RR, Kaufman DW, Shapiro S. Aspirin and congenital malformations. Lancet. 1976;1:1373–5.
148. www.reprotox.org. Aspirin. Accessed 2 Mar 2018.
149. Saxen I. Associations between oral clefts and drugs taken during pregnancy. Int J Epidemiol. 1975;4:37–44.
150. Daniel S, Matok I, Gorodischer R, Koren G, Uziel E, Wiznitzer A, Levy A. Major malformations following exposure to nonsteroidal anti-inflammatory drugs during the first trimester of pregnancy. J Rheumatol. 2012;39(11):2163–9.
151. Hammers AL, Sanchez-Ramos L, Kaunitz AM. Antenatal exposure to indomethacin increases the risk of severe intraventricular hemorrhage, necrotizing enterocolitis, and periventricular leukomalacia: a systematic review with meta-analysis. Am J Obstet Gynecol. 2015;212:505.e1–13.
152. Ericson A, Kallen BA. Nonsteroidal anti-inflammatory drugs in early pregnancy. Reprod Toxicol. 2001;15:371–5.
153. Ofori B, Oraichi D, Blais L, Rey E, Berard A. Risk of congenital anomalies in pregnant users of non-steroidal anti-inflammatory drugs: a nested case-control study. Birth Defects Res B Dev Reprod Toxicol. 2006;268-79(2006):77.
154. Padberg S, Tissen-Diabate T, Dathe K, Hultzsch S, Meixner K, Linsenmeier V, Meister R, Schaefer C. Safety of diclofenac use during early pregnancy: a prospective observational cohort study. Reprod Toxicol. 2018;77:122–9.
155. Lopes LM, Carrilho MC, Francisco RP, Lopes MA, Krebs VL, Zugaib M. Fetal ductus arteriosus constriction and closure: analysis of the causes and perinatal outcome related to 45 consecutive cases. J Matern Fetal Neonatal Med. 2016;29(4):638–45.
156. Nezvalova-Henriksen K, Spigset O, Nordeng H. Effects of ibuprofen, diclofenac, naproxen, and piroxicam on the course of pregnancy and pregnancy outcome: a prospective cohort study. BJOG. 2013;120(8):948–59.
157. Kuczkowski KM. Nonobstetric surgery during pregnancy: what are the risks of anesthesia. Obstet Gynecol Surv. 2004;59(1):52–6.
158. Kuczkowski KM. The safety of anaesthetics in pregnant women. Expert Opin Drug Saf. 2006;5(2):251–64.
159. McCann ME, de Graaff JC, Dorris L, Disma N, Withington D, Bell G, Grobler A, Stargatt R, Hunt RW, Sheppard SJ, Marmor J, Giribaldi G, Bellinger DC, Hartmann PL, Hardy P, Frawley G, Izzo F, von Ungern Sternberg BS, Lynn A, Wilton N, Mueller M, Polaner DM, Absalom AR, Szmuk P, Morton N, Berde C, Soriano S, Davidson AJ, GAS Consortium. Neurodevelopmental outcome at 5 years of age after general anaesthesia or awake-regional anaesthesia in infancy (GAS): an international, multicentre, randomised, controlled equivalence trial. Lancet. 2019;393(10172):664–77.
160. Lupattelli A, Chambers CD, Bandoli G, Handal M, Skurtveit S, Nordeng H. Association of mater-

nal use of benzodiazepines and Z-hypnotics during pregnancy with motor and communication skills and attention-deficit/hyperactivity disorder symptoms in preschoolers. JAMA Netw Open. 2019;2(4):e191435.
161. Grigoriadis S, Graves L, Peer M, Mamisashvili L, Dennis CL, Vigod SN, Steiner M, Brown C, Cheung A, Dawson H, Rector N, Guenette M, Richter M. Benzodiazepine use during pregnancy alone or in combination with an antidepressant and congenital malformations: systematic review and meta-analysis. J Clin Psychiatry. 2019;80(4):18r12412.
162. Crawford JS, Lewis M. Nitrous oxide in early human pregnancy. Anaesthesia. 1986;41:900–5.

Management of Pain During Maternal Critical Illness

39

Valerie Zaphiratos and Philippe Richebé

Bullet Points

- In developed countries, 0.05–1.7% of obstetric patients will be admitted to critical care units either antenatally or in the postpartum period.
- The physiology of pregnancy combined with untreated pain will alter both maternal and fetal homeostasis (maternal oxygenation, placental perfusion, and, as a result, fetal perfusion) and hence requires specific considerations in the obstetric population.
- Pharmacological analgesia is the first line of treatment for pain management in the ICU for obstetric patients.
- Pain management with regional or neuraxial medications is preferable for obstetric patients, as it decreases the need for systemic medications that cross the placenta.
- Optional regional analgesia techniques include neuraxial (epidural analgesia and intrathecal morphine), trunk, and limb blocks.
- Optional systemic analgesia medications include non-opiates (acetaminophen and nonsteroidal anti-inflammatory drugs), opioids, and adjuncts (e.g., ketamine, dexmedetomidine, and gabapentinoids).
- A combined analgesia regimen that includes both regional and systemic medications optimizes pain management.
- A multidisciplinary team that includes anesthesiologists, intensivists, neonatologists, and obstetricians should collaborate in creating the pain management plan.

39.1 Introduction

In developed countries, 0.05–1.7% of obstetric patients will be admitted to critical care units either antenatally or in the postpartum period [1]. Pain in the critically ill obstetric patient may be due to trauma (such as rib fractures) or a medical condition (such as pancreatitis) or in the context of surgical procedures (either non-obstetric surgery, cesarean delivery, or both) and may also be caused by a procedure that is part of the management plan in the intensive care unit (ICU).

V. Zaphiratos (✉) · P. Richebé
Department of Anesthesiology of Maisonneuve-Rosemont Hospital, CIUSSS de l'Est de l'Ile de Montréal, University of Montréal, Montréal, QC, Canada
e-mail: valerie@zaphiratos.ca; philippe.richebe@umontreal.ca

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_39

Similar to the critically ill non-obstetric patient, the use of pharmacological analgesia will be the first line to manage pain in the ICU. If women are able to communicate, evaluation of pain with the numeric rating scale (NRS) will help with titrated administration of analgesic medications. Appropriate pain control should minimize sedation requirements; however in some instances, sedation will be required to alleviate discomfort and excruciating pain in critical conditions. When sedation is needed, titration of analgesics might be eased using the well-validated Richmond Sedation and Agitation Score. However, it is important to bear in mind that most analgesic or sedative drugs administered systemically will cross the placenta (or breastmilk) and may result in fetal/neonatal sedation and potential respiratory depression; their pharmacology must be known to all prescribers. Optimizing pain management with regional or neuraxial medications may therefore be preferable, as these should not reach the fetus/neonate. Ideally, their indication should be decided by a multidisciplinary team that includes intensivists, neonatologists, obstetricians, and anesthesiologists. Often, a combined analgesia regimen that includes regional and systemic medications gives the best result for pain management.

In this chapter, we will focus on the pharmacological aspects of pain management for pregnant women admitted to the ICU presenting with non-labor pain. Pain management in laboring women, which includes neuraxial analgesia, or when contraindicated intravenous administration of fentanyl or remifentanil via patient-controlled analgesia (PCA), or inhaled nitrous oxide, will not be discussed here. Non-pharmacological means of pain management such as acupuncture, hypnosis, pressure points, mindfulness, and other modalities are also not covered in this chapter, though they may be useful as adjuncts or alternatives in some cases.

39.1.1 Pain in the Context of Pregnancy

Differentiating between somatic and visceral pain is as important for determining analgesic strategies in obstetric patients as it is in non-obstetric patients. *Somatic pain* is easily localized and characterized by sensations that are perceived very distinctly. It typically originates from joints, bones, muscles, and/or soft tissues. *Visceral* pain is diffuse and poorly localized. This type of pain is typically caused by distention of hollow internal organs, traction on the mesenterium, ischemia, and/or inflammation [2].

Certain analgesic modalities are effective for one type of pain and are not effective for the other, hence the importance of taking into consideration the origin of the pain—visceral, somatic, or both. For example, neuraxial analgesia (epidural or spinal or a combination of both) manages both somatic and visceral pain. However a regional block, such as a transversus abdominis plane (TAP) block, will only be effective for somatic pain resulting from abdominal wall pain.

In addition, it is important to consider the effects of medications on the fetus. A multimodal analgesia regimen which utilizes drugs with different mechanisms of action optimizes the analgesic effect of each drug while lowering the dose of opioids administered to the mother and thereby the fetus [3].

39.1.2 Physiologic Changes During Pregnancy and Their Impact on Pain Tolerance and Analgesia

Adaptive physiological changes occur during normal gestation that may impact tolerance to pain and the response to analgesic modalities. These changes require that a fine balance be achieved between the risk of undertreated pain and the risk of oversedation and respiratory depression in a population at peril for rapid oxygen desaturation (Table 39.1).

39.1.2.1 Pulmonary Physiology and Physiopathology

Pregnant women have a reduced pulmonary reserve due to a decrease in functional residual capacity (FRC), an increase in oxygen consumption and minute ventilation, as well as nasal congestion due to an increase in progesterone (see Chap. 20).

Table 39.1 During pregnancy several systems are affected by the change in physiology: pulmonary, cardiovascular, gastrointestinal, hematological and immune. These physiological changes have clinical impacts, and the addition of pain and analgesia further affect the function of these systems

Pregnancy changes	Pulmonary	Cardiovascular	Gastrointestinal	Hematological and immune
Physiology and physiopathology	↓ FRC ↑ O_2 consumption ↑ V_E ↑ Nasal congestion	↑ Cardiac output ↑ Stroke volume ↑ Heart rate ↓ Systemic vascular resistance	↓ LES tone	↑ Plasma volume by 50% ↑ Clotting factors impaired immune function
Clinical impact	↓ Pulmonary reserve Perceived dyspnea	↓ Blood pressure mid-pregnancy ↑ Risk of syncope	↑ Risk of aspiration	Anemia Thrombocytopenia Hypercoagulable state Possible iatrogenic anticoagulation ↑ Risk of infections
Consequences of pain	Hyperventilation Worsening respiratory alkalosis Possible fetal acidosis	↑ Cardiac output ↑ Systemic vascular resistance ↑ Blood pressure ↑ Stress hormones Possible fetal acidosis	↓ Gastric emptying	↓ Cellular immunity
Addition of analgesia	Risk of desaturation and apnea with opioids/sedation	↓ Stress hormones ↑ Uteroplacental blood flow	↓ Gastric emptying with opioids	Neuraxial blocks contraindicated if coagulopathy, severe thrombocytopenia, or sepsis

These changes contribute to the perceived dyspnea reported by many women during pregnancy. Labor pain leads to maternal hyperventilation with secondary respiratory alkalosis. This alkalosis may decrease placental transfer of oxygen. At the same time hyperventilation is accompanied by development of a compensatory maternal metabolic acidosis, which worsens as maternal pain progresses and, depending on its severity, can lead to fetal metabolic acidosis [4–12].

39.1.2.2 Cardiovascular Physiology and Physiopathology

In a normotensive woman, cardiac output, stroke volume, and heart rate all increase in the first trimester of pregnancy. Systemic vascular resistance is decreased throughout pregnancy due to the development of a low resistance vascular bed. Blood pressure measurements decrease in mid-pregnancy and return to baseline at term. In addition, aortocaval compression occurs in the supine position as of the second trimester and may decrease maternal blood pressure and uterine blood flow (see also Chap. 9). All of these place the pregnant woman at the edge of the physiological reserve for maintenance of blood pressure and cardiac output and therefore at risk of cardiovascular collapse.

At the same time pain, stress, and anxiety cause release of stress hormones such as cortisol and β-endorphins. The sympathetic nervous system response to pain is a marked increase in circulating catecholamines, such as norepinephrine and epinephrine. These hormonal effects may increase cardiac output and vascular resistance. The assumption is that these hemodynamic changes may not only adversely affect uterine activity and uteroplacental blood flow but also effect some degree of imbalance in maternal hemodynamics. The magnitude of these effects is unpredictable and differs between individuals [11–15]. In pregnant women with cardiac pathology, such as cardiomyopathy, valve pathologies, arrhythmia, or pulmonary hypertension, such changes are not desirable. Thus, pain management becomes that much more invaluable for lessening the stress response and its related hemodynamic consequences.

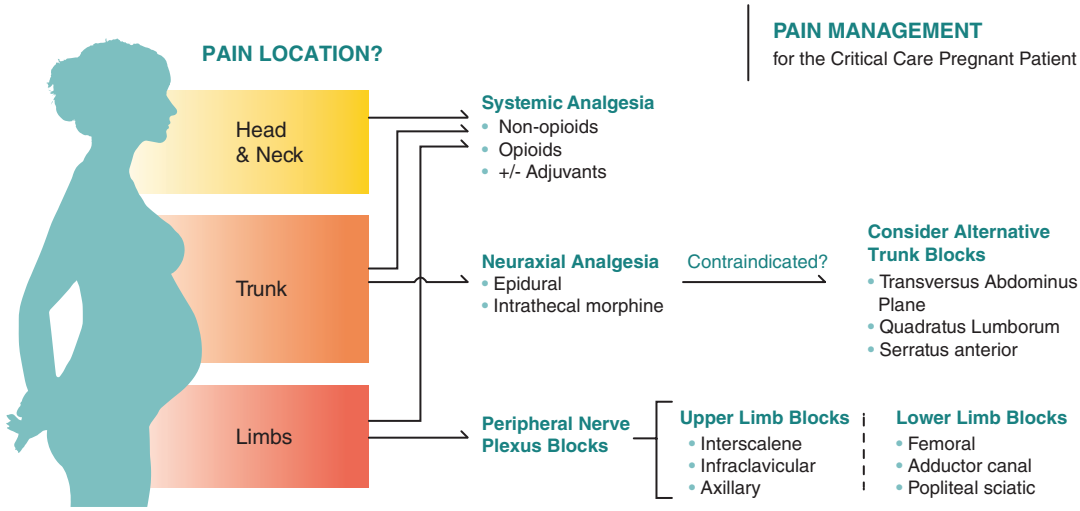


Fig. 39.1 Summary of possible analgesic modalities at different anatomical pain locations with the goal of optimizing multimodal analgesia

39.1.2.3 Gastrointestinal Physiology and Physiopathology

The thoracic cage increases in diameter, and the stomach is displaced upward. Progesterone relaxes the tone of the lower esophageal sphincter, contributing to the risk of aspiration that occurs as of the second trimester [16]. These changes may combine with the effect of pain and systemic opioids to increase the potential for delayed gastric emptying and increase the risk of regurgitation and aspiration [17].

39.1.2.4 Hematological and Immune Physiology and Physiopathology

Pregnancy is a hypercoagulable state (see Chap. 5). Many women may be receiving or may require treatment with anticoagulants during pregnancy, based on current recommendations to prevent thromboembolic events [17–19]. This requires special attention to prevent procedure-related hemorrhage. Despite an increase in leukocytes, immune function is also impaired during pregnancy (see Chap. 15). This may increase the risk for procedure-related infections.

In summary, in the context of pregnancy in a critically ill patient, pain-induced maternal stress may be particularly deleterious for both mother and fetus. Maternal pain induces a stress response and releases maternal cortisol and catecholamines and consequently impacts the maternal hemodynamic profile, oxygen consumption, and release. In addition, maternal pain has numerous negative effects in the fetus.

39.1.3 Pain Management in the Obstetric Population

Regional techniques often use a continuous infusion of a local anesthetic that surrounds the nerves and creates minimal plasma concentrations. The use of neuraxial or regional analgesia can therefore reduce, or even prevent, maternal systemic opioid intake. This is particularly important as a prolonged in utero fetal exposure to systemic opioids may result in opioid withdrawal at birth (neonatal opioid withdrawal syndrome, NOWS) and opioid tolerance. Thus, depending on the location and type of pain, if a neuraxial technique or a regional block is possible and available, these should be the preferred primary analgesic modality in pregnant women (Fig. 39.1).

39.2 Neuraxial Analgesia

Neuraxial analgesia includes (1) epidural analgesia and (2) injection of intrathecal morphine. Neuraxial analgesia procedures and administra-

tion of neuraxial medication is to be done by anesthesiologists.

39.2.1 Continuous Epidural Analgesia

39.2.1.1 Indications

Continuous epidural analgesia is best known for its use in obstetric anesthesia for provision of labor analgesia, in which case the epidural catheter is placed at the lumbar level [20]. Additional indications include postoperative analgesia after thoracic, abdominal, or bilateral hip surgery [21]. Depending on the surgical site, the epidural may be placed at the thoracic or lumbar level. Continuous epidural analgesia can also be used to manage nonsurgical gastrointestinal pain, such as pain from pancreatitis, and thoracic pain from rib fractures.

An epidural catheter may be left in place for several days. The insertion site should be checked regularly for signs of swelling, redness, or pain [22, 23]. Recent evidence suggests that tunneling the catheter subcutaneously may be associated with fewer catheter-related infections [24]. Therefore if the epidural catheter is tunneled under the skin, it may be kept in situ for much longer (up to several weeks). In the context of a pregnant woman admitted to the ICU for an extended period of time, this may be a very desirable solution for several pain problems. However, this option must be considered within days of hospital admission, since the risk of infectious complications increases with increasing length of stay. Unfortunately in some cases, other issues preclude this option within such a brief time frame (e.g., the risk of hemorrhage).

39.2.1.2 Procedure and Medications

An epidural catheter is placed between two vertebrae at the dermatomal levels approximating the location of the pain. With the catheter in place, a low dose/concentration of local anesthetic (typically bupivacaine or ropivacaine) is administered together with a lipophilic opioid (fentanyl or sufentanil). The spread of the epidural solution and the number of dermatomes covered is dependent on the total mass (concentration and volume) of local anesthetic injected and the site of the catheter (thoracic versus lumbar) [25], with a typical spread of several dermatomes above and below the level at which the epidural catheter is sited. It is believed that the presence of engorged epidural veins and additional epidural fat in pregnancy reduces the volume of local anesthetic required per dermatome [26, 27]. Continuous epidural infusion may be accompanied by patient-controlled epidural analgesia (PCEA) for self-administered boluses whenever possible.

When patient mobilization is possible and desired, an alternative may be sought for continuous epidural infusion of local anesthetic solution as this method may be accompanied by sympathetic and/or motor block. In such cases administration of repeated doses of epidural preservative-free morphine, which has no such side effects, is preferred. Repeated epidural injections of morphine (once or twice daily) may be maintained for several days.

39.2.1.3 Side Effects and Complications

Sympathetic Blockade and Hemodynamic Effects: The most rapid effect of neuraxial administration of local anesthetics is a sympathetic block which, depending on the dose/concentration, will result in maternal hypotension. For this reason, low concentrations of local anesthetics are typically used with the addition of low-dose short-acting opioids, and adequate monitoring of maternal hemodynamic parameters and fetal heart rate are essential at the time of initiation of neuraxial analgesia.

Uteroplacental blood flow: Maternal hypotension and fetal heart rate abnormalities may occur following initiation of labor epidural analgesia, with local anesthetics and or opioids, secondarily impairing uteroplacental blood flow. In the context of a contracting uterus, which also reduces uteroplacental blood flow, concerns have arisen regarding neonatal outcomes with labor epidural analgesia. However, these transient alterations have not been shown to affect neonatal outcome [28–30]. Regardless, vasopressors should be used to prevent and

treat maternal hypotension following initiation of epidural analgesia, even in the absence of labor.

Motor blockade: With higher doses or concentrations of local anesthetic solutions, motor blockade may occur, causing weakness of the lower limbs. In a critically ill patient, there are multiple additional reasons for motor weakness. Therefore, the severity and level of motor blockade should be constantly evaluated both before induction and during epidural analgesia [31]. When mobilization is an option, increased vigilance is required as there is an increased penchant for falls.

Accidental dural puncture: Accidental dural puncture is a complication of the epidural technique that occurs when the large epidural needle (17 or 18 gauge) unintentionally punctures the dura and subarachnoid, resulting in leakage of cerebrospinal fluid (CSF). The risk of accidental dural puncture in the obstetric population is considered to be in the order of or less than 1% in centers with experienced anesthesiologists [32]. Post-dural puncture headache (PDPH) may occur after accidental dural puncture or intended spinal anesthesia with a pencil-point atraumatic spinal needle. The risk of developing PDPH is the highest in young nonobese women and is estimated to be 50–80% after accidental dural puncture (with a 17G or 18G epidural needle) and much lower after intended spinal anesthesia with an atraumatic spinal needle (25G or 27G) [32, 33]. However, PDPH remains the most common serious complication after neuraxial procedures [34]. Epidural blood patch (i.e., a sterile injection of 10–30 mL autologous blood into the epidural space) is the most effective treatment for PDPH. After a single epidural blood patch, 65–90% of patients no longer present with headache symptoms [20].

An additional complication of accidental dural puncture is when it remains unidentified. In such cases high doses of local anesthetic are administered into the CSF (spinal canal) unknowingly. This causes a high neuraxial block which is accompanied by major potential for severe respiratory depression and cardiovascular collapse. A "high spinal" is one of the most common serious complications of obstetric anesthesia, with an incidence of somewhat less than 1:4000 neuraxial procedures [34].

39.2.2 Intrathecal Morphine

39.2.2.1 Indication

A single intrathecal injection of morphine may be beneficial when neuraxial analgesia is preferred, but an epidural catheter cannot be left in place. A typical example is the patient who will require therapeutic anticoagulation after the neuraxial procedure.

39.2.2.2 Procedure and Medication

Intrathecal morphine is administered as a single injection between two lumbar vertebrae, below the level of the conus medullaris (L2). Once cerebral spinal fluid (CSF) return is confirmed, preservative-free morphine is injected into the CSF. Morphine acts centrally on the opioid receptors in the substantia gelatinosa of the dorsal horn of the spinal cord and can provide pain relief for up to 12–24 h after injection [35, 36]. It has low lipid solubility which explains its slow onset and prolonged duration of action [36]. Typically, intrathecal morphine doses range between 0.1 and 0.3 mg in North American practice [37]. Less commonly, an intrathecal catheter may be left in place (e.g., after an unintended dural puncture), and repeated doses (once or twice daily) of intrathecal morphine may be given for several days.

39.2.2.3 Side Effects and Complications

Intrathecal morphine may cause nausea, vomiting, and pruritus, as well as respiratory depression due to rostral spread in cerebrospinal fluid with slow penetration into the brainstem [38–40]. Several studies have shown that with doses below 0.5 mg, analgesia is effective and maternal respiratory depression does not occur [41–44]. Extrapolating from several studies that describe the use of intrathecal morphine as an adjuvant for neuraxial labor analgesia used to prolong the effect of a single spinal dose during labor, none

reported any adverse neonatal outcomes with doses up to 0.25 mg [36, 42–45].

In morbidly obese pregnant women, with or without obstructive sleep apnea, the risk of respiratory depression is increased [46]. Nonetheless, obese pregnant women may be administered 0.1 mg–0.15 mg of intrathecal morphine for analgesia as the benefits outweigh the risks [38, 46]. Capnography is ideal to alert for apnea or hypercarbia but is not in routine clinical use [47]. Respiratory rate, sedation scores, and pulse oximetry are the tools commonly utilized to detect respiratory depression.

39.2.2.4 Absolute and Relative Contraindications for Neuraxial Procedures

Absolute contraindications for a neuraxial procedure include the presence of coagulopathy (either a medical condition or pharmacological anticoagulation), infection (sepsis, or at the site of puncture), and lack of resources to administer the technique [34, 48–52].

In the previously healthy pregnant woman, there are several obstetric pathologies that result in contraindications for neuraxial procedures, in particular (1) intrauterine fetal demise (IUFD) which may result in disseminated intravascular coagulation (DIC); (2) hypertensive disorders of pregnancy, such as preeclampsia with severe features, which may cause severe thrombocytopenia; and (3) fatty liver of pregnancy. In addition, women with a history of a thromboembolic event may have an indication for pharmacological anticoagulation, with either low molecular weight heparin (LMWH), unfractionated heparin (UFH), or even antiplatelet medications, such as clopidogrel.

In uncomplicated gestational thrombocytopenia, platelets remain functional. Recent studies support conducting a neuraxial technique in this situation provided the platelet count is over 70,000/μL [48–50]. In other situations, aside from platelet count, additional factors must be considered in a pregnant woman with thrombocytopenia. These include the rate and timeline of platelet decline (particularly, but not only, in preeclampsia or HELLP syndrome), the potential effect of the accompanying pathology on platelet function (e.g., DIC), and the experience and training of the anesthesiologist performing the technique [50].

Fatty liver of pregnancy is associated with an increasing international normalized ratio (INR). An INR below 1.5 is the recommended cutoff for safe neuraxial analgesia procedures in general, and this recommendation remains pertinent throughout pregnancy despite the hypercoagulable state of pregnancy [51]. Intrahepatic cholestasis occurring during pregnancy rarely results in coagulation abnormalities, and in these cases neuraxial technique can often be performed [53].

Relative contraindications to neuraxial analgesia procedures include severe and/or instrumented scoliosis and certain neuropathies. In these cases, the benefits of neuraxial analgesia should be weighed against the risks of alternative therapies [50].

39.3 Trunk Blocks

39.3.1 Indications

Although not as effective as neuraxial analgesia, trunk blocks may be a reasonable alternative for management of somatic thoracoabdominal pain [54–57]. Trunk blocks are performed in tissue planes and therefore require large volumes of local anesthetic to be effective. A recent review details the abdominal wall blocks that can be performed in adults [58]. However, caution must be used when performing such blocks in pregnant women as their abdominal anatomy may differ that of non-pregnant individuals. Trunk blocks must be performed with ultrasound guidance by an anesthesiologist with expertise in performing these blocks.

39.3.2 Procedures and Medications

39.3.2.1 Transversus Abdominis Plane (TAP) Block

Local anesthetic is injected between the internal oblique and transversus abdominis muscles. This can be done unilaterally or bilaterally and can be

administered as a single shot or as an infusion of local anesthetic using a catheter [59]. The TAP block provides somatic analgesia to the anterior abdominal wall from T6 to L1. TAP blocks are currently considered superior to no analgesia, but they provide only superficial abdominal wall analgesia (i.e., surgical incision for a limited amount of time (12–15 h), unless catheters are left in situ for reinjections). There is limited available data to support the use of long-acting liposomal bupivacaine to prolong analgesia for single-shot TAP blocks [60]; however this option is currently under investigation.

39.3.2.2 Quadratus Lumborum Block (QLB)

This block is a relatively novel approach that provides somatic and possibly visceral analgesia to the upper and lower abdominal wall (depending on the anatomical approach). Local anesthetic is injected around the quadratus lumborum, and analgesia is typically achieved from T4 to L1. The QLB can be done unilaterally or bilaterally and can be administered as a single shot or as an infusion of local anesthetic using a catheter [61, 62]. The QLB is more difficult to perform than the TAP block, and its comparative benefits for post-cesarean analgesia remain to be determined. One recent study of 48 cases comparing the QLB to placebo for post-cesarean pain demonstrated reduced postoperative morphine consumption in the QLB group when used with a standard post-cesarean analgesia regimen without intrathecal morphine [63].

39.3.2.3 Serratus Anterior Plane Block

The serratus anterior plane block provides analgesia to the hemithorax. It too can be performed unilaterally or bilaterally and can be administered either as a single shot or as an infusion of local anesthetic using a catheter. Local anesthetic is injected into the plane between the latissimus dorsi and serratus anterior muscles [64]. The serratus anterior block has been used for analgesia after thoracoscopy and breast surgery, as well as for pain management after rib fractures [65–67].

39.3.2.4 Additional Trunk Blocks

The paravertebral and intercostal nerve blocks can be useful for thoracic pain, such as that stemming from rib fractures. However, like epidural analgesia, these blocks are contraindicated in patients with coagulopathy.

39.3.3 Side Effects and Complications

Perforation of intra-abdominal organs (intestines, kidney, liver, and spleen) or injection into unintended structures has been described in the non-obstetric population [68, 69] and one case of transient femoral nerve palsy occurring with a TAP block after cesarean delivery [70]. These procedures should be performed with ultrasound guidance by experienced anesthesiologists. In addition, specific to the highly vascularized quadratum lumborum region, increased absorption of local anesthetic is a risk. As large volumes of local anesthetics are used for these blocks, it is important to calculate the appropriate dose with respect to patient size to prevent exceedingly high peak plasma concentrations. This is even more critical in frail patients and those with liver failure or when drug-drug interaction for competing hepatic metabolic pathways may become an issue.

39.4 Limb Plexus Blocks

39.4.1 Indications

For pain involving an arm or a leg, regional blockade of a nerve plexus is recommended. A brachial plexus block can provide analgesia for the hand, elbow, or shoulder depending on the location of needle insertion. Using a catheter, an interscalene block can provide continuous shoulder analgesia, whereas an infraclavicular block can provide continuous analgesia for the hand and forearm [71]. Also using a catheter, a femoral block or adductor canal block can provide continuous analgesia for the territory of the femoral nerve which becomes the saphenous nerve

distally. A popliteal sciatic block with catheter placement provides continuous analgesia for the back of the knee and the majority of the foot and ankle [71].

39.4.2 Procedures and Medications

These blocks are performed using ultrasound guidance; however in low resource settings, some of these blocks can also be performed using neurostimulation. A local anesthetic (typically bupivacaine or ropivacaine) is administered as a single injection (for an expected duration of action of approximately 10–12 h) or as an infusion through a catheter. In unsedated patients, patient-controlled self-administered boluses (PCA) of local anesthetic can be added for pain management if required. If therapeutic anticoagulation is planned and a deep block is necessary for analgesia, a single shot of local anesthetic can be injected, and the block can be prolonged (for up to a total of 20 h) with intravenous or perineural dexamethasone [72, 73].

39.4.3 Contraindications

Contraindications to regional plexus blocks of the limbs should be weighed case by case, and accordingly a single-shot procedure rather than a continuous approach should be considered, based on coagulopathy, systemic infection, and lack of resources [51, 52]. Pre-existing neuropathy should be well documented prior to performing the block and is considered a relative contraindication [74–77].

39.5 Systemic Analgesia

While it has been suggested that pain perception may be reduced during pregnancy, in a phenomenon termed "pregnancy-induced analgesia," reducing analgesic dosing is not the norm for pregnant women or in the postpartum period [78]. It is recommended to administer ideal weight adult doses of analgesics for parturients, as would be done for a non-pregnant adult. Although the volume of distribution, renal blood flow, and other parameters affecting drug pharmacokinetics are all altered during pregnancy, there are no recommendations to adapt medication doses to any of these. The multiple interactions between these factors seem to lead to an equilibrium similar to baseline; therefore systemic drug dosing remains unchanged throughout pregnancy.

39.5.1 Stepwise Systemic Multimodal Analgesia for the Obstetric Patient

The World Health Organization (WHO) pain ladder has been guiding clinicians for almost three decades with regard to multimodal systemic administration of analgesic drugs [79]. The WHO pain ladder recommends a stepwise multimodal approach, which involves starting with non-opioid pain medications such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), and progressing to opioids only if required for increasing pain. Adjuvant medications can be added at any stage of therapy. These include ketamine, dexmedetomidine, and gabapentinoids [80, 81]. Similar to the non-pregnant patient, pregnant and peripartum women will benefit from stepwise multimodal analgesia, which is intended to allow opioid-sparing pain management.

39.5.2 Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and Acetaminophen

39.5.2.1 Indication

A combination of NSAIDs and acetaminophen is recommended and effective for mild to moderate pain or in association with opioids for moderate or severe pain.

Over 14 years of recent data has accumulated regarding the association between maternal analgesic intake before conception until the end of the first trimester and the risk of birth defects [82]. Despite this, it remains unclear whether in

utero exposure to analgesics causes birth defects or if birth defects are related to the condition for which pregnant women were taking analgesic medications. In contrast to acetaminophen use, mothers taking NSAIDs have been reported to be more likely to have an offspring with birth defects. However, similar associations have been reported with most pain medications, including opioids [82]. Unfortunately the overwhelming majority of these studies are retrospective and therefore affected by reporting bias, or observational, where upon causation cannot be inferred. Therefore when a critically ill pregnant or peripartum patient is in pain and requires analgesia, her needs must be prioritized over that of the fetus. Ideally, a balance should be sought to cause the least harm while fulfilling these needs.

39.5.2.2 Contraindications

The use of NSAIDs during pregnancy, particularly in the first 8 weeks of gestation, has been reported to be associated with miscarriage [83, 84]. Although still subject to controversy, the use of NSAIDs does not seem to increase the risk of birth defects in the first trimester [85]. In addition, repeated systemic use of NSAIDs in the third trimester may cause constriction of the ductus arteriosus [86]. These potential risks should be carefully considered before administering NSAIDs to the pregnant patient. For women with preeclampsia, the use of NSAIDs postpartum, which were thought to be associated with an increased rate of persistent hypertension postpartum, is currently debated, and while historically not recommended, these recommendations may be changing [87]. The use of acetaminophen is cautioned in women with altered or compromised liver function (e.g., in fatty liver of pregnancy).

39.5.3 Opioids

39.5.3.1 Indication

Administration of systemic opioids is recommended in combination with acetaminophen and NSAIDs, if moderate to severe pain (breakthrough pain) occurs.

39.5.3.2 Medication and Mode of Administration

The route of opioid administration depends on the condition of the woman and her ability to ingest oral medication and/or to self-administer medication via intravenous patient-controlled analgesia (IV PCA). The most commonly used opioids for IV PCA in the ICU setting are morphine and hydromorphone as they seem to have the most predictable pharmacology. Fentanyl IV PCA has also been well studied in the obstetric setting because it is the most suited alternative for women unable to receive neuraxial analgesia during labor and delivery [88–91]. Protocols for morphine, hydromorphone, or fentanyl PCA should be similar to those used in any adult ICU patient.

In an awake and cooperative patient, if pain persists despite standard medication doses, higher doses of opioids in addition to sedatives may be useful, under cautious monitoring. For example, in some settings, severely morbidly obese (e.g., BMI > 50) pregnant women with or without obstructive sleep apnea may be admitted for monitoring of respiratory function (and CO_2 retention) throughout the duration of time they are receiving neuraxial or systemic opioids. Similarly women with congenital heart disease may require a monitored environment during the peripartum period when the risk of decompensation is most significant. However, most ICU patients experience some degree of pain and IV opioids are commonly used for pain control in both intubated and non-intubated women. Fentanyl is frequently used drug for this purpose in the ICU, and due to its prolonged and variable context-sensitive half-time, fentanyl can undergo substantial accumulation after several boluses and/or prolonged administration. Remifentanil is a possible alternative as it has a short, stable context-sensitive half-time of 3 min with predictable drug offset [92]. However, remifentanil may rapidly induce tolerance and opioid-induced hypersensitivity in ICU patients exposed to opioids for several days.

39.5.3.3 Contraindication

Contraindications in the obstetric population are not different from the general adult popula-

tion. The use of opioids will be subject to the same precautions and monitoring as those required for other adult populations.

39.5.3.4 Side Effects and Complications

Maternal

Maternal side effects are similar to those described in any general population of adult patients.

Fetal/Neonatal

ICU patients are often prescribed multiple respiratory depressants; the risk of additive effects and the need for fetal monitoring must be considered. Because opioids cross the placenta, neonatal respiratory depression is a serious risk even with ultra-short-acting opioids, such as IV remifentanil [93]. After prolonged exposure, NOWS is a serious risk that should be prevented with appropriate care [94, 95].

Morphine, hydromorphone, and fentanyl demonstrate a low risk of malformations when taken during pregnancy [82, 96]. These agents are classified as category D medications if used for an extended duration or in high doses [96].

The recent Committee for Opioid Use and Opioid Use Disorder in Pregnancy evaluated the effects of opioid use in pregnancy and pregnancy outcomes [97]. Literature from the 1980s reported that oxycodone, propoxyphene, and meperidine were not shown to increase the risk of birth defects [98, 99]. More recent studies evaluating the effects of morphine and hydromorphone report some risk of birth defects when these opioids were taken just before or during the first trimester of pregnancy [100, 101]. However, methodological problems exist in all of these studies, and the fact is that birth defects are rare and most studies show a very small increase in absolute risk.

Codeine use during the first trimester of pregnancy has been linked to congenital malformations in some studies [100, 102, 103], but not in others [104, 105]. This led to the conclusion that codeine should not be administered to pregnant women as alternative options exist which are safer for the fetus. More recently it has been suggested that codeine should be avoided altogether in the obstetric population and particularly postpartum in breastfeeding mothers, due to the risk of fatal infant overdose if the mother is a CYP2D6 ultrametabolizer [106, 107].

39.5.4 Ketamine

Ketamine is a hypnotic analgesic drug that acts mainly through blockade of the *N*-methyl-D-aspartate (NMDA) receptor as an antagonist. At high doses in rodents, ketamine is also able to induce neuroapoptosis and impair neuronal circuitry formation [108]. As an induction agent for general anesthesia for emergency surgery, including cesarean delivery, ketamine is safe. For sedation in the ICU, there are more appropriate agents, such as propofol.

For pain management in the ICU, low doses of ketamine may be given as a continuous infusion (2 mcg/kg/min) or in combination with morphine or hydromorphone PCA (0.5 or 1 mg/mL of ketamine in the morphine or hydromorphone syringe). Such treatment has been shown to reduce acute postoperative pain and pain in the ICU setting [81]. There is no data on the use of ketamine in association with PCA in ICU pregnant patients; however the literature from non-obstetric perioperative and ICU patients seems sufficiently robust to consider this therapeutic option for pregnant patients in the ICU [109]. Of note, in ICU mechanically ventilated adult patients, the use of ketamine is associated with decreased opioid use, but is also associated with increased use of dexmedetomidine and ziprasidone to achieve and maintain sedation [110].

39.5.5 Dexmedetomidine

Dexmedetomidine is a selective alpha-2 adrenergic receptor agonist that has both sedative and analgesic properties, with minimal respiratory

depression. Dexmedetomidine is rated category C in pregnancy [96]. Dexmedetomidine may be used as an analgesic and sedative agent for the pregnant patient admitted to the ICU with a painful condition. The suggested dosing is an infusion of 0.2–1.4 mcg/kg/h with or without a 1 mcg/kg bolus IV over 10–20 min [111–114]. The use of dexmedetomidine for pain management and/or sedation in the parturient has only recently begun to be reported [112–116]. At this time there are only a handful of studies available on its use specifically in the ICU in the pregnant population [113–115]. However, dexmedetomidine has minimal placental transfer and can modulate the release of catecholamines, which also makes it an interesting option for blood pressure control in women with preeclampsia. There is evidence to suggest its utility in women with ongoing severe hypertension from eclampsia as it blunts the adrenergic response, particularly in the post-partum management phase in the ICU [111, 113, 114, 117]. The use of intravenous dexmedetomidine several hours before cesarean delivery has been associated with either no effect on the neonate [116] or minor neonatal bradycardia [117].

39.5.6 Gabapentinoids

Gabapentinoids include structurally similar gabapentin and pregabalin. Their efficacy to treat neuropathic pain lies in their binding to voltage-gated calcium channels in the central nervous system which decreases neurotransmitter release by reducing calcium influx through these channels [118]. The advantage of pregabalin over gabapentin is a faster absorption and a more linear pharmacokinetic profile, as well as less risk of side effects such as sedation and dizziness [118]. Their indication to treat neuropathic pain is generally undisputed; however studies have been contradictory in their use as a component of multimodal analgesia to treat acute pain [119, 120]. In addition, the risk of congenital malformations when gabapentinoids are used during pregnancy cannot be ruled out [121]. Thus, based on recent data on uncertain benefits in acute pain and the potential for fetal risk, the addition of gabapentinoids for the treatment of acute pain in the critically ill pregnant patient needs to be evaluated on a case by case basis.

39.6 Systemic Sedation

When pain relief is difficult to achieve despite multimodal regional and systemic analgesia (with or without opioid IV PCA), sedation may be useful.

Propofol and volatile anesthetics (using the AnaConDa device, for instance) are both options for ICU sedation. Predicting fetal in utero exposure and possible toxicity of sedative agents is impossible, as it depends on maternal factors such as organ failure, blood flow and cardiac output, metabolism, genetics, and also on the extent (dose) and duration of the required sedation. The toxicity of most sedative drugs has been with regard to fetal brain development has been evaluated in multiple animal models. All anesthetic agents induce an increased rate of neuroapoptosis in the fetal brain [122]. Whether this neuroapoptosis using high doses of sedative agents has a significant impact on future brain development of the child and learning abilities remains unclear [123].

39.7 Clinical Scenarios Specific to the Obstetric Patient

39.7.1 The Opioid-Tolerant Obstetric Patient

In the United States, the prevalence of opioid abuse or dependence during pregnancy has quadrupled from 0.15% (1999) to 0.65% (2014), and this represents a major public health problem [124]. More women are using prescription opioids, illegal opioids, and opioid-substitution therapy. Pregnant women addicted to opioids often suffer from associated mental health conditions (e.g., depression, anxiety, trauma, and post-traumatic stress), present with lack of prenatal care, and have an increased risk of fetal growth

abnormalities or death [125]. These pregnant women are challenging to manage in the ICU due to their multiple, and often illicit, drug use.

Avoiding withdrawal is essential for the mother and the fetus/neonate (in utero or at birth). When admitted to the ICU, it is recommended to maintain the same opioid at the usual daily dose (possibly in divided doses) and treat any acute pain that may concurrently be present with additional analgesic strategies (neuraxial analgesia, blocks) and systemic adjuvants [97]. It is strongly recommended to involve the chronic pain team to create an adapted analgesia plan, particularly if women are on medication-assisted treatment (MAT). In women receiving stable doses of methadone or buprenorphine, maintaining usual therapy is crucial. Of note, buprenorphine has been associated with a lower risk of overdose [126], fewer drug interactions, and a decrease in illicit drug use compared to methadone [127], as well as lower rates of severe NOWS [127, 128]. However, in some cases receiving buprenorphine, treatment may be switched to conventional opioids if an elective procedure is indicated and time allows [129]. Recently, the FDA has approved a long-lasting implant that provides buprenorphine for as long as 6 months, but no data exist on its use in pregnant women.

Management of acute severe pain in women on MAT may require the use of adjuvants such as ketamine or dexmedetomidine. In terms of opioid choice, an IV PCA of hydromorphone, due to its high μ-opioid receptor affinity and low Ki value, has been suggested to be more effective than other opioids in overcoming the agonist/antagonist properties of buprenorphine [130].

39.7.2 Sickle Cell Crisis During Pregnancy

Women with sickle cell anemia are at significantly increased risk for vaso-occlusive crisis (VOC) and acute chest syndrome (ACS) during pregnancy due to the hypercoagulable state, worsening anemia, vascular stasis, and increased metabolic demands accompanying pregnancy [131, 132].

Risk factors for sickle cell crises include hypoxia, cold, dehydration, infection, and stress [131]. These women are often admitted for management of sickle-cell events during pregnancy, and over 50% will have at least one painful event during pregnancy [131, 133]. The risk of maternal mortality with sickle cell disease is over 14 times higher than for pregnancies without the disease [134]. The pain of VOC and ACS is typically ischemic pain; end-arterioles become occluded with sickled erythrocytes, eventually leading to hemolysis and end organ microinfarction [131, 132].

Systemic analgesia is beneficial mainly when combined with regional analgesia. Recommendations for pain management include systemic opioid analgesia; however it is often insufficient when given alone [131, 132]. We recommend that when possible and relevant, the first line of treatment for sickle cell crisis pain be regional analgesia (e.g., epidural or a regional plexus block). Several case reports describe the use of epidural analgesia for sickle cell crisis during pregnancy and conclude that neuraxial analgesia is highly recommended [132, 135, 136]. The advantages of neuraxial or regional analgesia are twofold. In addition to effective analgesia, local anesthetics also cause a sympathetic block. The vasodilation accompanying this block confers the additional benefit of treatment of the VOC [132].

39.7.3 Blunt Thoracic Trauma in the Obstetric Patient

Trauma is common in pregnant women (see Chap. 34). Rib fractures are the most common injury in blunt thoracic trauma, occurring in up to 7–10% of all trauma cases in some areas of the world [137]. The mortality rate accompanying multiple rib fractures may be as high as 10% [137, 138]. Many of the complications leading to poor outcomes are due to pain-related changes in breathing mechanics, including the inability to clear airway secretions by coughing and lack of deep breathing. In pregnancy, the mechanics of breathing are physiologically altered as described above. Therefore effective pain management is

crucial for prevention of complications. With one or two fractured ribs, the risk of complications and mortality is low since respiratory mechanics are only minimally impaired; therefore non-opioid analgesics suffice for pain management [139]. However, when three or more ribs are fractured, regional analgesic/anesthetic approaches such as thoracic epidural analgesia, paravertebral blocks, intercostal blocks, or a serratus anterior plane block are recommended [67, 137, 139, 140]. Ideally continuous regional analgesia should be provided for several days. This can be achieved using a catheter placed either epidurally or during a paravertebral or a serratus anterior plane block. A handful of reports have described an increased risk of rib fractures in pregnancy, often related to coughing—possibly related to a change in chest-wall mechanics with increased stress placed on the ribs [141, 142]. In one case a T9 rib fracture occurring at 28 weeks of gestation was treated with maternal intercostal nerve blocks at T8 and T9. The resultant pain relief lasted 16 h. To prevent the risks of repeated intercostal blocks, continuous thoracic epidural analgesia was then successfully administered at level T8-T9 with the catheter left in place for days [143].

39.7.4 Acute Pancreatitis

Has an overall mortality of 1%, which increases to 30% in its severe form. Pain from acute pancreatitis is typically extremely severe and requires adequate management. Thoracic epidural analgesia is usually effective in achieving adequate pain relief and provides a beneficial sympathectomy which improves splanchnic circulation [144, 145]. In animal models, thoracic epidural analgesia results in decreased severity of pancreatitis and better survival [146, 147].

A large multicenter study is underway in non-pregnant critically ill patients to test the hypothesis that thoracic epidural analgesia in addition to standard care will improve respiratory outcomes in patients with acute pancreatitis compared to standard care alone [148]. Although there are no reports on the use of epidural analgesia for acute pancreatitis in the obstetric population, such a recommendation may be extrapolated from recent clinical reports and a review of the literature which support the use of thoracic epidural analgesia for non-pregnant patients with acute pancreatitis to manage pain and improve perfusion [144–147].

In pregnancy, most cases of acute pancreatitis are secondary to gallstones. Less common, but also seen, are cases of hypertriglyceride-induced pancreatitis. Some women may require endoscopic sphincterectomy or stent placement as treatment. There are several reports on the obstetric management of acute pancreatitis in pregnant women, but few describe the management of analgesia throughout the acute episode or anesthetic management at delivery [149]. Many describe a fatal outcome [150–152], yet little address is given to the option of epidural analgesia as a treatment modality in this population [153]. Provision of epidural analgesia for management of pain during acute pancreatitis may be even more important in pregnancy, when regional analgesia and pain management may improve both maternal and neonatal outcomes.

39.7.5 Preeclampsia and Complications Associated with Hypertensive Disorders of Pregnancy

Preeclampsia is associated with life-threatening complications such as cerebral hemorrhage, liver rupture, and peripartum cardiomyopathy, and many women with preeclampsia are admitted to the ICU before or after delivery [154] (see Chap. 16).

Preeclampsia with severe features may be associated with right upper quadrant pain, pleuritic pain, or headache. Continuous, prolonged epidural analgesia is an effective solution for trunk pain. The benefits of epidural analgesia in these women extend beyond pain relief; local anesthetic infusion may contribute to antenatal and postpartum blood pressure control [155, 156]. A pilot study of antepartum continuous epidural analgesia (tunnelized at the thoracic

level) has been shown to improve splanchnic and uteroplacental blood flow in women with early-onset preeclampsia [129]. Therefore neuraxial analgesia should not be withheld for fear of adverse fetal outcomes in preeclamptic pregnancies. As previously discussed, careful assessment of platelet and coagulation function is mandatory prior to administering neuraxial analgesia.

39.7.6 Fatty Liver of Pregnancy

Acute fatty liver of pregnancy (AFLP) is a rare mitochondrial disease that manifests in the later stages of gestation with potentially fatal consequences to both mother and child (see Chap. 33). According to a 2008 UK cohort study, the incidence of AFLP is 5.0/100,000 maternities [157]. In the United States, a cohort study in 2013 reports an incidence of 1/10,000 births [158]. Although the mortality rates have much decreased since the disease was described in 1940 by Sheehan, the estimated maternal mortality still approximates 10% [159]. AFLP appears in the third trimester of pregnancy and seems to be a result of the buildup of metabolites from inherited maternal defects. The metabolites accumulate leaving microvesicular infiltrates or steatosis in hepatocytes that will likely result in severe hepatic dysfunction. AFLP has no medical treatment, but delivery of the fetus abates the disease. Postoperative pain management is an important aspect of patient care and is particularly challenging in these women. With impaired hepatic function, most opioids will be contraindicated as they will worsen mental status and increase the risk for respiratory depression. Acetaminophen is relatively contraindicated given the acute and severe hepatic dysfunction. Nonsteroidal anti-inflammatory drugs are also relatively contraindicated because of platelet aggregation inhibition in the postsurgical setting, as well as the likelihood of acute kidney disease often seen with AFLP [160].

AFLP also often presents with inherent coagulopathy, which is a major risk factor for the development of epidural hematoma with neuraxial techniques. Thus, neuraxial analgesia is contraindicated in these patients [51]. A TAP block may be suitable for postoperative analgesia after cesarean delivery to avoid the toxicities and side effects related to acetaminophen, NSAIDs, and opioids [58]. However, TAP blocks using 3 mg/kg of ropivacaine produce venous plasma concentrations that are potentially neurotoxic, although broadly consistent with plasma levels found after injection at other comparable sites [161]. This might be even more true in AFLP patients in the ICU with liver and renal dysfunction, where a TAP block may expose the patient to a high risk of toxicity [162].

In summary, for women with AFLP admitted to the ICU, recommendations for pain management include the use of titrated doses of opioids for sedation (remifentanil may be best suited), with monitoring of respiratory status, and whenever indicated and possible in combination with the use of regional analgesia such as TAP blocks. Regional analgesia should be used with caution; the initial and maintenance doses should be decreased, and if local anesthesia toxicity (LAST) is suspected, plasma concentrations of the local anesthetics should be evaluated and appropriate treatment offered.

39.7.7 Specific Postpartum Considerations in the Breastfeeding Patient

In the past, breastfeeding was considered contraindicated during treatment with opioids or sedative drugs. Recent recommendations make this no longer true, and in general, a mother may resume breastfeeding once awake, stable, and alert despite receiving anesthesia or sedation [163, 164]. In 2017, the FDA issued a warning against the use of codeine and tramadol in pregnant patients and particularly in breastfeeding women [165]. These drugs are metabolized by CYP2D6, and a subset of the population are ultra-metabolizers. Postpartum, this characteristic leads to excessive amounts of morphine in maternal breastmilk, which may increase the risk of neonatal overdose and respiratory depression.

The current recommendation is to favor multimodal opioid-sparing strategies and to limit the use of opioids *whenever possible* in order to avoid unnecessary maternal and neonatal sedation [106, 166, 167].

39.8 Conclusion

As in all instances of pain management in critically ill patients, and in the specific context of the pregnant patient admitted to the ICU, several key elements are important. Appropriately treating maternal pain benefits both the mother and the fetus. Untreated pain may negatively impact maternal oxygenation, placental perfusion, and hence fetal acid base status. A multimodal analgesia regimen, which includes regional analgesia whenever possible, is the optimal approach to pain control. This approach diminishes the likelihood of unwanted medication effects on both mother and child. Pain management for pregnant patients in an ICU setting requires several types of expertise; therefore it warrants a multidisciplinary approach. Anesthesiologists, intensive care physicians, obstetricians, and neonatologists must all be involved. Finally, the analgesia plan must take into account the resources available and the expertise of the clinicians providing care.

References

1. Baskett TF. Epidemiology of obstetric critical care. Best Pract Res Clin Obstet Gynaecol. 2008;22(5):763–74.
2. Bielefeldt K, Gebhart GF. Visceral pain: basic mechanisms. In: McMahon SB, Koltzenburg M, editors. Wall and melzack's textbook of pain. 5th ed. Philadelphia: Elsevier; 2006. p. 721–36.
3. ACOG Committee Opinion No. 742: Postpartum Pain Management. Obstet Gynecol. 2018;132(1):e35-e43.
4. Motoyama EK, Rivard G, Acheson F, Cook CD. Adverse effect of maternal hyperventilation on the foetus. Lancet. 1966;1(7432):286–8.
5. Pearson JF, Davies P. The effect on continuous lumbar epidural analgesia on maternal acid-base balance and arterial lactate concentration during the second stage of labour. J Obstet Gynaecol Br Commonw. 1973;80(3):225–9.
6. Pearson JF, Davies P. The effect of continuous lumbar epidural analgesia on the acid-base status of maternal arterial blood during the first stage of labour. J Obstet Gynaecol Br Commonw. 1973;80(3):218–24.
7. Pearson JF, Davies P. The effect of continuous lumbar epidural analgesia upon fetal acid-base status during the second stage of labour. J Obstet Gynaecol Br Commonw. 1974;81(12):975–9.
8. Pearson JF, Davies P. The effect of continuous lumbar epidural analgesia upon fetal acid-base status during the first stage of labour. J Obstet Gynaecol Br Commonw. 1974;81(12):971–4.
9. Thalme B, Belfrage P, Raabe N. Lumbar epidural analgesia in labour. I. Acid-base balance and clinical condition of mother, fetus and newborn child. Acta Obstet Gynecol Scand. 1974;53(1):27–35.
10. Huch R. Maternal hyperventilation and the fetus. J Perinat Med. 1986;14(1):3–17.
11. Reynolds F. The effects of maternal labour analgesia on the fetus. Best Pract Res Clin Obstet Gynaecol. 2010;24(3):289–302.
12. Reynolds F. Labour analgesia and the baby: good news is no news. Int J Obstet Anesth. 2011;20(1):38–50.
13. Lederman RP, Lederman E, Work BA Jr, McCann DS. The relationship of maternal anxiety, plasma catecholamines, and plasma cortisol to progress in labor. Am J Obstet Gynecol. 1978;132(5):495–500.
14. Ohno H, Yamashita K, Yahata T, Doi R, Kawamura M, Mure K, et al. Maternal plasma concentrations of catecholamines and cyclic nucleotides during labor and following delivery. Res Commun Chem Pathol Pharmacol. 1986;51(2):183–94.
15. Segal S, Wang SY. The effect of maternal catecholamines on the caliber of gravid uterine microvessels. Anesth Anal. 2008;106(3):888–92. table of contents.
16. Everson GT. Gastrointestinal motility in pregnancy. Gastroenterol Clin N Am. 1992;21(4):751–76.
17. Gaiser R. Chapter 2: physiologic changes of pregnancy. In: Chestnut's obstetric anesthesia. Amsterdam: Elsevier; 2014. p. 15–38.
18. D'Alton ME, Friedman AM, Smiley RM, Montgomery DM, Paidas MJ, D'Oria R, et al. National partnership for maternal safety: consensus bundle on venous thromboembolism. Anesth Analg. 2016;123(4):942–9.
19. Leffert L, Butwick A, Carvalho B, Arendt K, Bates SM, Friedman A, et al. The society for obstetric anesthesia and perinatology consensus statement on the anesthetic management of pregnant and postpartum women receiving thromboprophylaxis or higher dose anticoagulants. Anesth Analg. 2018;126(3):928–44.
20. Hawkins JL. Epidural analgesia for labor and delivery. N Engl J Med. 2010;362(16):1503–10.
21. Block BM, Liu SS, Rowlingson AJ, Cowan AR, Cowan JA Jr, Wu CL. Efficacy of postoperative epidural analgesia: a meta-analysis. JAMA. 2003;290(18):2455–63.
22. Morin AM, Kerwat KM, Klotz M, Niestolik R, Ruf VE, Wulf H, et al. Risk factors for bacterial cath-

eter colonization in regional anaesthesia. BMC Anesthesiol. 2005;5(1):1.
23. Wang LP, Hauerberg J, Schmidt JF. Incidence of spinal epidural abscess after epidural analgesia: a national 1-year survey. Anesthesiology. 1999;91(6):1928–36.
24. Bomberg H, Kubulus C, Herberger S, Wagenpfeil S, Kessler P, Steinfeldt T, et al. Tunnelling of thoracic epidural catheters is associated with fewer catheter-related infections: a retrospective registry analysis. Br J Anaesth. 2016;116(4):546–53.
25. Visser WA, Lee RA, Gielen MJ. Factors affecting the distribution of neural blockade by local anesthetics in epidural anesthesia and a comparison of lumbar versus thoracic epidural anesthesia. Anesth Analg. 2008;107(2):708–21.
26. Barclay DL, Renegar OJ, Nelson EW Jr. The influence of inferior vena cava compression on the level of spinal anesthesia. Am J Obstet Gynecol. 1968;101(6):792–800.
27. Hirabayashi Y, Shimizu R, Fukuda H, Saitoh K, Furuse M. Anatomical configuration of the spinal column in the supine position. II. Comparison of pregnant and non-pregnant women. Br J Anaesth. 1995;75(1):6–8.
28. Patel NP, El-Wahab N, Fernando R, Wilson S, Robson SC, Columb MO, et al. Fetal effects of combined spinal-epidural vs epidural labour analgesia: a prospective, randomised double-blind study. Anaesthesia. 2014;69(5):458–67.
29. Van de Velde M, Teunkens A, Hanssens M, Vandermeersch E, Verhaeghe J. Intrathecal sufentanil and fetal heart rate abnormalities: a double-blind, double placebo-controlled trial comparing two forms of combined spinal epidural analgesia with epidural analgesia in labor. Anesth Anal. 2004;98(4):1153–9. table of contents.
30. Abrao KC, Francisco RP, Miyadahira S, Cicarelli DD, Zugaib M. Elevation of uterine basal tone and fetal heart rate abnormalities after labor analgesia: a randomized controlled trial. Obstet Gynecol. 2009;113(1):41–7.
31. Lanz E, Theiss D, Kellner G, Zimmer M, Staudte HW. Assessment of motor blockade during epidural anesthesia. Anesth Analg. 1983;62(10):889–93.
32. Van de Velde M, Schepers R, Berends N, Vandermeersch E, De Buck F. Ten years of experience with accidental dural puncture and post-dural puncture headache in a tertiary obstetric anaesthesia department. Int J Obstet Anesth. 2008;17(4):329–35.
33. Franz AM, Jia SY, Bahnson HT, Goel A, Habib AS. The effect of second-stage pushing and body mass index on postdural puncture headache. J Clin Anesth. 2017;37:77–81.
34. D'Angelo R, Smiley RM, Riley ET, Segal S. Serious complications related to obstetric anesthesia: the serious complication repository project of the Society for Obstetric Anesthesia and Perinatology. Anesthesiology. 2014;120(6):1505–12.
35. Dahl JB, Jeppesen IS, Jorgensen H, Wetterslev J, Moiniche S. Intraoperative and postoperative analgesic efficacy and adverse effects of intrathecal opioids in patients undergoing cesarean section with spinal anesthesia: a qualitative and quantitative systematic review of randomized controlled trials. Anesthesiology. 1999;91(6):1919–27.
36. Baraka A, Noueihid R, Hajj S. Intrathecal injection of morphine for obstetric analgesia. Anesthesiology. 1981;54(2):136–40.
37. Booth JL, Harris LC, Eisenach JC, Pan PH. A randomized controlled trial comparing two multimodal analgesic techniques in patients predicted to have severe pain after cesarean delivery. Anesth Analg. 2016;122(4):1114–9.
38. Carvalho B. Respiratory depression after neuraxial opioids in the obstetric setting. Anesth Analg. 2008;107(3):956–61.
39. Bromage PR, Camporesi EM, Durant PA, Nielsen CH. Nonrespiratory side effects of epidural morphine. Anesth Analg. 1982;61(6):490–5.
40. Bromage PR, Camporesi EM, Durant PA, Nielsen CH. Rostral spread of epidural morphine. Anesthesiology. 1982;56(6):431–6.
41. Abboud TK, Dror A, Mosaad P, Zhu J, Mantilla M, Swart F, et al. Mini-dose intrathecal morphine for the relief of post-cesarean section pain: safety, efficacy, and ventilatory responses to carbon dioxide. Anesth Analg. 1988;67(2):137–43.
42. Hess PE, Vasudevan A, Snowman C, Pratt SD. Small dose bupivacaine-fentanyl spinal analgesia combined with morphine for labor. Anesth Anal. 2003;97(1):247–52. table of contents.
43. Yeh HM, Chen LK, Shyu MK, Lin CJ, Sun WZ, Wang MJ, et al. The addition of morphine prolongs fentanyl-bupivacaine spinal analgesia for the relief of labor pain. Anesth Analg. 2001;92(3):665–8.
44. Vasudevan A, Snowman CE, Sundar S, Sarge TW, Hess PE. Intrathecal morphine reduces breakthrough pain during labour epidural analgesia. Br J Anaesth. 2007;98(2):241–5.
45. Rust LA, Waring RW, Hall GL, Nelson EI. Intrathecal narcotics for obstetric analgesia in a community hospital. Am J Obstet Gynecol. 1994;170(6):1643–6. discussion 6–8.
46. Ladha KS, Kato R, Tsen LC, Bateman BT, Okutomi T. A prospective study of post-cesarean delivery hypoxia after spinal anesthesia with intrathecal morphine 150mug. Int J Obstet Anesth. 2017;32:48–53.
47. American Society of Anesthesiologists Task Force on Neuraxial Oioids, Horlocker TT, Burton AW, Connis RT, Hughes SC, Nickinovich DG, et al. Practice guidelines for the prevention, detection, and management of respiratory depression associated with neuraxial opioid administration. Anesthesiology. 2009;110(2):218–30.
48. Lee LO, Bateman BT, Kheterpal S, Klumpner TT, Housey M, Aziz MF, et al. Risk of epidural hema-

toma after neuraxial techniques in thrombocytopenic parturients: a report from the multicenter perioperative outcomes group. Anesthesiology. 2017;126(6):1053–63.
49. Goodier CG, Lu JT, Hebbar L, Segal BS, Goetzl L. Neuraxial anesthesia in parturients with thrombocytopenia: a multisite retrospective cohort study. Anesth Analg. 2015;121(4):988–91.
50. Camann W. Obstetric neuraxial anesthesia contraindicated? Really? Time to rethink old dogma. Anesth Analg. 2015;121(4):846–8.
51. Horlocker TT, Wedel DJ, Rowlingson JC, Enneking FK, Kopp SL, Benzon HT, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine evidence-based guidelines (third edition). Reg Anesth Pain Med. 2010;35(1):64–101.
52. Horlocker TT, Wedel DJ. Infectious complications of regional anesthesia. Best Pract Res Clin Anaesthesiol. 2008;22(3):451–75.
53. DeLeon A, De Oliveira GS, Kalayil M, Narang S, McCarthy RJ, Wong CA. The incidence of coagulopathy in pregnant patients with intrahepatic cholestasis: should we delay or avoid neuraxial analgesia? J Clin Anesth. 2014;26(8):623–7.
54. Kanazi GE, Aouad MT, Abdallah FW, Khatib MI, Adham AM, Harfoush DW, et al. The analgesic efficacy of subarachnoid morphine in comparison with ultrasound-guided transversus abdominis plane block after cesarean delivery: a randomized controlled trial. Anesth Analg. 2010;111(2):475–81.
55. Loane H, Preston R, Douglas MJ, Massey S, Papsdorf M, Tyler J. A randomized controlled trial comparing intrathecal morphine with transversus abdominis plane block for post-cesarean delivery analgesia. Int J Obstet Anesth. 2012;21(2):112–8.
56. Brogi E, Kazan R, Cyr S, Giunta F, Hemmerling TM. Transversus abdominal plane block for postoperative analgesia: a systematic review and meta-analysis of randomized-controlled trials. Can J Anaesth. 2016;63(10):1184–96.
57. McDonnell JG, Curley G, Carney J, Benton A, Costello J, Maharaj CH, et al. The analgesic efficacy of transversus abdominis plane block after cesarean delivery: a randomized controlled trial. Anesth Anal. 2008;106(1):186–91. table of contents.
58. Chin KJ, McDonnell JG, Carvalho B, Sharkey A, Pawa A, Gadsden J. Essentials of our current understanding: abdominal wall blocks. Reg Anesth Pain Med. 2017;42(2):133–83.
59. Bollag L, Richebe P, Ortner C, Landau R. Transversus abdominis plane catheters for post-cesarean delivery analgesia: a series of five cases. Int J Obstet Anesth. 2012;21(2):176–80.
60. Oppenheimer AJ, Fiala TGS, Oppenheimer DC. Direct transversus abdominis plane blocks with exparel during abdominoplasty. Ann Plast Surg. 2016;77(5):499–500.
61. Kadam VR. Ultrasound guided quadratus lumborum block or posterior transversus abdominis plane block catheter infusion as a postoperative analgesic technique for abdominal surgery. J Anaesthesiol Clin Pharmacol. 2015;31(1):130–1.
62. Gomez-Rios MA, Gomez-Rios D. Continuous bilateral quadratus lumborum block after abdominal surgery. J Anaesthesiol Clin Pharmacol. 2017;33(2):261–2.
63. Blanco R, Ansari T, Girgis E. Quadratus lumborum block for postoperative pain after caesarean section: a randomised controlled trial. Eur J Anaesthesiol. 2015;32(11):812–8.
64. Mayes J, Davison E, Panahi P, Patten D, Eljelani F, Womack J, et al. An anatomical evaluation of the serratus anterior plane block. Anaesthesia. 2016;71(9):1064–9.
65. Kunigo T, Murouchi T, Yamamoto S, Yamakage M. Injection volume and anesthetic effect in serratus plane block. Reg Anesth Pain Med. 2017;42(6):737–40.
66. Kim DH, Oh YJ, Lee JG, Ha D, Chang YJ, Kwak HJ. Efficacy of ultrasound-guided serratus plane block on postoperative quality of recovery and analgesia after video-assisted thoracic surgery: a randomized, triple-blind, placebo-controlled study. Anesth Anal. 2018;126:1353.
67. Kunhabdulla NP, Agarwal A, Gaur A, Gautam SK, Gupta R, Agarwal A. Serratus anterior plane block for multiple rib fractures. Pain Physician. 2014;17(5):E651–3.
68. Lancaster P, Chadwick M. Liver trauma secondary to ultrasound-guided transversus abdominis plane block. Br J Anaesth. 2010;104(4):509–10.
69. Farooq M, Carey M. A case of liver trauma with a blunt regional anesthesia needle while performing transversus abdominis plane block. Reg Anesth Pain Med. 2008;33(3):274–5.
70. Salaria ON, Kannan M, Kerner B, Goldman H. A rare complication of a TAP block performed after caesarean delivery. Case Rep Anesthesiol. 2017;2017:1072576.
71. Ilfeld BM. Continuous peripheral nerve blocks: an update of the published evidence and comparison with novel, alternative analgesic modalities. Anesth Anal. 2017;124(1):308–35.
72. Chalifoux F, Colin F, St-Pierre P, Godin N, Brulotte V. Low dose intravenous dexamethasone (4 mg and 10 mg) significantly prolongs the analgesic duration of single-shot interscalene block after arthroscopic shoulder surgery: a prospective randomized placebo-controlled study. Can J Anaesth. 2017;64(3):280–9.
73. Baeriswyl M, Kirkham KR, Jacot-Guillarmod A, Albrecht E. Efficacy of perineural vs systemic dexamethasone to prolong analgesia after peripheral nerve block: a systematic review and meta-analysis. Br J Anaesth. 2017;119(2):183–91.
74. Lirk P, Rutten MV, Haller I, Stevens MF, Laudolff-Birmingham J, Hollmann M, et al. Management of the patient with diabetic peripheral neuropathy

presenting for peripheral regional anesthesia: a European survey and review of literature. Minerva Anestesiol. 2013;79(9):1039–48.
75. Ten Hoope W, Looije M, Lirk P. Regional anesthesia in diabetic peripheral neuropathy. Curr Opin Anaesthesiol. 2017;30(5):627–31.
76. Dhir S, Balasubramanian S, Ross D. Ultrasound-guided peripheral regional blockade in patients with Charcot-Marie-tooth disease: a review of three cases. Can J Anaesth. 2008;55(8):515–20.
77. Patzkowski MS. Peripheral nerve blocks in patients with Ehlers-Danlos syndrome, hypermobility type: a report of 2 cases. J Clin Anesth. 2016;29:50–3.
78. Carvalho B, Granot M, Sultan P, Wilson H, Landau R. A longitudinal study to evaluate pregnancy-induced endogenous analgesia and pain modulation. Reg Anesth Pain Med. 2016;41(2):175–80.
79. WHO's cancer pain ladder for adults. http://www.who.int/cancer/palliative/painladder/en/. Accessed 11 Jun 2018
80. Helander EM, Menard BL, Harmon CM, Homra BK, Allain AV, Bordelon GJ, et al. Multimodal analgesia, current concepts, and acute pain considerations. Curr Pain Headache Rep. 2017;21(1):3.
81. Schwenk ES, Viscusi ER, Buvanendran A, Hurley RW, Wasan AD, Narouze S, et al. Consensus guidelines on the use of intravenous ketamine infusions for acute pain management from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of pain medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med. 2018;43(5):456–66.
82. Interrante JD, Ailes EC, Lind JN, Anderka M, Feldkamp ML, Werler MM, et al. Risk comparison for prenatal use of analgesics and selected birth defects, National Birth Defects Prevention Study 1997-2011. Ann Epidemiol. 2017;27(10):645–53.e2.
83. Li DK, Ferber JR, Odouli R, Quesenberry C. Use of nonsteroidal antiinflammatory drugs during pregnancy and the risk of miscarriage. Am J Obstet Gynecol. 2018;219(3):275.e1–8.
84. Nakhai-Pour HR, Broy P, Sheehy O, Berard A. Use of nonaspirin nonsteroidal anti-inflammatory drugs during pregnancy and the risk of spontaneous abortion. CMAJ. 2011;183(15):1713–20.
85. Dathe K, Fietz AK, Pritchard LW, Padberg S, Hultzsch S, Meixner K, et al. No evidence of adverse pregnancy outcome after exposure to ibuprofen in the first trimester—evaluation of the national Embryotox cohort. Reprod Toxicol. 2018;79:32–8.
86. Tanaka S, Hori S, Satoh H, Sawada Y. Prediction of fetal ductus arteriosus constriction by systemic and local dermatological formulations of NSAIDs based on PK/PD analysis. Int J Clin Pharmacol Ther. 2016;54(10):782–94.
87. Viteri OA, England JA, Alrais MA, Lash KA, Villegas MI, Ashimi Balogun OA, et al. Association of nonsteroidal antiinflammatory drugs and postpartum hypertension in women with preeclampsia with severe features. Obstet Gynecol. 2017;130(4):830–5.
88. Nikkola EM, Ekblad UU, Kero PO, Alihanka JJ, Salonen MA. Intravenous fentanyl PCA during labour. Can J Anaesth. 1997;44(12):1248–55.
89. Morley-Forster PK, Reid DW, Vandeberghe H. A comparison of patient-controlled analgesia fentanyl and alfentanil for labour analgesia. Can J Anaesth. 2000;47(2):113–9.
90. Marwah R, Hassan S, Carvalho JC, Balki M. Remifentanil versus fentanyl for intravenous patient-controlled labour analgesia: an observational study. Can J Anaesth. 2012;59(3):246–54.
91. Miyakoshi K, Tanaka M, Morisaki H, Kim SH, Hosokawa Y, Matsumoto T, et al. Perinatal outcomes: intravenous patient-controlled fentanyl versus no analgesia in labor. J Obstet Gynaecol Res. 2013;39(4):783–9.
92. Kapila A, Glass PS, Jacobs JR, Muir KT, Hermann DJ, Shiraishi M, et al. Measured context-sensitive half-times of remifentanil and alfentanil. Anesthesiology. 1995;83(5):968–75.
93. Aaronson J, Abramovitz S, Smiley R, Tangel V, Landau R. A survey of intravenous remifentanil use for labor analgesia at academic medical centers in the United States. Anesth Analg. 2017;124(4):1208–10.
94. Stover MW, Davis JM. Opioids in pregnancy and neonatal abstinence syndrome. Semin Perinatol. 2015;39(7):561–5.
95. Pryor JR, Maalouf FI, Krans EE, Schumacher RE, Cooper WO, Patrick SW. The opioid epidemic and neonatal abstinence syndrome in the USA: a review of the continuum of care. Arch Dis Child Fetal Neonatal Ed. 2017;102(2):F183–F7.
96. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 11th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2017.
97. Committee on Obstetric P. Committee opinion no. 711: opioid use and opioid use disorder in pregnancy. Obstet Gynecol. 2017;130(2):e81–94.
98. Bracken MB, Holford TR. Exposure to prescribed drugs in pregnancy and association with congenital malformations. Obstet Gynecol. 1981;58(3):336–44.
99. Jick H, Holmes LB, Hunter JR, Madsen S, Stergachis A. First-trimester drug use and congenital disorders. JAMA. 1981;246(4):343–6.
100. Broussard CS, Rasmussen SA, Reefhuis J, Friedman JM, Jann MW, Riehle-Colarusso T, et al. Maternal treatment with opioid analgesics and risk for birth defects. Am J Obstet Gynecol. 2011;204(4):314 e1–11.
101. Yazdy MM, Mitchell AA, Tinker SC, Parker SE, Werler MM. Periconceptional use of opioids and the risk of neural tube defects. Obstet Gynecol. 2013;122(4):838–44.
102. Rothman KJ. Causes. Am J Epidemiol. 1976;104(6):587–92.
103. Zierler S, Rothman KJ. Congenital heart disease in relation to maternal use of Bendectin and

other drugs in early pregnancy. N Engl J Med. 1985;313(6):347–52.
104. Shaw GM, Malcoe LH, Swan SH, Cummins SK, Schulman J. Congenital cardiac anomalies relative to selected maternal exposures and conditions during early pregnancy. Eur J Epidemiol. 1992;8(5):757–60.
105. Nezvalova-Henriksen K, Spigset O, Nordeng H. Effects of codeine on pregnancy outcome: results from a large population-based cohort study. Eur J Clin Pharmacol. 2011;67(12):1253–61.
106. Martin E, Vickers B, Landau R, Reece-Stremtan S. ABM clinical protocol #28, peripartum analgesia and anesthesia for the breastfeeding mother. Breastfeed Med. 2018;13(3):164–71.
107. Koren G, Cairns J, Chitayat D, Gaedigk A, Leeder SJ. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. Lancet. 2006;368(9536):704.
108. Obradovic AL, Atluri N, Dalla Massara L, Oklopcic A, Todorovic NS, Katta G, et al. Early exposure to ketamine impairs axonal pruning in developing mouse hippocampus. Mol Neurobiol. 2018;55(1):164–72.
109. Wang L, Johnston B, Kaushal A, Cheng D, Zhu F, Martin J. Ketamine added to morphine or hydromorphone patient-controlled analgesia for acute postoperative pain in adults: a systematic review and meta-analysis of randomized trials. Can J Anaesth. 2016;63(3):311–25.
110. Pruskowski KA, Harbourt K, Pajoumand M, Chui SJ, Reynolds HN. Impact of ketamine use on adjunctive analgesic and sedative medications in critically Ill trauma patients. Pharmacotherapy. 2017;37(12):1537–44.
111. Eskandr AM, Metwally AA, Ahmed AA, Elfeky EM, Eldesoky IM, Obada MA, et al. Dexmedetomidine as a part of general anaesthesia for caesarean delivery in patients with pre-eclampsia: a randomised double-blinded trial. Eur J Anaesthesiol. 2018;35(5):372–8.
112. El-Tahan MR, Mowafi HA, Al Sheikh IH, Khidr AM, Al-Juhaiman RA. Efficacy of dexmedetomidine in suppressing cardiovascular and hormonal responses to general anaesthesia for caesarean delivery: a dose-response study. Int J Obstet Anesth. 2012;21(3):222–9.
113. Esmaoglu A, Ulgey A, Akin A, Boyaci A. Comparison between dexmedetomidine and midazolam for sedation of eclampsia patients in the intensive care unit. J Crit Care. 2009;24(4):551–5.
114. Rashid MR, Najeeb R, Mushtaq S, Habib R. Comparative evaluation of midazolam, dexmedetomidine, and propofol as intensive care unit sedatives in postoperative electively ventilated eclamptic patients. J Anaesthesiol Clin Pharmacol. 2017;33(3):331–6.
115. Duan M, Lee J, Bittner EA. Dexmedetomidine for sedation in the parturient with respiratory failure requiring noninvasive ventilation. Respir Care. 2012;57(11):1967–9.
116. Palanisamy A, Klickovich RJ, Ramsay M, Ouyang DW, Tsen LC. Intravenous dexmedetomidine as an adjunct for labor analgesia and cesarean delivery anesthesia in a parturient with a tethered spinal cord. Int J Obstet Anesth. 2009;18(3):258–61.
117. Abu-Halaweh SA, Al Oweidi AK, Abu-Malooh H, Zabalawi M, Alkazaleh F, Abu-Ali H, et al. Intravenous dexmedetomidine infusion for labour analgesia in patient with preeclampsia. Eur J Anaesthesiol. 2009;26(1):86–7.
118. Bockbrader HN, Wesche D, Miller R, Chapel S, Janiczek N, Burger P. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. Clin Pharmacokinet. 2010;49(10):661–9.
119. Canihuante J, Molina I, Altermatt F. Is perioperative pregabalin effective for reducing postoperative pain in major surgery? Medwave. 2017;17(9):e7115.
120. Pogatzki-Zahn EM, Segelcke D, Schug SA. Postoperative pain-from mechanisms to treatment. Pain Rep. 2017;2(2):e588.
121. Patorno E, Bateman BT, Huybrechts KF, MacDonald SC, Cohen JM, Desai RJ, et al. Pregabalin use early in pregnancy and the risk of major congenital malformations. Neurology. 2017;88(21):2020–5.
122. Soriano SG, Vutskits L, Jevtovic-Todorovic V, Hemmings HC, Neurotoxicology BJA, Neuroplasticity SG. Thinking, fast and slow: highlights from the 2016 BJA seminar on anaesthetic neurotoxicity and neuroplasticity. Br J Anaesth. 2017;119(3):443–7.
123. Davidson AJ, Disma N, de Graaff JC, Withington DE, Dorris L, Bell G, et al. Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. Lancet. 2016;387(10015):239–50.
124. Haight SC, Ko JY, Tong VT, Bohm MK, Callaghan WM. Opioid use disorder documented at delivery hospitalization—United States, 1999-2014. MMWR Morb Mortal Wkly Rep. 2018;67(31):845–9.
125. Medication-assisted treatment for opioid addiction during pregnancy. Medication-assisted treatment for opioid addiction in opioid treatment programs Treatment Improvement Protocol Series. Rockville MD: Substance Abuse and Mental Health Services Administration; 2005. p. 211–24.
126. Mozurkewich EL, Rayburn WF. Buprenorphine and methadone for opioid addiction during pregnancy. Obstet Gynecol Clin N Am. 2014;41(2):241–53.
127. Wachman EM, Warden AH, Thomas Z, Thomas-Lewis JA, Shrestha H, Nikita FNU, et al. Impact of psychiatric medication co-exposure on neonatal abstinence syndrome severity. Drug Alcohol Depend. 2018;192:45–50.
128. Minozzi S, Amato L, Bellisario C, Ferri M, Davoli M. Maintenance agonist treatments for opiate-dependent pregnant women. Cochrane Database Syst Rev. 2013;23(12):CD006318.
129. Anderson TA, Quaye ANA, Ward EN, Wilens TE, Hilliard PE, Brummett CM. To stop or not, that

is the question: acute pain management for the patient on chronic buprenorphine. Anesthesiology. 2017;126(6):1180–6.
130. Leighton BL, Crock LW. Case series of successful postoperative pain management in buprenorphine maintenance therapy patients. Anesth Analg. 2017;125(5):1779–83.
131. Patil V, Ratnayake G, Fastovets G. Clinical 'pearls' of maternal critical care part 2: sickle-cell disease in pregnancy. Curr Opin Anaesthesiol. 2017;30(3):326–34.
132. Verstraete S, Verstraete R. Successful epidural analgesia for a vaso-occlusive crisis of sickle cell disease during pregnancy: a case report. J Anesth. 2012;26(5):783–5.
133. Powars DR, Sandhu M, Niland-Weiss J, Johnson C, Bruce S, Manning PR. Pregnancy in sickle cell disease. Obstet Gynecol. 1986;67(2):217–28.
134. Oteng-Ntim E, Meeks D, Seed PT, Webster L, Howard J, Doyle P, et al. Adverse maternal and perinatal outcomes in pregnant women with sickle cell disease: systematic review and meta-analysis. Blood. 2015;125(21):3316–25.
135. Finer P, Blair J, Rowe P. Epidural analgesia in the management of labor pain and sickle cell crisis—a case report. Anesthesiology. 1988;68(5):799–800.
136. Winder AD, Johnson S, Murphy J, Ehsanipoor RM. Epidural analgesia for treatment of a sickle cell crisis during pregnancy. Obstet Gynecol. 2011;118(2 Pt 2):495–7.
137. Jensen CD, Stark JT, Jacobson LL, Powers JM, Joseph MF, Kinsella-Shaw JM, et al. Improved outcomes associated with the liberal use of thoracic epidural analgesia in patients with rib fractures. Pain Med. 2017;18(9):1787–94.
138. Flagel BT, Luchette FA, Reed RL, Esposito TJ, Davis KA, Santaniello JM, et al. Half-a-dozen ribs: the breakpoint for mortality. Surgery. 2005;138(4):717–23. discussion 23–5.
139. Ho AM, Karmakar MK, Critchley LA. Acute pain management of patients with multiple fractured ribs: a focus on regional techniques. Curr Opin Crit Care. 2011;17(4):323–7.
140. Malekpour M, Hashmi A, Dove J, Torres D, Wild J. Analgesic choice in management of rib fractures: paravertebral block or epidural analgesia? Anesth Analg. 2017;124(6):1906–11.
141. Savage D. Stress fracture of ribs in pregnancy. Lancet. 1956;270(6920):420–1.
142. Even-Tov I, Yedwab GA, Persitz E, David MP. Stress fracture of ribs in late pregnancy. Int Surg. 1979;64(5):85–7.
143. Amagada JO, Joels L, Catling S. Stress fracture of rib in pregnancy: what analgesia? J Obstet Gynaecol. 2002;22(5):559.
144. Windisch O, Heidegger CP, Giraud R, Morel P, Buhler L. Thoracic epidural analgesia: a new approach for the treatment of acute pancreatitis? Crit Care. 2016;20(1):116.
145. Sadowski SM, Andres A, Morel P, Schiffer E, Frossard JL, Platon A, et al. Epidural anesthesia improves pancreatic perfusion and decreases the severity of acute pancreatitis. World J Gastroenterol. 2015;21(43):12448–56.
146. Demirag A, Pastor CM, Morel P, Jean-Christophe C, Sielenkamper AW, Guvener N, et al. Epidural anaesthesia restores pancreatic microcirculation and decreases the severity of acute pancreatitis. World J Gastroenterol. 2006;12(6):915–20.
147. Bachmann KA, Trepte CJ, Tomkotter L, Hinsch A, Stork J, Bergmann W, et al. Effects of thoracic epidural anesthesia on survival and microcirculation in severe acute pancreatitis: a randomized experimental trial. Crit Care. 2013;17(6):R281.
148. Bulyez S, Pereira B, Caumon E, Imhoff E, Roszyk L, Bernard L, et al. Epidural analgesia in critically ill patients with acute pancreatitis: the multicentre randomised controlled EPIPAN study protocol. BMJ Open. 2017;7(5):e015280.
149. Pandey R, Jacob A, Brooks H. Acute pancreatitis in pregnancy: review of three cases and anaesthetic management. Int J Obstet Anesth. 2012;21(4):360–3.
150. Chibber T, Gibson PS. Fatal abdominal compartment syndrome due to severe triglyceride-induced pancreatitis in early pregnancy. J Obstet Gynaecol Can. 2018;40(5):609–13.
151. Ilhan M, Ilhan G, Gok AFK, Gunay K, Ertekin C. The course and outcomes of complicated gallstone disease in pregnancy: experience of a tertiary center. Turk J Obstet Gynecol. 2016;13(4):178–82.
152. Lawani I, Kpossou AR, Noukpozounkou B, Gnangnon FHR, Souaibou YI, Gbessi DG, et al. Severe acute pancreatitis during pregnancy among black African women: about a case. Pan Afr Med J. 2017;26:175.
153. Hino H, Nagano K, Yamanaka I, Suzuki R, Okada T. Anesthetic management in a patient with severe acute pancreatitis during pregnancy. Masui. 2000;49(1):45–8.
154. Sjaus A, McKeen DM, George RB. Hypertensive disorders of pregnancy. Can J Anaesth. 2016;63(9):1075–97.
155. Kanayama N, Belayet HM, Khatun S, Tokunaga N, Sugimura M, Kobayashi T, et al. A new treatment of severe pre-eclampsia by long-term epidural anaesthesia. J Hum Hypertens. 1999;13(3):167–71.
156. Ginosar Y, Nadjari M, Hoffman A, Firman N, Davidson EM, Weiniger CF, et al. Antepartum continuous epidural ropivacaine therapy reduces uterine artery vascular resistance in pre-eclampsia: a randomized, dose-ranging, placebo-controlled study. Br J Anaesth. 2009;102(3):369–78.
157. Knight M, Nelson-Piercy C, Kurinczuk JJ, Spark P, Brocklehurst P, System UKOS. A prospective national study of acute fatty liver of pregnancy in the UK. Gut. 2008;57(7):951–6.
158. Nelson DB, Yost NP, Cunningham FG. Acute fatty liver of pregnancy: clinical outcomes and expected

duration of recovery. Am J Obstet Gynecol. 2013;209(5):456 e1–7.
159. Bacq Y, Assor P, Gendrot C, Perrotin F, Scotto B, Andres C. Recurrent acute fatty liver of pregnancy. Gastroenterol Clin Biol. 2007;31(12):1135–8.
160. Gregory TL, Hughes S, Coleman MA, De Silva A. Acute fatty liver of pregnancy; three cases and discussion of analgesia and anaesthesia. Int J Obstet Anesth. 2007;16(2):175–9.
161. Griffiths JD, Barron FA, Grant S, Bjorksten AR, Hebbard P, Royse CF. Plasma ropivacaine concentrations after ultrasound-guided transversus abdominis plane block. Br J Anaesth. 2010;105(6):853–6.
162. Naidu RK, Richebe P. Probable local anesthetic systemic toxicity in a postpartum patient with acute fatty liver of pregnancy after a transversus abdominis plane block. A A Case Rep. 2013;1(5):72–4.
163. Wanderer JP, Rathmell JP. Anesthesia & breastfeeding: more often than not, they are compatible. Anesthesiology. 2017;127(4):A15.
164. Reece-Stremtan S, Campos M, Kokajko L, Academy of Breastfeeding M. ABM clinical protocol #15: analgesia and anesthesia for the breastfeeding mother, revised 2017. Breastfeed Med. 2017;12(9):500–6.
165. FDA warns against use of codeine and tramadol in children and breastfeeding women. Med Lett Drugs Ther. 2017;59(1521):86–8.
166. Committee on Practice B-O. Practice bulletin no. 177: obstetric analgesia and anesthesia. Obstet Gynecol. 2017;129(4):e73–89.
167. Landau R, Bateman B, Leffert L, Carvalho B. Comments in response to the ACOG/SMFM Practice Advisory on Codeine and Tramadol for Breastfeeding Women. https://soap.org/soap-response-acog-smfm-advisory.pdf. Accessed 10 Jun 2017.

Anaphylaxis in Pregnancy

40

Nadav Levy and Carolyn F. Weiniger

Bullet Points

- Pregnancy is associated with multiple causes for cardio-respiratory collapse, but anaphylaxis should always be considered in the differential diagnosis of shock in pregnant women.
- Anaphylaxis is a rare, life-threatening event that may carry serious morbidity or mortality to the mother and neonate.
- Early signs of anaphylaxis may be confused with the effects of normal labor.
- The definitive diagnosis of anaphylaxis is made through measuring mast cell tryptase, but the results of this test are only available long after the anaphylaxis has been treated.
- Treatment is comprised mainly of epinephrine and fluid resuscitation.
- Early intubation may be necessary in women showing signs of angioedema, as they may deteriorate quickly, and are considered candidates for a difficult airway scenario.
- In the ICU, anaphylaxis may be masked by pathologies such as ARDS or sepsis with hemodynamic instability.
- Treating teams should consider anaphylaxis in any previously stable pregnant woman, as they would for the non-obstetric population.

N. Levy (✉)
Division of Anesthesiology, Critical Care and Pain Medicine, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA
e-mail: nlevy@bidmc.harvard.edu

C. F. Weiniger
Division of Anesthesia, Critical Care and Pain, Tel Aviv Sourasky Medical Center, Tel Avysrael
e-mail: carolynfweiniger@gmail.com

40.1 Introduction

Anaphylaxis is a rare, life-threatening event that may carry serious morbidity or mortality to the mother and neonate [1]. In pregnant women, the recognition of anaphylaxis and the initiation of treatment may be slower than in the non-obstetric population [2]. This is due to the multitude of alternative causes for cardio-respiratory collapse which may occur during the peripartum period. For this reason, anaphylaxis should always be considered in the differential diagnosis of both cardiovascular and respiratory collapse in pregnant women. The equipment and medications required to treat this complication should be available, and treatment algorithms should be practiced by medical and nursing staff in every obstetric unit. In this

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9_40

chapter we will discuss life-threatening anaphylaxis that may cause severe cardio-respiratory instability requiring intensive care treatment and that which occurs during treatment of the pregnant woman for another condition.

40.2 Risk Factors

Information regarding a personal or family history of atopy, food and drug allergies and previous reactions to anesthetics should be gathered for every pregnant woman who presents for treatment. Women who present in extremis due to another severe condition may be unable to impart this information. Thus, alternative information sources, such as family or electronic medical records, should be consulted if required. Women with a higher risk for latex sensitivity should be identified. These include women with a history of previous latex exposure (e.g. healthcare workers or those with prior surgery, particularly cesarean delivery) and women with allergies to certain food products (kiwi, peach, banana, avocado, chestnuts, nuts, potatoes, tomatoes) or other trigger substances [3, 4].

40.3 Causes

The etiologies of anaphylaxis in pregnant women are similar to those in the general population. These include foods, insect bites and venom, latex and medications [5]. The most common triggers for anaphylaxis occurring during labor and delivery; these include antibiotics, latex, local anesthetics, neuromuscular blocking agents, oxytocin and transfusion of blood/blood products [1, 5].

40.4 Symptoms

During obstetric emergencies, efforts should be invested in treating all possible causes, including anaphylaxis, while reassessing the situation to determine the next diagnostic or therapeutic step. The clinical criteria for defining anaphylaxis are detailed in Box 40.1 [1].

Box 40.1 Clinical Criteria for Defining Anaphylaxis

The presence of at least one of the following:

1. A life-threatening airway problem is taken to include:
   (a) Laryngeal or pharyngeal edema.
   (b) Hoarse voice.
   (c) Stridor.
2. A life-threatening breathing problem is taken to include:
   (a) Shortness of breath and raised respiratory rate.
   (b) Wheeze.
   (c) Decreased oxygen saturations.
   (d) Confusion secondary to hypoxia.
   (e) Cyanosis.
   (f) Respiratory exhaustion or respiratory arrest.
3. A life-threatening circulatory problem is taken to include:
   (a) Signs of shock such as faintness, pallor or clammy skin.
   (b) Tachycardia >100 bpm.
   (c) Systolic BP <90 mmHg.
   (d) Decreasing level of consciousness.
   (e) Signs of ischemia on ECG.
   (f) Cardiac arrest.

Adapted from McCall et al., BJOG 2018 and used without modification thus meeting the reproduction conditions.

During pregnancy, the clinical signs of anaphylaxis may involve multiple organ systems, resembling anaphylaxis in the non-obstetric population. The skin, respiratory, cardiovascular and central nervous system may all be involved. Anaphylaxis in a pregnant women may manifest as vulvar and vaginal itching, low back pain, uterine cramps, fetal distress and preterm labor [5].

The early signs of anaphylaxis may be confused for the effects of normal labor; signs such as facial edema, flushing and back pain caused by an anaphylactic reaction may go unnoticed. In

many cases of anaphylaxis in pregnant women, a complaint of 'feeling unwell', or sneezing [6] preceded the onset of hypotension and other clinical signs [2]. The diagnostic challenge is even greater when the patient is ventilated during anesthesia or in the intensive care unit; additional signs such as pharyngeal edema and bronchospasm may be masked. Since the intensity and characteristics of the signs and symptoms of anaphylaxis differ between patients [5], anaphylaxis should be included in the differential diagnosis of every clinical deterioration occurring during pregnancy and labor. The diagnosis of an anaphylactic reaction in this clinical situation may be based solely on the medical history of the patient.

40.5 Differential Diagnosis

As noted above, many emergency obstetric/anesthesia conditions may resemble an anaphylactic reaction. The differential diagnosis of a sudden, symptomatic, clinical presentation consistent with anaphylaxis includes local anesthetic toxicity, hypotension associated with vasodilatation during neuraxial anesthesia, aortocaval compression, cardiac failure, pulmonary aspiration/edema, hemorrhage, thromboembolism, amniotic fluid emboli, pre-eclampsia and sepsis.

The urgent symptomatic treatment and supportive care indicated for each of these conditions should not be delayed due to attempts to reach a definitive diagnosis. In some cases, the medical history of the patient, the chain of events and the presenting symptoms may all be misleading and an alternative diagnosis is reached instead of anaphylaxis. This could become a serious problem if the option of anaphylaxis has not even been considered and the patient remains exposed to potential triggering substances. Thus, a high index of suspicion is required.

40.6 Diagnosis

The definitive diagnosis of anaphylaxis is made in the laboratory through measuring serum levels of mast cell tryptase. Release of tryptase from the secretory granules is a characteristic feature of mast cell degranulation. Elevated serum mast cell tryptase levels are highly suggestive of an immunologically mediated reaction [7]. However, normal levels are not sufficient to exclude an allergic reaction [4]. Mast cell tryptase levels should ideally be measured three times in three separate blood samples. These should be taken immediately after resuscitation, then 1–2 h after the event and then at least 24 h after the suspected event (as a "washout" comparator which assumedly reflects baseline levels) [2].

40.7 Management

As stated above, during pregnancy and labor, the main challenge to timely initiation of the treatment of anaphylaxis is the decision-making process. Given the wide differential diagnosis, delays may occur in initiation of treatment [2]. The mainstays of treatment for anaphylaxis are administration of epinephrine and fluid resuscitation. The management of anaphylaxis is outlined in Box 40.2. These management steps should be implemented as soon as an anaphylactic reaction is suspected.

40.7.1 Caveats to Application of Anaphylaxis Treatment Protocols During Late Pregnancy and in Labor

Airway management may be challenging in the obstetric population as is discussed in Chap. 21. The risks and benefits of intubation should therefore be weighed carefully during management of anaphylaxis in each case. On the one hand, early intubation is vital to securing the airway in women showing signs of angioedema. On the other hand, the situation may easily deteriorate to a difficult airway scenario. Impending airway obstruction should therefore be identified and prevented early. At the same time it is important that the treating team avoid fixation on airway management, as this could potentially delay administration of epinephrine and provision of circulatory support. Correct dosing and timely administration of epinephrine is expected to reduce airway edema and

Box 40.2 The Ten Steps of Management of Anaphylaxis

1. Remove/discontinue potential causative agents.
2. Provide 100% O2 at a high flow rate (>10 L/min).
3. Give intravenous fluid bolus 20 cc/kg.
4. **Give epinephrine IV[a].**
5. Consider intravenous vasopressin bolus/infusion or norepinephrine infusion.
6. Consider inhaled β2 agonist to treat bronchospasm.
7. Consider a large bore IV access and arterial line placement.
8. Consider early intubation to secure the airway.

After initial patient stabilization:

9. Consider H1, H2 antagonist and corticosteroids.
10. Measure serum tryptase levels. Repeat test within 1–2 h and over at least 24 h.

[a]Epinephrine should be administered in escalating doses. Start at 10–100 μg IV and increase the dose every 2 min until clinical improvement is noted. Start infusion of epinephrine early [11].

bronchospasm, thus facilitating ventilation and airway protection if needed. Fluid resuscitation may require volumes of 2–4 L of crystalloids. [4, 8] These women should be carefully monitored both during fluid administration and in the hours following it due to the increased risk of pulmonary edema after labor.

Phenylephrine was the vasopressor most commonly used in cases of anaphylaxis in obstetric patients, as reported by the 6th National Audit Project of the Royal College of Anaesthetists [2]. Phenylephrine is a relatively safe vasopressor which is commonly used and is often immediately available in the labor ward [9]. It may therefore be used as the initial treatment should hemodynamic compromise occur. However, as epinephrine decreases mediator release from mast cells, it may be life-saving during anaphylaxis; thus, epinephrine remains the drug of choice. Administration of epinephrine should not be delayed for the sake of administering drugs with no immediate life-saving benefits such as glucocorticoids and H2 blockers [5, 8].

A biphasic reaction to the triggering agent is experienced by up to 23% of non-obstetric anaphylaxis patients. Thus, there is a significant likelihood of symptom recurrence after the initial improvement observed in response to treatment [3, 10] This phenomenon mandates that the patient remain under observation for a period even after stabilization. Although there are no specific recommendations regarding the length of observation in non-obstetric patients, 6–8 h has been recommended in otherwise stable patients [10].

40.8 Summary

Life threatening anaphylaxis in pregnancy may occur as an isolated phenomenon or in the context of critical illness. Anaphylaxis is particularly difficult to diagnose in critically ill patients. This is precisely why it should always be considered in the differential diagnosis of a critically ill pregnant women patient who deteriorates despite seemingly adequate supportive care. The challenge, as in other populations, remains early identification. Timely identification of anaphylaxis enables rapid initiation of treatment, thereby preventing further clinical deterioration. The management of anaphylaxis in pregnant women is generally similar to that recommended for the non-pregnant population. If intubation is required for such a woman, the airway should ideally be managed by a trained and experienced clinician.

References

1. McCall S, Bunch K, Brocklehurst P, et al. The incidence, characteristics, management and outcomes of anaphylaxis in pregnancy: a population-based descriptive study. BJOG. 2018;125(8):965–71.
2. Cook TM, Harper NJN, Farmer L, et al. Anaesthesia, surgery, and life-threatening allergic reactions: protocol and methods of the 6th National Audit Project (NAP6) of the Royal College of Anaesthetists. Br J Anaesth. 2018;121(1):124–33.
3. LoVerde D, Iweala OI, Eginli A, Krishnaswamy G. Anaphylaxis. Chest. 2018;153(2):528–43.
4. Adriaensens I, Vercauteren M, Soetens F, Janssen L, Leysen J, Ebo D. Allergic reactions during labour analgesia and caesarean section anaesthesia. Int J Obstet Anesth. 2013;22(3):231–42.
5. Simons FE, Schatz M. Anaphylaxis during pregnancy. J Allergy Clin Immunol. 2012;130(3):597–606.
6. Péer L, Brezis ML, Shalit M, et al. Evaluation of a prospectively administered written questionnaire to reduce the incidence of suspected latex anaphylaxis during elective cesarean delivery. Int J Obstet Anesth. 2014;23(4):335–40.
7. Payne V, Kam PC. Mast cell tryptase: a review of its physiology and clinical significance. Anaesthesia. 2004;59(7):695–703.
8. Hepner DL, Castells M, Mouton-Faivre C, Dewachter P. Anaphylaxis in the clinical setting of obstetric anesthesia: a literature review. Anesth Analg. 2013;117(6):1357–67.
9. Kinsella SM, Carvalho B, Dyer RA, et al. International consensus statement on the management of hypotension with vasopressors during caesarean section under spinal anaesthesia. Anaesthesia. 2018;73(1):71–92.
10. Lieberman PL. Recognition and first-line treatment of anaphylaxis. Am J Med. 2014;127(Suppl 1):S6–11.
11. Group SACA. Emergency manual: cognitive aids for perioperative critical events. http://emergencymanual.stanford.edu/downloads.html. Last Accessed 26 Dec 2018.

Appendix

Table 1 Differential diagnosis of some of the possible causes of seizures in pregnancy and the peripartum period, with an accompanying list of the chapter(s) that address each potential cause

Pathology	Etiology	Chapter
Direct CNS	Embolus/thrombosis	5, 8, 15
	Hemorrhage	5, 6, 34, 36
	Infection	17–19
	Space occupying lesion	36
Indirect CNS	Drug toxicity	38
	Eclampsia	16
	Endocrine and metabolic	33
	Infection	17–19
	Intentional or accidental poisoning	38

Table 2 Differential diagnosis of some of the possible causes of hypoxemia in pregnancy and the peripartum period, with an accompanying list of the chapter(s) that address each potential cause

Immediate cause	Underlying pathology		Chapter
Low FiO_2 (ambient hypoxia)	Inappropriate ventilator settings		23
Decreased respiratory drive	Iatrogenic/ self-induced	Drugs	38
	Isolated CNS pathology	Stroke (ischemic or hemorrhagic)	25
		Traumatic brain injury	34
		Seizures	36
	Systemic disease	Preeclampsia	16
		Sepsis	18
		Hepatic encephalopathy	33
		Autoimmune (thrombotic thrombocytopenic purpura, hemolytic uremic syndrome)	5
		Viral infection	17

(continued)

S. Einav et al. (eds.), *Principles and Practice of Maternal Critical Care*,
https://doi.org/10.1007/978-3-030-43477-9

Table 2 continued

Immediate cause	Underlying pathology		Chapter
Inspiratory airway obstruction	Kinked tubing		20
	Upper airway obstruction		21
	Small airway disease		23
Hyperinflation, air trapping	Lower airway disease		23
Ineffective A-a gas diffusion	Alveolar disease		23
Shunting/dead space ventilation	Embolic disease	Pulmonary embolism, amniotic fluid embolism	8
		Liver disease	33
	Abnormal/low flow states	Hemorrhage	6, 34
		Pulmonary disease	23
		Cardiac disease	10–12
		Anaphylaxis	40
		Others (refer to hemodynamic instability table)	
Mitochondrial dysfunction	Sepsis		18

Table 3 Differential diagnosis of some of the possible causes of hemodynamic instability in pregnancy and the peripartum period, with an accompanying list of the chapter/s that address each potential cause

Type of hemodynamic instability	Cause		Refer to Chapter
Hemorrhagic	Obstetric hemorrhage	Antenatal hemorrhage Placenta accreta spectrum Placental abruption Uterine atony Uterine rupture Vaginal tears Ectopic pregnancy 4 T's Tone, Thrombus, Tissue, Trauma	6 for further diagnoses and management
	Nonobstetric	Aortic dissection	34
		Trauma	34
Cardiogenic	Cardiomyopathy		11
	Decompensation of pre-existing congenital cardiac condition		10
	Myocardial ischemia		8
	Pulmonary hypertension		12
	Secondary myocardial dysfunction (e.g., late sepsis)		19
Distributive	Anaphylaxis and local anesthetic systemic toxicity (LAST)		40
	Drug overdose		Not in the book
	Sepsis		17, 18, 19
	Amniotic fluid embolism		8
Obstructive	Pulmonary embolism		8
	Tamponade		28
Neurogenic	Intracranial hemorrhage	Eclampsia	6
		Trauma	34
		Space occupying lesion	36
	Vascular occlusion	Stroke	25
		Hypercoagulable state	5