Infections and Pregnancy

Sumita Mehta
Anshul Grover
Editors

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To our beloved parents, Mrs. Shanta Mehta and late Sh Parshotam Dutt Mehta and Mrs. Indu Grover and late Sh Rajender Lal Grover, who have been our inspiration then, now, and always.

To our spouses, Dr. Avdesh Mehta & Dr. Ashish Rohatgi and our children Aditya, Akshaj, Ananya, & Riddhiman for their unconditional love, patience, and support.

Preface

Pregnancy is a unique condition in which interplay of endocrine and immune influences leads to altered severity and susceptibility to infectious diseases. This book discusses infections across the continuum of pregnancy, childbirth, and postpartum period and describes in detail the clinical presentation, course, associated maternal and fetal risks, and evidence based management of important infections.

The book has been divided into ten parts for the readers' convenience. Part 1 discusses the changing epidemiology of infections seen in pregnancy. The complex interplay between pregnancy-induced physiological changes and the altered susceptibility and severity to various infections has been highlighted in a separate chapter. An overview of the microbiome in healthy pregnant women and the impact of dysbiosis on maternal and infant health has also been included.

Part 2 to 7 discuss the common infections in pregnancy. Pregnant and postpartum women with influenza, ILI, and the more recent COVID-19 infection are more likely to develop a serious illness and these have been discussed in part 2. It has a dedicated chapter on tuberculosis which is still a major cause of morbidity and mortality resurfacing especially during the immunocompromised pregnant state. Part 3 deals with the common viral infections including CMV, Parvovirus B19, rubella, varicella, hepatitis and viral hemorrhagic fevers. Part 4 discusses parasitic infections affecting pregnancy and gives a detailed description of early recognition, timely and optimal management of such patients. There is a separate section on major vector borne diseases, their impact on pregnancy outcomes, current treatment and vaccination.

STDs including HIV are associated with a number of adverse pregnancy outcomes. Part 6 discusses the prevalence, their consequences on pregnancy, and recent recommendations for screening and management of STDs.

Part 7 includes other important maternal infections like Listeriosis, Group B streptococcus, and Gastroenteritis. It also includes a chapter on dermatological infections during pregnancy which discusses the current knowledge on the clinical and therapeutic aspects of the common bacterial, viral, fungal, and parasitic skin infections. A chapter discussing the therapeutic approach to leprosy in pregnancy is also included. Non-obstetrical surgical emergencies may be difficult to recognize in pregnant women and a chapter in this part analyzes the prevalence, clinical presentation, pregnancy outcomes, and treatment options in such conditions. Pregnant women are susceptible to a wide range of oral health conditions which can be detrimental to their own

health as well as fetal health. The part includes a chapter emphasizing the importance and recommended guidelines for dental care of pregnant women.

Part 8 focusses on postpartum infections which account for a significant and often preventable part of the global healthcare burden. Postpartum infections comprise a wide range of entities including endometritis, puerperal sepsis, infections of the skin and soft tissues or episiotomy site and they have all been discussed in separate chapters in the part.

Part 9 is dedicated to the fetal outcomes associated with maternal infections. There is substantial evidence that potentially preventable infections account for miscarriages and preterm birth. There are separate chapters in this part which critically review this evidence and discuss strategies for risk reduction, timely diagnosis and treatment of maternal infections. Another chapter elaborates the fetal manifestation, prenatal diagnosis, and currently available limited therapeutic options for the common congenital infections. Maternal infections have attracted a lot of attention as an important cause of childhood allergic disorders. The role of maternal infections influencing fetal immunity and recommendations for clinical practice are discussed in depth in a separate chapter. Genetic syndromes grouped as pseudo-TORCH mimic congenital TORCH infections and it is important to differentiate the two as the genetic syndromes have high recurrence rates. A dedicated chapter discusses the various conditions included in the pseudo-TORCH syndrome, the diagnostic approach and their management.

Part 10 concentrates on infection prevention strategies in obstetrics. Cesarean delivery is now the most frequently performed major operation and post-operative infection is its commonest complication. The evidence based review of the key preventive measures to reduce the risk of such infections is discussed in a separate chapter in the part. Inappropriate use of antibiotics in pregnancy has short- and long-term effects on the infant and a chapter discussing the strategies to optimize the use of antibiotics has been included in the part. An ideal therapeutic option during pregnancy would be one that is very target specific. Bacteriophage therapy as an alternative to antibiotics in pregnancy has been thoroughly reviewed in another chapter. It is important to ensure that infection prevention elements are incorporated during planning and design of the healthcare facility. A chapter on engineering designs and important processes for infection control in obstetrics has also been thus included.

All the authors who have contributed to the book are experts in their respective fields and we thank all of them for their contribution. Prevention and management of maternal infections offers complex challenges and it is our honest endeavor to bring out the book which would be a comprehensive reference for implementation in daily practice.

Delhi, India — Sumita Mehta
New Delhi, Delhi, India — Anshul Grover

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Editors and Contributors

About the Editors

Sumita Mehta is a Senior Specialist and In-charge, Obstetrics and Gynecology at Babu Jagjivan Ram Memorial Hospital, Delhi. She graduated from Lady Hardinge Medical College and completed her postgraduate degree at Maulana Azad Medical College, Delhi University. She is a certified trainer for colposcopy for the state of Delhi as well as the International Agency for Research on Cancer (IARC) and was the secretary of the Indian Society of Colposcopy and Cervical Pathology (ISCCP). She is an executive member of National Association for Reproductive and Child Health of India (Delhi branch) and has previously also served as an executive member and editor for the Association of Obstetricians and Gynecologists of Delhi. She has conducted several colposcopy workshops all over India and has delivered numerous lectures in various academic forums. She is the author of 9 books and has over 75 publications in national and international journals of repute. Her primary areas of interest are high-risk obstetrics and preventive oncology. Her peers hold her in high esteem for her academic and professional acumen.

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Part I

Changes in Pregnancy: An Overview

1 Changing Epidemiology of Infections in Pregnancy: A Global Perspective

Jyoti Joshi Jain

1.1 Introduction

Infectious disease agents or microbes co-exist with us and are present in almost every available ecological niche of the external environment, which we continue to change, thereby creating greater opportunities for interactions with these agents. Most microbes live on or inside humans or within the environment without causing any disease in humans yet maintaining the ecosystem. Many microbes may not affect humans directly while some, may either peacefully co-exist or are already pathogenic to the animals and plants on which we depend for survival, and can be an indirect threat to human health (if and when they jump species). Infectious disease agents quickly adapt when threatened—greater selective pressures such as the use of antimicrobials, by humans, ecological devastation with climate change to name a few, and this continually challenges our responses to disease control and prevention [1].

With the rapid globalization of the world economies and increasing international travel, the various parts of the world are coming closer. This allows for infectious agents to travel freely across borders endangering human health especially pregnant women [2]. Globally, the mortality rates from non-communicable causes, such as heart disease, stroke, and injuries, have increased while the number of deaths from established infectious diseases, such as malaria, tuberculosis, and vaccine-preventable diseases has decreased, and new infectious diseases such as MERS, SARS-COV2 have emerged. Many developing countries are today faced with this "dual burden" of diseases: to continue the prevention, control, and management of infectious diseases, along with managing the health threats from non-communicable diseases and environmental health risks. With the social and economic changes in developing countries, efforts have focused on improving health systems and disease surveillance. There is also a greater focus on the control and management of non-communicable diseases, substance abuse disorders, mental health, and injuries (both intentional and unintentional).

Case identification and control of emerging infectious diseases is important for health promotion and prevention of the international spread of the disease. The revised International Health Regulations (IHR 2005) [3] identifies the various threats to global public health with its "all-hazards approach." They have designed regulations to prevent the international spread of diseases, without causing interruption of world travel and trade. These regulations promote international cooperation in sharing information about

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known diseases and public health events of international concern. Factors that have helped decrease the burden of infectious diseases on health over the past few decades include global economic growth and development, improvement in access to clean drinking water and sanitation, vaccines, and better access to healthcare including antibiotics to treat infections.

Maternal health in the past three decades has witnessed an increase in economic disparities while there is also the trend of increased user-friendly technologies that can be used by health specialists to make pregnancy safer. Well-resource settings in developed as well as developing countries have embraced the technological advances in providing organ support in critical care units, while low-resource settings have recognized the preventability of infections in pregnancy and consequently the cost-savings that can be created [4].

In the 1800s and 1900s, infections in pregnancy were the main cause of death in Europe, accounting for 50% of maternal deaths [5]. With improvement in living conditions, the use of antibiotics, and advances in acute hospital care and the availability of medical specialists, a complete turnaround of the situation took place with a decline in infections and direct maternal deaths.

Increasingly within public health there is the concept of One Health [6]. This concept recognizes the symbiotic relationship between health of people and animals which is further linked to the environment; one interconnected biome. It has been brought into the limelight the needs for sustainable alignment of prevention and treatment of infections in humans including pregnant women. In fact, among the Sustainable Development Goals (SDG), countries have committed to reducing the global Maternal Mortality Ratio (MMR) to <70 per 100,000 births. The aim is that no country should have a maternal mortality rate greater than twice the global average. Several interventions such as regular antenatal care and institutional delivery helped put the spotlight on improving maternal health and reducing maternal mortality. But these are mostly in high and upper-middle-income countries with fewer than half of all births in several low-income and lower-middle-income countries conducted without skilled health personnel [7]. However, maternal mortality still remains unacceptably high mostly due to preventable or treatable complications during pregnancy and childbirth. Many other complications which are existing prior to pregnancy, may get worsened during pregnancy, especially if not managed as part of the woman's care. Infections account for a bulk of maternal deaths [8]; including infections (after childbirth), infections such as malaria that co-exist with pregnancy, and chronic conditions like cardiac diseases or diabetes.

Despite all these developments, diagnosing maternal infection microbiologically remains a challenge. Genital swabs may not be able to identify the correct causative organism due to contamination with natural vaginal flora rather than infection. Overall, maternal infections can be classified into different categories: infections specific to pregnancy; infections exacerbated by pregnancy; and infections incidental to pregnancy. These categories which are aligned with the WHO classification are used globally for the classification of maternal mortality into direct, indirect, and incidental deaths (Table 1.1).

Pregnancy is a period of adaptation in the immune system of a woman to be able to accept

Table 1.1 Classification of maternal infection aligned with WHO

1. Pregnancy-specific infections
Chorioamnionitis
Endometritis
Lactational mastitis
Site of perineal trauma
Surgical site, e.g., cesarean
2. Infections exacerbated by pregnancy, including
Urinary tract infection
Influenza
Listeriosis
Hepatitis E
Herpes simplex virus
Malaria
3. Incidental infections, including
Lower respiratory tract infection
Tuberculosis
Sexually transmitted diseases

Adapted from Irish Maternity Early Warning System [9]

a genetically foreign fetus [10]. It is an accepted fact that during pregnancy there occurs a shift from cell-mediated immunity toward humoral immunity which may alter a woman's susceptibility to and severity of infectious diseases. Such changes and the effect of infectious diseases on the growing fetus make the diagnosis, prophylaxis, and treatment of infections in the pregnant woman difficult. Infectious diseases in pregnancy have usually been described by the organ system affected such as Urinary Tract Infections (UTIs), Sexually Transmitted Diseases (STIs), and management led by a broad syndromic case management strategy that can be applied in even primary healthcare settings where exact diagnosis through lab investigation and microbiological analysis is difficult.

This chapter thus describes the changing epidemiology of infectious diseases in global health and pregnancy and the factors that have led to these developments. It shows how the health of the pregnant woman is influenced by the varied infectious organisms that exist around them and highlights their impact on pregnancy.

1.2 Emerging Pathogens and Pregnancy

An emerging pathogen is an infectious disease-causing agent whose incidence increases when it jumps from one species to another [11] or whose incidence is increasing in an existing population as a result of long-term changes in its genetic makeup. Although each emerging pathogen is unique, the basic approach that defines their rise, spread, changing epidemiology, and consequently control and response in the form of recognition, communication, and mitigation are similar.

The recent emerging infectious diseases witnessed in the last decade include Zika virus, Severe acute respiratory syndrome (SARS)-related coronavirus, Middle East respiratory syndrome-related coronavirus (MERS-CoV), Influenza H1N1, malaria parasites, dengue virus, and SARS-CoV2. It has been noted that these infecting agents have particularly affected pregnant women because of their relative immunosuppressed state, restricted cardiorespiratory capacity, and the potential for adverse pregnancy or perinatal outcomes (e.g., vertical transmission, preterm birth, fetal growth restriction, fetal anomalies, and death). There is a need for large cohort studies to have accurate risk estimates for pregnant women from a global perspective [12]. In addition, key strategies for preparedness and response include disease-specific delineation of transmission dynamics (for each emerging pathogen), understanding of pathogen-specific effects on both pregnant women and fetus, advanced planning and management, and initiating communication among public health experts, clinicians, and patients.

Over the past decade, with an increase in human-animal interactions, Zika infection [13], MERS-COV-2, and SARS-COV-2 infection have come up as a significant threat to public health. The increasing burden of emerging pathogens like various arboviral diseases and the increase in the geographical range of mosquitoes can be attributed to climate change, increasing urbanization, global travel, and growth in the human population. Today the total biomass of humans and livestock (cattle, pigs, etc.) far exceeds that of wild mammals on the planet [14] and the total biomass of domesticated poultry is three-fold higher than wild birds. However, with the help of effective surveillance studies integrated with accurate and rapid diagnosis and the development of specific antivirals and vaccines, we could prepare ourselves for better management and control of emerging infections.

1.3 Mitigating Challenges in the Management of Emerging Pathogens

As human-animal-environment interface has been intensified by anthropogenic activities, there have been many such outbreaks, each with its own unique implications for pregnant women and the fetus. Their management, mitigation, and response has provided valuable learnings to

health care researchers and the implementation agencies. These include outbreaks of Severe acute respiratory syndrome (SARS), the 2009 H1N1 pandemic influenza, Ebola virus, the Zika virus, and COVID-19 causing SARS-COV2. Though each of the pathogens with its peculiar characteristics required tailored responses, there are similarities in the underlying principles for the recognition, communication, and mitigation of such infections [15].

The devastating impact of emerging infections such as the Zika virus in pregnancy and the effects on the unborn fetus highlight the need for therapies and vaccines during the pregnancy period [16]. The management response of these infectious diseases is handicapped by long timelines for the development of new prevention and treatment strategies in pregnancy. Majority of the medicines (antibiotics such as Cefazolin, antivirals such as Oseltamivir) usage in pregnancy is off-label, as pregnant women are excluded from participation in clinical trials of new pharmaceutical agents. However, a critical milestone in this is the development and increasing usage of pregnancy registries. These registries will provide a platform for the systematic data collection on the outcome of exposures to drug products in pregnancy. Long-term prospective data collected from these registries including the limitations can help to revolutionize the treatment and management of infections in pregnancy [17].

1.4 Rise of Antimicrobial Resistance and Syndromic Management Protocols

Antimicrobial resistance (AMR) is a natural mechanism that allows microorganisms to survive by adapting to the increased selective pressure of antibiotics in their environment. The process is accelerated by increasing levels of antibiotic use: the selective pressure enables the spread of mutations that promote survival, shortening the time bacteria need to acquire resistance to new drugs. It has contributed to alarming rates of resistance for selected pathogens for which few treatment options are available [18]. Studies [19] have shown that a major fall was witnessed in the prevalence of syphilis, gonorrhea, trichomoniasis, chancroid, and chlamydial infection (all sexually transmitted infections, STIs) in South Africa between 1995 and 2005, by the universal practice of syndromic management approach. A 33% (95% CI: 23–43%) reduction in the prevalence of syphilis, a 6% (95% CI: 3–11%) decline in the prevalence of gonorrhea, a 5% (95% CI: 1–13%) fall in bacterial vaginosis prevalence and a substantial decline in the cases of chancroid was observed in the reproductive age group by use of the syndromic management. But this intervention did not bring about a change in the prevalence of other STIs. Thus, it was postulated that the modeled reduction in STI prevalence between 1995 and 2005 may have been due to increased condom usage and/or mortality due to AIDS co-infection. Similarly, other studies have criticized the syndromic approach to be inaccurate, imprecise, responsible for overtreatment in a high percentage of patients, and contributing to antibiotic resistance [20].

The advantage of syndromic approach is its usefulness in diagnosis and immediate treatment of STIs in resource-poor settings where laboratory diagnosis is limited. It is cost-effective and simple. It is recommended that where ever possible the approach should be validated with other population data and periodically evaluated [21] as it has inherent limitations which lead to misdiagnosis and overtreatment. Evidence-based management requires a switch to more accurate diagnostic methods such as Polymerase Chain Reaction (PCR) or other points of care tests. The need of the hour is to develop easy-to-use, low-cost nucleic acid-based diagnostic methods which can be used by untrained workers in poor resource settings. This will help in the indiscriminate use of antibiotics and also prevent transmission of infection to their sexual partner or infants.

Resistance to Drugs is a major threat to the ongoing drug treatments of chronic diseases of public interest such HIV, tuberculosis, and malaria. It also is of concern to the rise in the incidence of hospital- and community-acquired infections from common Gram-positive and Gram-negative bacteria.

Vaccination programs have also suffered setbacks due to various reasons such as lack of vaccine confidence and misconceptions. These setbacks can cause the re-emergence of highly infectious viruses, such as those causing measles or rubella, as witnessed in the UK.

The global food production and distribution chains are changing rapidly. These alterations are bringing a change in the pathogenic strains responsible for disseminated foodborne infections. The *E. coli* O104:H4 infection which originated from Germany is one such example [22].

STIs are a group of diseases that predominantly spreads via sexual contact. The WHO fact sheet for 2019 indicates that STI incidence rates have stagnated. Only congenital syphilis has been shown to show a slow decline [23]. In fact, in several countries, sexually transmitted infections are on the rise due to men who have sex with men. Of these, four infections—syphilis, gonorrhea, chlamydia, and trichomoniasis are currently curable, while four others—hepatitis B, herpes simplex virus (HSV or herpes), HIV, and human papillomavirus (HPV) are incurable viral infections whose symptoms can only be reduced or modified through treatment.

In 2016, WHO estimated [23] 376 million new infections with one of four being STIs: chlamydia (127 million), gonorrhea (87 million), syphilis (6.3 million), and trichomoniasis (156 million). More than 500 million people are living with genital HSV (herpes) infection and an estimated 300 million women have an HPV infection, the primary cause of cervical cancer. An estimated 240 million people are living with chronic hepatitis B globally. More than one million STIs are acquired every day. A WHO surveillance study in 2016, found that the African Region accounted for the highest prevalence for trichomoniasis in women, chlamydia in men, and gonorrhea and syphilis in both women and men together. The prevalence of all four STIs, in both women and men, was highest in the Western Pacific Region. (Fig. 1.1) 68 million people in the USA [24] were almost affected by at least one sexually transmitted infection in 2018, with almost 26 million new infections in 2018 itself. (Fig. 1.2).

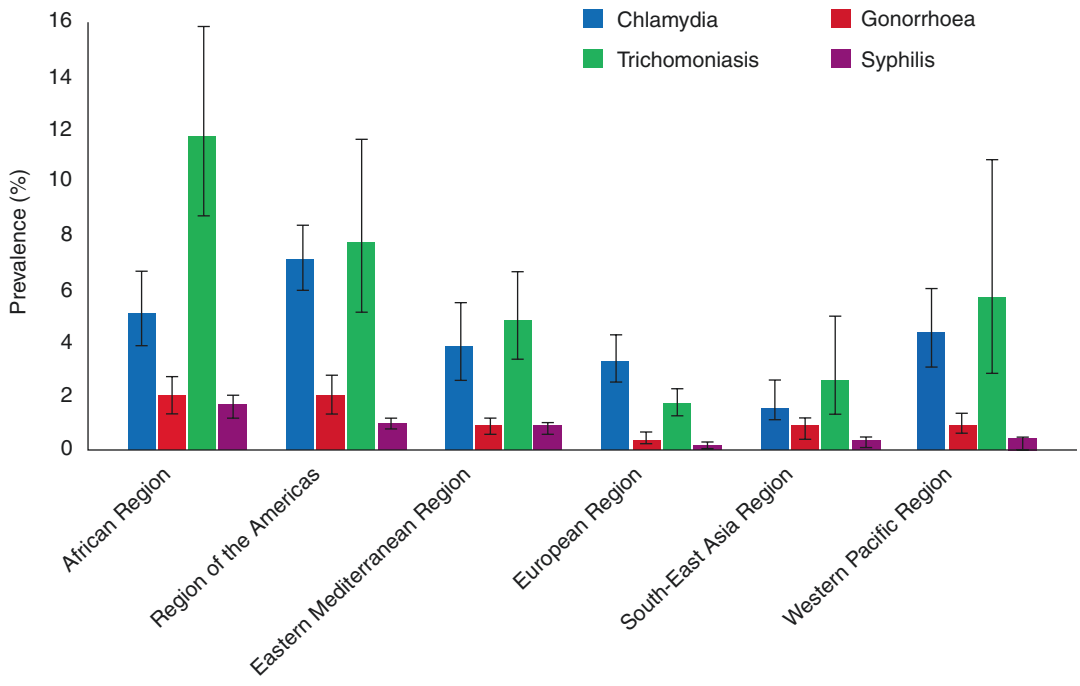

Fig. 1.1 Estimated prevalence of chlamydia, gonorrhea, trichomoniasis & active syphilis in women aged 15–49 years (Source: WHO report on STIs based om2009–2016 data)

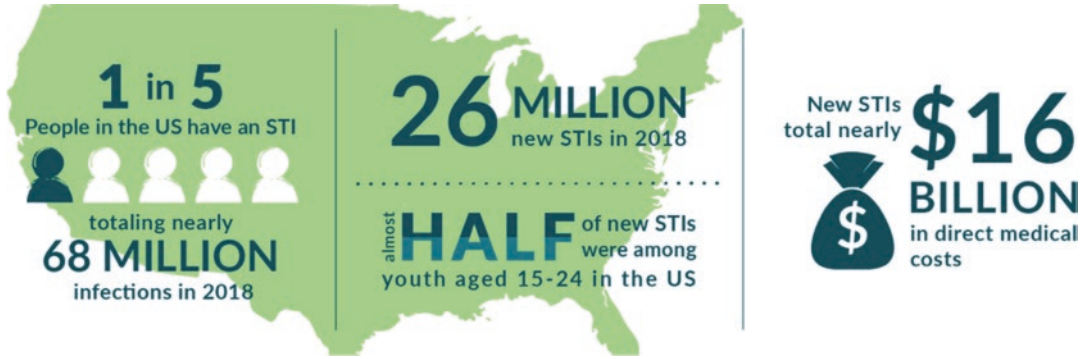

Fig. 1.2 Economic and epidemiological burden of STIs in the USA (credit: US CDC https://www.cdc.gov/std/statistics/prevalence-incidence-cost-2020.htm)

Screening and treatment of syphilis during pregnancy and especially with HIV co-infection has seen remarkable progress in vertical transmission reduction [25].

- In 70% of countries at least 95% of pregnant women are screened for HIV and/or syphilis.
- Prior to screening for HIV and/or syphilis, a free and informed consent is taken from 95% of the pregnant women.
- 90% of pregnant women living with HIV receiving effective treatment
- At least 95% of syphilis-seropositive pregnant women are treated with at least one dose of intramuscular benzathine penicillin or other effective regimens.

For many sexually transmitted infections among targeted vulnerable populations such as women and sexual minorities, no further decline in incidence has been achieved after the initial reduction. These diseases continue to be a major public health problem. WHO's Global Health sector strategy [24] on STIs (2016–2021) aims to end the STI epidemic based on the following principles:

1. By achieving universal health coverage
2. Use of evidence-based interventions and policies
3. Promoting human rights, gender equality, and health equity
4. Working through partnerships
5. Integration across relevant sectors
6. Engagement and empowerment of people most affected by STIs

To measure progress against the Strategy's goal, key targets have been identified to be achieved by 2030:

- ≤50 cases of congenital syphilis per 100,000 live births in 80% of countries
- 90% reduction in T. pallidum incidence globally (2018 global baseline)
- 90% reduction in N. gonorrhea incidence globally (2018 global baseline)
- 90% national vaccination coverage and at least 80% district coverage in countries with HPV vaccine in their national immunization program.

1.5 Immunization, Vaccines and their Untapped Potential in Pregnancy

Some of the recent emerging pathogens like Zika and SARS-COV2 have shown a greater predilection for pregnant women and threaten the developing fetus. Immunization is one of the most cost-effective preventive interventions in public health. Its use in use in pregnancy has been limited with the exception of the vaccination of pregnant mothers for eliminating neonatal tetanus. Congenital Rubella Syndrome in the Americas and Europe has been radically reduced as a result of a two-pronged strategy targeting different pop-

ulations: Vaccination of children and adolescents with combined measles, mumps, and rubella (MMR) vaccine and standardized testing during pregnancy for susceptibility to rubella along with postpartum immunization of women lacking immunity [26]. The American Committee of Immunization Practices (ACIP) in the USA currently recommends only two vaccines, namely; the inactivated influenza vaccine and the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) for all pregnant women [27].

Despite the benefits of vaccines in pregnancy, vaccine uptake remains sub-optimal due to the traditional mindset of avoiding any external interference in pregnancy, reactive medicine, and increasing vaccine hesitancy. To date, there is extensive evidence of the safety of immunization in pregnancy using non-live vaccines. These include inactivated tetanus toxoid/seasonal or pandemic influenza/, mono- or combined polysaccharide or conjugated meningococcal/human papillomavirus, acellular pertussis/cholera/hepatitis A/Japanese encephalitis,/rabies vaccines, and anthrax vaccine [28].

The rise of pertussis in 0–3-month-old infants led to the use of the strategy for maternal immunization and cocooning (which involves parents, caregivers, and others in close proximity of the infant). Evaluation of efficacy and cost-effectiveness of maternal vaccination vs. the cocooning strategy has revealed that immunization during pregnancy is more efficacious in reducing the prevalence of pertussis as compared to cocooning (33% vs 20%), reduction in hospital stay (38% vs 19%) and decline in IMR b 49% vs 16%. The cost of vaccinating the woman during pregnancy is about one-third of the cost of cocooning (which is approximately $1200).

Researchers have developed a conceptual framework for the known barriers to maternal acceptance of vaccination in pregnancy (for influenza and pertussis) [29]. These include:

- Lack of knowledge about susceptibility to severe influenza disease in pregnancy and susceptibility to severe pertussis disease in newborns
- Misinformation regarding effectiveness of the vaccine
- Lack of knowledge about safety profile of the vaccine
- Lack of guidance from the care giver
- General mistrust toward allopathic healthcare system.
- Fear of needles
- Lack of health care facilities

1.6 Evolving Challenge of Maternal Sepsis

Maternal sepsis is the final manifestation of an infection during pregnancy. Any infection either directly arising from the genital tract or indirectly as a consequence of systemic infection if severe, can evoke a response in the body which brings about tissue and organ destruction. This is the pathophysiology of maternal sepsis and it is a life-threatening condition [30].

Maternal sepsis is the third most common direct cause of maternal deaths. It is responsible for 11% of maternal deaths worldwide (9.7%, 11.6%, and 7.7% of maternal deaths in Africa, Asia and Latin America/Caribbean respectively) [31]. Its incidence in Low- and middle-income countries (LMIC) is 10.7% as compared to 4.7% in high-income countries (HIC). The greatest burden in this regard is borne by the Southern Asian (13.7%) and Sub-Saharan African (10.3%) regions, but maternal infections are an important cause of mortality in the developed countries also [32–34]. Infections like malaria, dengue, pyelonephritis, influenza-like illness, and HIV/AIDS are important indirect causes of maternal deaths [35].

It is a difficult issue to address through public health programs due to the unpredictable emergence of causative organisms such as novel influenza serotypes and other spread of factors speculated to contribute to its burden—maternal age, co-morbidities, increased antibiotic resistance, and an increased incidence of particular infections by Escherichia coli and group A streptococcal infections [36].

1.7 Conclusion

Infections during pregnancy are a key contributor to maternal mortality and can be prevented by simple healthcare solutions available through access to high-quality care in pregnancy, and during and after childbirth.

Infection control practices if carried out stringently can prove to be the most effective intervention for preventing infections in pregnancy and reducing the incidence of maternal sepsis. Handwashing with soap or other disinfectants can be critical in preventing nosocomial transmission of infections in pregnant and post-partum women.

In the case of sexually transmitted infections esp. diseases like gonorrhea which are experiencing a resurgence, renewed efforts are needed to strengthen surveillance. These measures include: following the globally accepted standard definition of case, reporting of every case including nil case, adopting sentinel surveillance or syndromic surveillance (in resource-limited settings) according to prevalence in that area, and provision of laboratory testing of the case if required. Additionally, surveillance for antimicrobial resistance is needed to conserve the efficacy of antibiotics and prepare effective treatment protocols for all settings.

Further research and data is required to justify the role of antibiotic prophylaxis in operative vaginal delivery in preventing maternal sepsis. The Cochrane review in this regard fails to provide sufficient evidence to determine whether prophylactic antibiotics given with operative delivery or following third- or fourth-degree perineal tears reduce infectious postpartum morbidities [37]. A Cochrane review provides moderate-quality evidence for the use of prophylactic antibiotics after cesarean section to lower risks of endometritis, wound infection, and serious maternal infectious complications [38].

Most of all, maternal deaths can be avoided by preventing unwanted pregnancies. Safe, respectful, and easy access to safe abortion practices, provision of quality post-abortion care and contraception services can go a long way in preventing infections in pregnancy and reducing maternal mortality.

Key Points

- There is the concept of "One Health" within public health which recognizes the symbiotic relationship of the health of people and the health of animals. It also links humans, animals, their environment and their stresses into one interconnected biome.
- The WHO fact sheet (2019) indicates that STI rates are not declining except for a slowdown in rates of congenital syphilis.
- According to the WHO Surveillance study (2016), the Western Pacific region has the highest prevalence of all four STIs in both men and women.
- WHO's Global Health sector strategy on STIs (2016–2021) aims to end the STI epidemic and has defined targets to be achieved by 2030 toward achieving the goal.
- ACIP currently recommends only two vaccines, namely; the inactivated influenza vaccine and the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) for safe use in all pregnant women.
- Maternal sepsis is the third most common direct cause of maternal deaths. It is responsible for 11% of maternal deaths worldwide (9.7%, 11.6%, and 7.7% of maternal deaths in Africa, Asia, and Latin America/Caribbean respectively).
- A Cochrane review provides moderate-quality evidence for the use of prophylactic antibiotics after cesarean section to lower risks of endometritis, wound infection, and serious maternal infectious complications.
- Maternal deaths can be avoided by preventing unwanted pregnancies. Safe, respectful, and easy access to contraception and comprehensive abortion services can go a long way in preventing infections in pregnancy and reducing maternal mortality.

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2 Pregnancy Changes Predisposing to Infections

Sumita Mehta and Ankita Mann

2.1 Introduction

Pregnancy is a unique state of host-graft response which is characterized by immune suppression to prevent rejection of paternal antigens and tolerate a genetically foreign fetus but at the same time maintain immunity to other pathogenic infections. There occur many anatomical, physiological and immunological changes during normal pregnancy to accommodate the growing fetus. However, such changes can make pregnant women more susceptible to certain infections as well as increase the severity of others. Even milder infections during pregnancy can flare up leading to serious illness. This is especially true for infections such as influenza virus, hepatitis E virus, herpes and malaria infection. These infections during the course of normal pregnancy should have a lower threshold for diagnostic evaluation, hospitalization, and treatment.

Under WHO/HRP initiative, research from the Global Maternal Sepsis Study (GLOSS), showed that infection has a much larger impact on global maternal mortality and morbidity than previously thought. Globally, 11 women per 1000 live births have had an infection in pregnancy which is associated with severe maternal outcomes [1]. In low-middle-class countries like India, overcrowded health facilities, poorly resourced women, and unawareness of health workers in early recognition of signs and symptoms of sepsis, and as well as lack of timely intervention make the condition more vulnerable [2].

The main alterations in pregnancy that lead to an increased risk of infections are:

1. Maternal anatomical and physiological changes seen normally in pregnancy
2. Changing microbiome of normal pregnancy
3. Modulated immunology in pregnancy
4. Placenta (maternal-fetal interface) as an active immunologic site
5. Spectrum of microorganisms causing infection in pregnancy.

We will discuss each of these factors in detail in the chapter with relevance to only those changes which predispose a pregnant woman to increased susceptibility or severity of various infections.

2.2 Anatomical and Physiological Changes of Pregnancy

The pregnant woman undergoes several physiological adaptations affecting various systems and the correct interpretation of these changes is required for the management of infectious com-

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plications during pregnancy. The relevant changes which predispose the pregnant woman to infections will be discussed for each system separately in the section that follows.

2.2.1 Respiratory System

The anatomical and functional changes during pregnancy affect the pulmonary function, ventilatory pattern, and gas exchange seen normally in the respiratory system. Respiratory infections are not more frequent in pregnancy than in non-pregnant women but they result in greater morbidity and mortality secondary to the physiologic adaptations that occur during pregnancy. Pregnancy seems to increase the risk of major complications of pulmonary infectious diseases such as respiratory failure, empyema, and pneumothorax. A careful interpretation of these changes is required for the management of respiratory disorders in pregnancy.

Anatomical changes

- Hyperemia, hypersecretion, and mucosal edema of the upper respiratory tract and airway mucosa are seen normally in pregnancy and are mainly due to increased levels of estrogen which causes capillary congestion and hyperplasia of mucus glands.
- The diaphragm is displaced cephalad by about 4 cm by the enlarging pregnant uterus; the anteroposterior and transverse diameter of the thorax also increase thereby increasing the circumference of the thoracic cage by 5–7 cm [3, 4].

Mechanical effects

- The enlarged gravid uterus leads to changes in lung volume and chest wall leading to a decrease in functional residual capacity (FRC) from 10 to 25% and a decrease in ERV (Expiratory reserve volume) [5].
- There is a minimal decrease in total lung capacity as the thoracic cage widens to compensate the lung capacity.

Pulmonary function changes

- Minute ventilation starts increasing in the first trimester and reaches 20–40% above baseline at term. Alveolar ventilation also increases by 50–70% and tidal volume by 30–35%. High levels of progesterone lead to an increased respiratory drive which in turn leads to an increase in ventilation.
- Forced expiratory volume (FEV_1) and lung compliance remain unchanged, but chest wall and total respiratory compliance are reduced.
- Oxygen carrying consumption increases because of the demand of fetus and maternal metabolic processes.
- Pregnant women are more prone to pulmonary edema which is mostly cardiogenic due to increased cardiac output, heart rate, and decreased systemic vascular resistance and colloid osmotic pressure.

Arterial blood gases

- Oxygen consumption which starts to increase at the beginning of the first trimester, reaches a level up to 33% more than baseline by term. This is because of increased fetal demands and maternal metabolic processes.
- Pregnancy-induced decrease in functional residual capacity combined with a rise in oxygen consumption lowers the oxygen reserve of the mother [6].
- Respiratory alkalosis is common in pregnancy due to physiological hyperventilation; the arterial bicarbonate level is decreased to 18–21 mEq/L. This effect is caused by increased progesterone levels which stimulate an increase in ventilation and tidal volume resulting in mild respiratory alkalosis with compensatory renal excretion of bicarbonate ($PaCO_2$ 28–32 mmHg).

Clinical Implications

- Anatomical changes of the thoracic cage may decrease the pregnant woman's ability to clear secretions.

- The decrease in functional residual capacity and increase in fluid in lungs seen during pregnancy further make infectious pulmonary injury common during pregnancy.
- In active labor, hyperventilation and tachypnea result in marked hypocapnia and respiratory alkalosis which can decrease uterine blood flow. Arterial PCO_2 levels decrease with each contraction while at full dilatation of the cervix, the levels decrease even between contractions [7].
- Weight gain and nasal obstruction during pregnancy can contribute to sleep breathing disorders. The enlarged uterus also causes a decrease in FRC and hypoxemia and can exacerbate obstructive sleep apnea [8].
- The pregnant woman seems to be more susceptible to the development of acute respiratory distress syndrome (ARDS) than non-pregnant patients due to increased circulating volume, hypoalbuminemia, and immunological factors. Inflammatory changes seem to occur in the lung as a result of pregnant state or the process of labor and delivery, priming it for the development of ARDS [9].
- Coccidioidomycosis (fungal pneumonia) is a significant opportunistic infection and as pregnancy is characterized by impaired cell-mediated immunity, cases of this infection have been seen in immunocompetent pregnant women. Presently there is insufficient data to suggest whether the incidence of pulmonary cryptococcosis actually increases during pregnancy; this infection should be kept as a differential diagnosis of pneumonia and hypoxemia in a pregnant patient [10].

2.2.2 Cardiovascular System

Hemodynamic changes

- Heart rate increases progressively throughout pregnancy with a 20–25% increase over baseline by the third trimester [11].
- Cardiac output increases by 20% by 8 weeks gestation and this is primarily due to peripheral vasodilatation which in turn is mediated by increased levels of estrogen, nitric oxide, and prostaglandinI_2 seen during pregnancy. Cardiac output reaches a peak of 30–50% more than baseline by 28 weeks of pregnancy and at this time is mainly due to an increase in stroke volume and heart rate [12] (Table 2.1).
- There is systemic vasodilation with a decrease in peripheral vascular resistance and pulmonary resistance but the pulmonary capillary wedge pressure (PCWP) remains the same. The serum colloid osmotic pressure (OP) is reduced by 10–15% in pregnancy and this coupled with unchanged PCWP reduces the colloid OP/PCWP gradient by about 30% making the pregnant women susceptible to the development of pulmonary edema.

Table 2.1 Physiologic changes in pregnancy

Parameter	
Respiratory	
Functional residual capacity	Decrease 10%–25%
Minute ventilation	Increase 20%–40%
Tidal volume	Increase 30–35%
FEV1	Unchanged
Oxygen consumption	Increase by 33%
Arterial Blood Gases	
PaO_2	Unchanged
$PaCO_2$	Reduced to 28–32 mmHg
Serum bicarbonate	Reduced to 18–21 mEq/L
Cardiac	
Heart rate	Increase 25%–30%
Cardiac Output	Increase 30%–50%
Systemic vascular resistance	Decrease 20%–30%
Pulmonary vascular resistance	Decrease 20%–30%
Pulmonary capillary wedge pressure	No change
Renal	
Glomerular filteration rate	Increased by 50%
Intravesical Pressure	Increase
Urinary excretion of glucose	Increase

Renin-Angiotensin-Aldosterone system

- Estrogen secreted during pregnancy increases angiotensinogen production and subsequently angiotensin levels. This leads to increase in

plasma volume which starts at 6–8 weeks of pregnancy and rises up to 28–30 weeks. This helps to maintain blood pressure and helps in salt and water retention [13].
- Relaxin stimulates increased vasopressin secretion causing an increase in water retention through increase in water resorption in collecting ducts.
- Progesterone which is a potent aldosterone antagonist allows natriuresis despite the sodium retaining properties of aldosterone. It also has anti-kaliuretic effects and prevents hypokalemia [14].

Clinical Implications

- Cardiopulmonary adaptive changes occurring during pregnancy such as increased heart rate and stroke volume and reduced pulmonary residual capacity may increase the risk of hypoxemia in pregnant females [15].
- Pregnant women are also more susceptible to the development of pulmonary edema due to reduced colloid OP/PCWP gradient.

2.2.3 Urinary System

Urinary tract infections (UTI) are commonly seen in pregnancy and account for 3–5% of all antepartum admissions [16]. These include asymptomatic bacteriuria (ASB), cystitis, and pyelonephritis; of these pyelonephritis is the most common cause of septic shock in pregnant women. Acute pyelonephritis may complicate 2% of pregnancies and is most commonly associated with untreated ASB; pyelonephritis can develop in about 25–30% of untreated ASB cases [17]. Organisms causing UTI in a pregnant woman are the same as those seen in non-pregnant with E. coli being the most common pathogen [18].

Anatomical changes

- Renal size increases by 1–1.5 cm due to increase in renal blood flow; it reaches maximal size by mid-pregnancy.
- The kidneys, pelvis, calyceal systems and ureters dilate due to the compressive effect of the pregnant uterus leading to physiological hydronephrosis seen in approximately 80% of pregnant women [19].
- The enlarged uterus also compresses the urinary bladder causing an increase in intravesical pressure which may lead to urinary retention and vesicoureteral reflux. These anatomical changes are mediated by progesterone which causes smooth muscle relaxation of the ureters and urinary bladder and decrease in ureteral tone and peristalsis [20].

Biochemical changes

- Reabsorption of glucose in the proximal and collecting tubules is less effective during pregnancy and about 90% of pregnant women with normal blood glucose levels excrete glucose in urine (Table 2.1).
- The excretion of proteins also increases during pregnancy due to an increase in glomerular filtration rate and glomerular capillary permeability.

Clinical Implications

- The increase in renal size is associated with an increase in interstitial volume and urinary dead space which predisposes to infection.
- Urinary stasis in the renal collecting system favors growth of microorganisms. Also, there is increase in vesicoureteral reflux under the effect of progesterone which also contributes to infection.
- Urine in pregnancy has higher amounts of glucose, amino acids, and hormone degradation products which make the urine more alkaline and prone to infection [21].

2.3 Changes in Microbiome During Pregnancy

2.3.1 Gut Microbiome

Progesterone leads to increased growth of Bifidobacterium. High levels of estrogen and progesterone during pregnancy increase the susceptibility of pregnant women to Listeria monocytogenes infection [22].

Table 2.2 Changes in microbiota during pregnancy

Oral Microbiota	Viable counts ↑ Porphyromonas gingivalis ↑ Candida ↑
Gut Microbiota	Actinobacteria ↑ Proteobacteria ↑ Faecolibacterium ↓ α-diversity (within particular ecosystem) ↓ β-diversity (comparison of diversity between ecosystems) ↑
Vaginal Microbiota	Lactobacillus ↑ Acitinobacter ↑ α-diversity ↓ β-diversity ↓ Stability ↑

Proteobacteria and members of Enterobacteriaceae and streptococcus spp. increase during the third trimester while Proteobacteria and Actinobacteria have been seen to increase from 5.1% to 9.3% in approximately 50% of pregnant women [23].

2.3.2 Vaginal Microbiome

The vaginal microbiome undergoes a shift in the diversity of microorganisms during pregnancy in which there is dominance of Lactobacillus species, Clostridiales and Acetinobacter [24]. This change is linked to rise in the levels of estrogen and progesterone during pregnancy. (Table 2.2).

Bacterial vaginosis is caused by dysbiosis in the vaginal microbiome wherein there is decrease in Lactobacillus species and increase in anaerobes such as Gardnerella and mycoplasma. This can subsequently lead to chorioamnionitis and intra-amniotic infection [25].

2.4 Modulated Immunology in Pregnancy

The immunology of pregnancy is a unique host-graft response that is characterized by immune suppression to tolerate a genetically foreign fetus but at the same time maintains immunity to other pathogenic infections. It is the immunologic alterations that occur during the course of a normal pregnancy that also play an important role in increased severity and susceptibility to infections. Though the changes in immune system are not well understood, a shift from cell-mediated immunity to humoral immunity is seen during pregnancy. As pregnancy progresses, the interplay between sex hormones and immune system affects many organ systems. Due to downregulation of cell-mediated immunity, maternal lymphocytes shows diminished proliferative response to soluble antigens and allogenic lymphocytes.

2.4.1 Immune Cell Types

- uNK cells (uterine natural killer cells): They account for approximately 70% of decidual leukocytes in first trimester. They are weakly cytotoxic as compared to peripheral NK cells. They are also a source of cytokines and matrix metalloproteinases both of which mediate trophoblast invasion and angiogenesis. They are in maximum number at 20 weeks gestation and are not seen at term pregnancy [26].
- Decidual macrophages: They comprise about 20% of the decidual leukocyte population in the first trimester. They play an important role in angiogenesis, spiral artery remodeling, and apoptosis.
- T cells: They comprise 10–20% of the leukocyte population in the decidua. They are further of two types: CD4+ T cells (30–45%) and CD 8+ T cells (45–75%).
  - CD8+ T cells: They have cytotoxic action and increase production of cytokines like interferon–gamma (IF) and IL-8.
  - CD4+ T cells: They help in promoting tolerance to the immunogenic fetus [27].

2.4.2 Th1 to Th2 Shift

Humoral immunity which is also known as antibody-mediated immunity is most effective against extracellular pathogens. Bacterial antigens present stimulate B lymphocytes specific to the pathogen and this effect is augmented by

T-helper type II (Th2) lymphocytes. Cell-mediated immunity which is essential for killing intracellular pathogens involves recognition followed by the destruction of the infected host cells. This immune response is augmented by T-helper type I (Th1) cells. In general, low estradiol levels promote CD4+ type1 helper T cell (Th1) response and cell-mediated immunity whereas high estradiol levels can augment CD4 + type2 helper cell (Th2) response and humoral immunity. The switch to Th2 cells is both due to the migration of these cells to the maternal-fetal interface and the action of progesterone, estradiol and prostaglandin D2 which also promote Th2 [28].

Th2 causes increase in the secretion of cytokines IL-4, IL-10, and monocyte colony-stimulating factors which has immunosuppressive effect. PGD2 is produced by the placenta which in turn chemoattracts Th2 cells to the maternal-fetal interface. In addition, IL-10 and IL-4 have anti-inflammatory action and inhibit Th1 cells, macrophages, TNF-alpha, and cyclooxygenase −2 (COX-2). Levels of inflammatory cytokines (alpha-interferon, monocyte chemoattractant protein 1, and Eotaxin) are decreased during pregnancy whereas tumor necrosis factor, interleukin-10, and granulocyte colony-stimulating factors may rise. Tregs (Regulatory T cells) increase in number during pregnancy and can be found in blood and lymph nodes. They have an immunosuppressive function and help in maintaining maternofetal tolerance [29]. Table 2.3 summarizes the regulation of immune function in pregnancy.

Table 2.3 Endocrine regulation of Immune system in pregnancy

Hormone	Th1 pathway	Th2 pathway	Effect on immune cells
Estradiol	Inhibits via decrease in IL-6, IL-1b & TNF-alpha	Stimulates via increase in IL-4, IL-10	• Increases in Treg proliferation & suppressive function
Progesterone	Inhibits via decrease in IL-6 & TNF-alpha	Stimulates via IL-4 & IL-10	• Increases in Treg proliferation & suppressive function • Suppresses T cell activation
Human chorionic gonadotropin (hCG)	Inhibits via decrease in TNF-alpha	Stimulates via TGF beta, IL-8 & IL-10	• Attracts Treg • Induces uNK cell proliferation • Promotes monocyte proliferation and function

2.4.3 Clinical Implications of Altered Immunology in Pregnancy

The modulated immune system in pregnancy leads to differential responses to various pathogens. It increases the risk of susceptibility to certain viral, bacterial and parasitic diseases. This is mainly due to suppression of cell-mediated immunity subsequent to a shift from Th1 to Th2 immune environment. This is mainly true for altered responses to respiratory infections and increased severity of infections like influenza and coccidioidomycosis. Also, some infections are more severe during pregnancy as compared to non-pregnant women. Decrease in adaptive immunity in later stages of pregnancy could be responsible for increase in the severity of infectious diseases during late pregnancy. Decrease in the number and function of CD4+, CD8+, and natural killer cells could affect antiviral, antifungal, antiparasitic response and delay clearance of offending microorganisms.

2.5 Maternal-Fetal Interface

The placenta with the fetal membranes (amnion and chorion) is described as the maternal-fetal interface. The fetal side of the interface is comprised of the placenta and the membranes and the maternal side is comprised of the uterine decidua which is in contact with the placenta. The placenta is an active immunologic site, capable of interacting and responding to pathogens and it

plays an important part in the overall susceptibility and severity of infectious diseases during pregnancy. The various intrinsic immune responses of placenta include:

2.5.1 Structure and Location of Placenta

The placenta which has a continuous cell layer of syncytiotrophoblast is the strongest cellular defense. There are no cellular junctions in this cell layer and so it cannot be exploited by pathogens or be modulated by inflammatory signals.

The syncytiotrophoblast cells also have a dense cytoskeletal network which protects them from direct microbial invasion. For example, toxoplasmosis gondii infection is restricted at the interface via a specific plasma membrane composition which does not allow parasite attachment [30, 31].

2.5.2 Antiviral Factors

The placenta secretes antiviral molecules like the vesicle enclosed placental microRNAs (miRNA) which restrict viral infections through autocrine and paracrine signals [32, 33].

2.5.3 Passive Immunity Transfer

The placenta also actively transports IgG antibodies from the mother to the fetal compartment. This transplacental passage begins at 16 weeks of gestation and increases throughout pregnancy [34].

2.5.4 Intracellular Defense

Placental trophoblasts possess high rates of autophagy through which they can restrict replication of intracellular pathogens; they also have the ability to recognize pathogens and trigger the antimicrobial signaling pathways [35].

2.6 Microbiology

There is difference in spectrum of infectious agents in pregnant women as compared with non-pregnant patients. This difference is due to altered cell-mediated immunity and risk of infections by organisms arising from genital tract during pregnancy. The spectrum of organisms responsible for obstetric infections includes vaginal, enteric, sexually transmitted organisms, anaerobes, and L. monocytogenes. Pregnant women are more at risk of human immunodeficiency virus infection and associated opportunistic infections; pregnancy also increases susceptibility for toxoplasmosis. The common microorganisms causing infections during pregnancy are shown in Table 2.4. A detailed discussion of various infections in pregnancy is provided in later chapters.

2.7 Pregnancy and Severity of Infection

Increased predisposition to infections during pregnancy can be due to physiological changes of pregnancy and immunological alteration with advancing pregnancy which may impair pathogen clearance resulting in increased severity to some pathogens. As compared to non-pregnant women, pregnant women have increased severity of disease with influenza virus, herpes simplex virus, malaria, and hepatitis E infection. Similar evidence for increased severity of measles and varicella infection in pregnancy is limited (Table 2.5).

2.7.1 Influenza Virus Infection

It has been seen that influenza infection is more severe in pregnant women. The maternal mortality rate during the influenza pandemic in 1918 was 27%and during the pandemic in 1957, 50% of fatalities that were seen in the reproductive age group were among pregnant women [38, 39]. During the influenza A pandemic in 2009, 509 pregnant women out of a total of 788 were hospi-

Table 2.4 Microorganisms causing infections during pregnancy

	Predisposing factor/source	Organisms
Obstetric sepsis	Anemia Obesity Impaired glucose tolerance Prolonged rupture of membranes Impaired immunity Invasive procedures like amniocentesis	Str Pyogenes (GAS) Escherichia coli Staphylococcus aureus Streptococcus spp. Enterobacter spp. Enterococcus spp. Clostridium spp. Mycoplasma hominis Peptostreptococcus spp. Morganella morganii Neisseria gonorrhea Chlamydia trachomatis L. monocytogenes
Respiratory	Usual organisms	Streptococcus pneumonia Staphylococcus aureus Klebsiella pneumonia Hemophilus influenza Mycoplasma pneumonia Legionella
	Altered cell-mediated immunity	Influenza virus Herpes zoster virus Coccidioidomycosis
Renal	Urinary stasis Smooth muscle relaxation Vesicoureteral reflux Ureteric obstruction	E. coli (80–90% cases) [36] Klebsiella pneumoniae Proteus mirabilis Group B streptococci Staphylococcus saprophyticus Less common-Gardnerella vaginalis, Enterococci, and Ureaplasma urealyticum
Gastroenteritis	Increased progesterone Elevated prostaglandins	Escherichia coli Salmonella typhi Shigella spp. Vibrio cholerae Campylobacter Clostridium difficile Listeria monocytogens Giardia Cryptosporidium

talized; 22.6% of these required ICU admission and 6% died [39]. The study also found that women in their third trimester had more severe diseases which required ICU admission. Other studies also found that pregnant women had more severe influenza disease than the general population [40–42]. Pramanick et al. in their study from south India found that the H1N1 pandemic in 2009 was associated with an increased mortality rate of 25% vis-à-vis 8% found in non-pregnant women [43]. Similar studies during this pandemic in developed countries did not observe a high case fatality rate in pregnant women which could be explained by early initiation of antiviral therapy [44, 45]. Infections with influenza B has not been seen to be associated with complicated disease [46].

2.7.2 Herpes Simplex Hepatitis

Pregnancy is a risk factor for herpes simplex virus (HSV) hepatitis most probably due to the immunosuppressive effect of pregnancy on the cell-mediated immunity [47]. HSV hepatitis is seen more commonly in pregnant women and

Table 2.5 Infections associated with increased susceptibility/severity in pregnancy [37]

Infection	Increased susceptibility	Increased severity	Management strategies
Strong Evidence			
Influenza	No	Yes	Early identification Early antiviral therapy Supportive care
Herpes simplex virus	No	Yes	Early antiviral therapy Supportive care High index of clinical suspicion
Malaria	Yes	Yes	Appropriate antimalarial therapy
Hepatitis E	No	Yes	High index of clinical suspicion Supportive care
Listeriosis	Yes	No	Appropriate antimicrobial therapy Care of the newborn
Limited Evidence			
Measles	No	Yes	High index of clinical suspicion Supportive care
Varicella	No	Yes	Antiviral therapy Supportive care
Human Immunodeficiency Virus	Yes	No	Early identification Antiretroviral therapy
Coccidioidomycosis	No	Yes	Early identification Antifungal therapy

carries a high mortality rate of up to 39% in them. The authors found that the most consistent feature seen in all the pregnant women with the condition was transaminitis and also a positive viral culture which was seen in 85% [48]. Various other studies have also shown a high incidence of HSV hepatitis during pregnancy [37, 49, 50].

2.7.3 Hepatitis E Infection

Hepatitis E infection is usually a self-limiting disease but has shown to be associated with 30% mortality in pregnant women especially in the third trimester [51]. The reason for the high mortality in this group is not known but the incidence of hepatic failure in pregnancy is high in HEV infection endemic areas of India, south-east Asia, and Africa. Khuroo et al. in 2003 reviewed all consecutive cases of acute liver failure between 1989 and 1996 diagnosed in young women. He found that 49 out of 83 women with acute liver failure were pregnant and 47 had HEV infection [52]. Another review by Aggarwal et al. concluded the fatality rate of HEV infection was higher in pregnant women as compared to the general population, 15–25% vis-à-vis 0.5 to 4% [53]. In the study by Jaiswal et al., 58% of pregnant women who had HEV infection developed fulminant liver failure with a mortality rate as high as 56% among them [54]. The exact pathogenesis of increased severity of hepatitis E infection in pregnancy is not known but altered immunity and hormonal factors have a causal role to play [55].

2.7.4 Varicella Infection

Chickenpox in pregnancy is seen in about 0.7–3/1000 pregnancies [56]. The morbidity and mortality of varicella pneumonia which complicates 10–20% of cases of chickenpox in pregnancy are higher than in non-pregnant women [57]. Studies indicate that up to 40% of pregnant women with varicella pneumonia might require mechanical ventilation and mortality is between 3 and 14% in this group [58, 59]. The increased severity of varicella infection in pregnancy is mainly attributed to the decrease in cell-mediated immunity during pregnancy which is seen to increase with gestational age.

2.7.5 Coccidioidomycosis

Pregnancy is a known risk factor for the development of severe coccidioidomycosis infection. This is especially true when the infection is acquired later in pregnancy; the greatest severity is seen in women who get the infection in the postpartum period [60]. Caldwell et al. reviewed pregnant women who developed coccidioidomycosis during the 1993 epidemic in California. Of the 32 pregnant women, 12 (38%) were diagnosed during the third trimester [61]. There are many case series and individual case reports which highlight the increased severity of coccidioidomycosis during pregnancy [60]. The main reason for the dissemination of coccidioidomycosis during pregnancy seems to be due to the decrease in cellular immunity normally seen during this time. This may also explain the increased rates of reactivation of the disease seen in pregnant women with a previous history of coccidioidomycosis [62].

2.8 Pregnancy and Increased Susceptibility to Infection

There is a Th1 to Th2 shift in pregnancy both at the maternal-fetal interface and also systemically. Systemic suppression of cell-mediated immunity (CMI) contributes to increased susceptibility to some infections such as toxoplasmosis, malaria, and listeriosis. To address the question of increased susceptibility of pregnant women to infections, more studies with larger sample size including non-pregnant control groups and with long prospective follow-up periods are required.

2.8.1 Malaria

Pregnant women are susceptible to malarial infection mainly because of placental sequestration of plasmodium. Plasmodium falciparum interacts with chondroitin sulfate A (CSA) present in the placental syncytiotrophoblasts and thus accumulates in the placenta [63]. Lack of immunity to these pregnancy-specific surface antigens increases malaria susceptibility during pregnancy [64]. So, pregnant women have been seen to have threefold risk of severe malaria as compared to non-pregnant women and a mortality rate of approximately 39%. The severity of malarial infection is high in primigravidas; the severity decreases with subsequent pregnancies which is probably due to acquisition of immunity to parasite expressing pregnancy-specific variant surface antigen [65]. Accumulation of P. vivax in the placenta has not been reported yet.

2.8.2 Listeriosis

Listeriosis is primarily a food-borne disease that spreads through contaminated vegetables, raw meat, or milk. Though Listeriosis is a rare infection, it is 20 times more commonly seen in pregnant women than in the general population;12/100,000 in pregnancy vis-à-vis 0.7/100,000 in the general population [66]. Listeria is a unique organism as it has an intracellular life cycle and CMI is the main host defence against infection by this pathogen. As pregnancy is associated with decrease in CMI, it makes pregnant women more susceptible to this infection. Also because of its intracellular transmission, Listeria monocytogenes is able to cross the placental barrier leading to preterm delivery, stillbirths, and neonatal disease [67].

2.9 Conclusion

The changes in pregnancy are multidimensional with anatomical, physiological, and hormonal changes playing an important role in the pathogenesis of the disease and its severity. Estrogen and progesterone have an important role in the modulation of the immune system during pregnancy causing a shift from Th1 to Th2 responses. The complex relationships between pregnancy-induced immunologic changes and infections may explain the altered severity and susceptibility to some infectious processes during pregnancy. Also, the role of placenta as an active immunologic site has recently been elucidated

and the placental tropism of specific pathogens has been described. Interfering with interaction between pathogens and placenta can be a potential strategy for vaccines against HSV, HEV, malaria parasites and emerging novel pathogens like SARS Cov2. The education of pregnant women about the prevention of infections and early identification and appropriate treatment of infectious diseases during pregnancy remain important strategies for protecting maternal and infant health.

Key Points

- The anatomical and functional changes during pregnancy affect the pulmonary function, ventilatory pattern, and gas exchange seen normally in the respiratory system.
- Weight gain and nasal obstruction during pregnancy can contribute to sleep breathing disorders. The enlarged uterus also causes decrease in FRC and hypoxemia and can exacerbate obstructive sleep apnea.
- Cardiopulmonary adaptive changes occurring during pregnancy such as increased heart rate and stroke volume and reduced pulmonary residual capacity increase risk of hypoxemia and pulmonary edema in pregnant women.
- The increase in renal size is associated with increase in interstitial volume and urinary dead space which predisposes to infection in pregnancy. Urinary stasis in the renal collecting system and increase in vesicoureteral reflux under the effect of progesterone also contribute to increased urinary infection during pregnancy.
- Placenta is an active immunologic site, capable of interacting and responding to pathogens and it plays an important part in the overall susceptibility and severity of infectious diseases during pregnancy.
- Pregnant women have increased severity of disease with influenza virus, herpes simplex virus, malaria, and hepatitis E infection as compared to non-pregnant women.
- Systemic suppression of cell-mediated immunity (CMI) contributes to increased susceptibility to some infections such as toxoplasmosis, malaria, and listeriosis.
- Pregnant women are susceptible to malarial infection mainly because of placental sequestration of plasmodium which interacts with chondroitin sulfate A (CSA) present in the placental syncytiotrophoblasts and thus accumulates in the placenta.
- Listeriosis is a rare infection but it is 20 times more commonly seen in pregnant women than the general population; 12/100,000 in pregnancy vis-à-vis 0.7/100,000 in the general population.

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Microbiome in Pregnancy

3

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3.1 Introduction

The human body has a complex association with the microbial community residing in the ecosystem of our body. It harbors trillions of bacteria as well as viruses, fungi, protozoans which have established intricate symbiotic or pathogenic relationships with the human system forming the part of the human microbiome. Many projects and studies are being carried out in order to study and characterize various microbes consisting of the human microbiome including the Human Microbiome Project by the National Institute of Health, USA; the METAHIT Project—Metagenomics of the Human Intestinal Tract supported by the European Commission with collaboration from various institutes across eight countries; and the International Human Microbiome Consortium.

The role of microbiota and its complex functional interactions with human health and disease is now less obscure [1]. Revised estimates reported that throughout the life span we are carrying microbes, almost equal in numbers to our own body cells [2]. Though as per the earlier belief, the microorganisms in our human body consisted of up to 100 trillion cells amounting to tenfold of human cells, encoding hundred times more unique genes than the human genome [3, 4].

It is often claimed that Joshua Lederberg gave the term "microbiome" in 2001; however, many articles point out the fact that the term microbiome has been used in literature before 2001 as well [5, 6].

Initial researches of the gut microbiome include data based largely on culture-dependent techniques being able to cultivate only 10–30% of gut microflora [7]. The development of better technologies in the fields of genome sequencing and bioinformatics has facilitated studies granting better insights into the microbiome, their interaction with the human body, and function. Recent technology of Next Generation Sequencing (NGS) has helped in the identification of uncultivable microorganisms. Recent DNA sequencing-based studies have achieved genome resolution that enabled host-specific association of microbial communities.

The microbiome has an indispensable role in normal functioning of human physiology, proper nutrition, human health, and regulating immunity. The human microbiome is influenced by different factors including genetic makeup, age, sex, dietary habits, and geographic location of individuals. The composition of microbial flora can vary at different sites and can be influenced by various environmental factors like oxygen concentration, humidity, temperature.

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During pregnancy, the mother's body undergoes various biological changes including changes in the hormones, immune system, and other metabolic changes for normal development of the fetus. The immunological and metabolic changes during pregnancy have been vastly studied, however, changes in the maternal microbiome are relatively underexplored. Understanding the role of alteration in maternal microbiome during pregnancy is crucial to fill the gaps in knowledge pertaining to its impact on the infant and maternal health and its role in diseases.

Earlier studies indicated the fetus to be in a completely sterile environment, however, recent literature suggests otherwise. There are studies suggesting the existence of local microbiomes in the placenta, amniotic cavity, and even meconium. The possibility of transmission of microbiota from the mother to form a part of the fetus microbiome highlights the importance of a healthy maternal microbiome.

3.2 Gut Microbiome

The microbiome of the human gut is among the most complex communities that play important multi-factorial roles in human physiology. The mucosal surface of the human gut spans an area of around 200–300 m^2 with $10^{13–14}$ bacteria belonging to various species and subspecies colonizing the tract [8]. These numerous and diverse microorganisms in the human gastrointestinal tract establish a complex ecological system that is influenced by environmental factors and interact with host in a symbiotic fashion by contributing to metabolism, immune response, and intestinal architecture [9]. There are several ecosystems all throughout the gastrointestinal tract that are still unmapped in terms of metagenomic diversity [10]. This diversity of the human intestinal microbiome adds to the uniqueness of each individual's microbiota. The gut microbiota can also be influenced by physiological factors, host genotype, habitat [10, 11] and geographical location, as dietary and lifestyle patterns often vary in different areas [12]. These environmental exposures especially the ones early on in life and the maternal flora have an impact on the composition of the gut microbiota [3].

The gut microbiome forms an essential component of human metabolism and overall health. The development of the gut microbiota begins even before birth and starts resembling the microbiota of the adult by around 3 years of age. The early colonizers include Enterobacteria and Bifidobacteria. It is influenced by the maternal microbiome, the method of delivery—vaginal delivery or cesarean section, type of feeding (exclusive breastfeeding or formula-based diet), and other environmental factors. The use of antimicrobials during pregnancy and in adulthood can also alter the healthy balanced gut microbiota and can even contribute to the build-up of multidrug-resistant microorganisms. In the entire gastrointestinal tract, the intestine harbors the most abundant and rich microflora in terms of diversity. The importance of gut microbiome in human health has been well established. The gut flora serves some very important functions notably, nutrient metabolism, drug metabolism, preventing pathogenic microorganisms from colonizing, regulation of systemic and local immune system, maintenance of intestinal integrity by maintaining the gut mucosal barrier.

The major function of the human gut is digestion and absorption of nutrients and excretion of waste products. Apart from these basic functions, gut plays a crucial role in the regulation of immune functions, mucosal defence, and microbial homeostasis. The intestine epithelial cells respond to microorganisms in the gut by providing a physical barrier and by functioning as an immune cell by inducing cytokines and chemokines and expressing receptors for microbial-associated molecular patterns. The interaction between microflora and enterocytes plays an important role in immunomodulation. With exposure to a wide range of microbes, it contributes to postnatal immune system development. Hence, the component of microbiome acquired during and shortly after birth is imperative in the development of newborn's systemic and mucosal immunity. Recent literature suggests the role of certain microorganisms in influencing various components of the immune system including the

epithelial immune cells of the lamina propria. Through stimulation of cytokine release and activation of T-cell immune response along with increased production of IgA, certain beneficial microflora and probiotics can influence mucosal immunity. The gastrointestinal tract contains almost 80% of all human plasma cells producing higher amounts of IgA than any other isotype.

3.2.1 Composition of Gut Microbiome in Healthy Individual

The human intestine harbors bacteria belonging majorly to Firmicutes (30%–50%) and Bacteroidetes (20%–40%) phyla. The other common phyla include *Actinobacteria* (1%–10%), *Proteobacteria,* and *Verrucomicrobia*. Most of these are nonpathogenic and have established a symbiotic relationship in the intestinal milieu. The gut contains strict and facultative anaerobes including *Bacteroides*, *Eubacterium, Fusobacterium*, *Bifidobacteria* along with *Peptostreptococci, Lactobacilli.* It also harbors *Enterococcus spp. Streptococcus spp.* and members of the *Enterobacteriaceae* family.

Due to the presence of gastric acid in stomach, bile, and pancreatic secretions in the proximal duodenum, these areas of the gut have a lower bacterial density (10^1–10^3cfu/mL). However, it increases through jejunum, ileum (10^4-10^7 cfu/mL) to colon (10^{11}-10^{12} cfu/mL) [13].

This temporal variation can also be seen in the terms of diversity. Gram-positive cocci including *Gamella, Rothia, Streptococci*; Gram-negative anaerobic cocci like *Megasphaera, Veillonella*, Gram-negative bacilli including *Prevotella, Pseudomonas* are common flora in the esophagus. In the gastric region, *Streptococcus, Lactobacillus, Prevotella, Helicobacter, Enterococcus* are common. Besides *Bacteroides, Clostridia*, the small intestine has *Lactobacilli, Streptococci,* and *Enterococci*. Again Firmicutes and Bacteroidetes are the predominant flora of the large intestine. *Fecalibacterium*, *Fusobacterium* are common in the cecum along with *Ruminococci, Lachnospira*. *Clostridia, Ruminococci, Streptococci, Peprostreptococci, Enterococci, Lactobacilli* are common in colon. *Prevotella, Porphyromonas, Eubacterium, Fusobacterium* are also present in the colon [14]. In addition to these microorganisms, various pathogenic bacteria such as *Salmonella, Vibrio,* etc. may also be present and though miniscule, may also contribute to the gut microbiome.

In addition to the temporal variation, there is difference in the predominant flora of the gut lumen as compared to the mucosal surface. While the lumen contains more anaerobes to aerobes as compared to a lower anaerobes to aerobes ratio at the mucosal surface. *Bacteroides, Bifidobacterium* along with *Streptococci, Enterococci, Clostridia, Lactobacilli,* and members of the *Enterobacteriacae* family are predominant in the lumen while *Clostridia, Lactobacilli, Enterococci* and *Akkermansia* are more common at mucosal site.

Bacteroides, Clostridia, and *Lactobacilli* produce short-chain fatty acids which are utilized by the gut to maintain homeostasis and can also induce secretion of glucagon-like peptide and peptide YY [15] which allows absorption of nutrients from the gut lumen.

Any imbalance in the normal composition of this flora can result in dysbiosis which can contribute to diseases like inflammatory bowel diseases, obesity, cancer. A relative decrease in Firmicutes and Bacteroidetes and an increase in Proteobacteria has been seen in inflammatory bowel diseases.

3.2.2 Gut Microbiome in Pregnancy

The interplay of hormonal variations along with diet, genetics, and changes in immunological states during pregnancy can have an impact on the gut microbiome and the overall health.

Recent studies indicate that the modifications of human microbiome during pregnancy may help in sustaining homeostasis and also the physiological changes that take place in human body in pregnancy [16]. Environmental factors, diet, and lifestyle are regulating factors that can affect the brain-gut axis and long-term health of women

and infants. The extent to which the gut microbiome contributes to the neuro-development, immunological and intestinal health of the pregnant woman and fetus is now beginning to be assessed. Therapies to promote eubiosis and treat dysbiosis of the maternal gut are still in infancy and need to be explored. The gut microbiota during pregnancy is essential due to its critical roles in nutrient absorption, immune-modeling, and infection protection [17]. The maternal gut microbiome composition contributes to obstetric outcomes with long-term health effects for mother and child [18].

In a normal healthy pregnancy, the gut microbiome undergoes variation over the course of pregnancy. Studies have reported an increase in β-diversity while a decrease in α-diversity and more abundance of Proteobacteria and Actinobacteria [19].

Bacteroides, *Staphylococcus* spp. have been found to be significantly higher and associated with weight gain during pregnancy while other studies have shown reduction in *Bifidobacterium, Akkermansia muciniphila,* and lower α-diversity [20].

Diet can affect the gut microbiota. Food rich in fat and sugar content promotes dysbiosis and can increase weight while consumption of lean meat, proteins, fiber promotes a healthy and stable gut microbiota. Many animal and human studies have shown that maternal obesity and high-fat diets can impact the abundance and diversity of the gut microbiome which may in turn alter the gut microbiota of the child. Chu et al. observed a relative decrease in *Bacteroides* in neonates of mothers on high-fat gestational diet [21]. In another study, *Parabacteroides* and *Oscillibacter* spp. were found to be higher along with *Blautia* and *Eubacterium* spp. in offspring of obese women from a higher socioeconomic status [22] This variation of the gut microbiota may partly contribute to the risk of obesity in the offspring of these obese women.

Altered profiles of microbiota can contribute to various changes in metabolism. *Collinsella* has been linked to insulin, triglycerides, and very-low-density lipoproteins while relationship of *Sutterella* with C-reactive protein has been studied. *Bacteroidaceae* and ghrelin relation has also been evaluated. *Faecalibacterium/ Fusobacterium* ratios have been suggested to be inversely related to blood glucose [20, 23]. A study by Gomez-Angro et al. revealed a positive correlation of gastrointestinal polypeptide with *Coprococcus* and a negative correlation with Ruminococcaceae [23].

3.3 Oral Microbiome

The oral microbiome has the second largest collection of microbes following the gut microbiome. There are approximately 700 predominant species of organisms in the oral microbiome of which almost one third have not been grown in vitro subgingival crevice offers maximum diversity of these organisms while the tongue, palate, buccal mucosa, tonsils, and the tooth are the other niches providing suitable environment to these organisms to flourish. The organisms from these sites slough off and can form a part of the flora of the saliva. Dysbiosis can lead to dental caries, periodontal infections, endodontic lesions, halitosis, and other infections.

3.3.1 Composition of Oral Microbiome of Healthy Individual

Firmicutes, Bacteroidetes, Fusobacteria, Proteobacteria, Actinobacteria are the common phyla of the oral microbiome. The presence of Spirochaetes, Synergistetes, Saccharibacteria (TM7), and Gracilibacteria (GN02) are also reported. The predominant genera comprising the oral microbiota are shown in Fig. 3.1.

Over 75 genera have been reported to form a part of the oral mycobiome. The most predominant are *Candida, Cladosporium, Aureobasidium, Aspergillus* [26]. Dupuy and colleagues have also reported *Malassezia* spp. as an abundant commensal of the oral cavity [27].

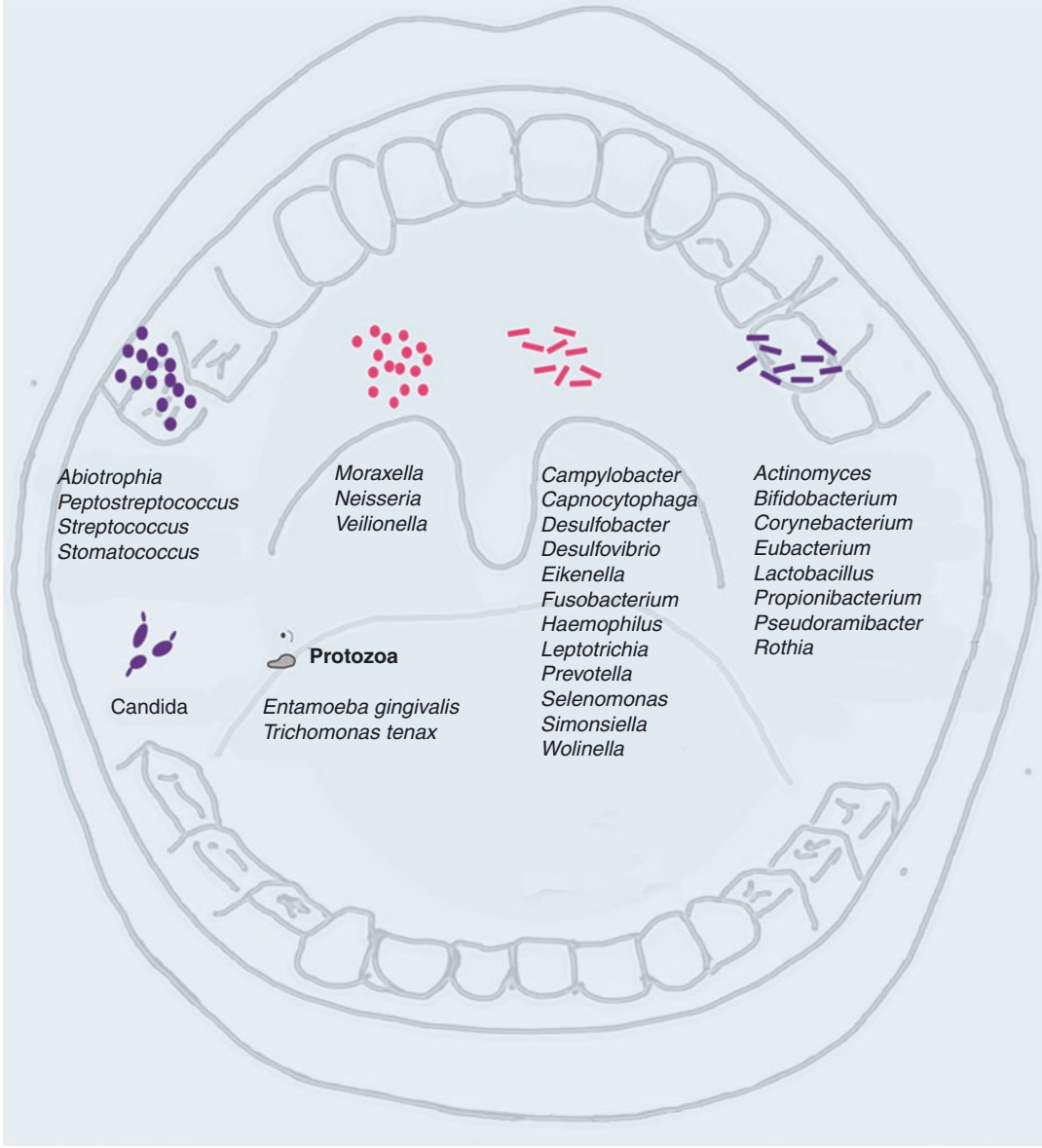

Fig. 3.1 Oral microbiome (Compiled and modified from Marsh et al. [24] and Deo et al. [25])

Many factors may influence the growth of organisms in the oral cavity. The range of the pH of saliva is around 6.75–7.25 favoring the growth of many organisms. During the metabolism of the dietary sugars, the pH of the plaque may fall. The differences in the oxygen gradient in the plaques may favor the growth of obligate anaerobes. Additionally, various nutrients, antimicrobials, temperature may also alter the composition of the oral microbiome.

Many cross-kingdom interactions especially the fungal-bacterial interactions have been described in the oral ecosystem. *C. albicans* has been reported to interact synergistically with *Streptococcus oralis*. Their interaction can result in increased levels of a proteolytic enzyme—μ-calpain which causes degradation of oral epithelial junctions and increased tissue invasion.

C. albicans and *Streptococcus mutans* interaction can result in increased biofilm production

and increase in glucan production and can coinfection result in the development of severe early childhood caries [28].

3.3.2 Oral Microbiome in Pregnancy

Higher prevalence of periodontal pathogens and increase in microbial load of oral flora has been described. *Aggregatibacter actinomycotemcomitans* have been found to be higher in pregnant females. *Porphyromonas gingivalis* was also reported significantly higher in the subgingival plaque in pregnant females in their early and mid-pregnancy. Candida species levels and the oral alpha-diversity index also have been reported to increase during later stages of pregnancy. Increase in the hormone levels of estrogen and progesterone has been suggested as one of the possible explanations.

The amount of literature on effect of pregnancy on oral microbiota and its implications is limited. There are certain studies that have reported the association of certain bacteria from the oral microbiome with adverse outcomes in pregnancy [29]. Another study reported *F. nucleatum* in amniotic fluid in preterm labor patients [30]. These raise more questions than answers on the mode of transmission of these bacteria from oral cavity to the placenta and warrant the need for more studies in this regard.

3.4 Placental Microbiome

For long, the fetus, placenta, and amniotic fluid were considered sterile. This classical thought, the sterile womb paradigm, has been challenged by various studies. Researchers have also suggested existance of a low biomass microbial community in the normal placenta. Placenta has been reported to harbor low abundant and metabolically rich microbiota with Firmicutes, Tenericutes, Proteobacteria, Bacteroidetes, Fusobacteria as the predominant phyla [31]. Studies based on techniques like whole-genome sequencing have shown similarities of the placental microbiome to the oral microbiome. Transfer of microbes via hematogenous route from oral cavity has been postulated. However, there are studies that urge to consider the possibility of the low microbial biomass detected in the placenta as a background contamination hence questioning the existence of the placental microbiome [32].

With the presence of microbes in the amniotic fluid, its ingestion by the fetus can aid in the microbial colonization of the fetal gut. *Enterococcus faecalis*, *Staphylococcus epidermidis*, *Escherichia coli, Bifidobacterium* have been reported in the first pass meconium samples of neonates [33, 34].

3.5 Vaginal Microbiome

The human vaginal microbiome plays a vital role in the prevention of various diseases like bacterial vaginosis, sexually transmitted diseases, and urinary tract infections. The *Lactobacilli* produce various bacteriostatic and bacteriocidal compounds and metabolic products like lactic acid lowering the pH which becomes inhibitory to many bacteria.

3.6 Composition of Vaginal Microbiome in Healthy Individual

The vaginal microbiome keeps changing throughout the various phases of the life a woman. Under the influence of low levels of estrogen and a relatively thinner mucosa, the microbiota during childhood is more diverse consisting of both anaerobic and aerobic bacteria. These include cocci like *Peptococci, Peptostreptococci, Veillonella, Staphylococci,* and *Enterococci*. Amongst the bacilli Bacteroides, Fusobacterium, Bifidobacterium, Propionibacterium are present. In the prepubertal phase, relative decrease in *Lactobacillus* spp., *Gardnerella,* and *Prevotella* has been reported. While during puberty, under the influence of estrogen, the epithelium of the vagina is thicker and Lactobacilli are the predom-

inant species. Staphylococci, Streptococci, genital Mycoplasmas have also been reported. While, *Corynebacterium, Gardnerella, Mobiluncus, Prevotella* are amongst the other genera [35].

Ravel et al. described the composition of vaginal microbiome in asymptomatic women from different races and ethnic groups in North American women [36]. They described five vaginal bacterial community state types of which four were dominated by different *Lactobacilli* spp., *L. crispatus* (Type I), *L. gasseri* (Type II), *L. iners* (Type III), and *L. jensenii* (Type V) while Type IV had less Lactobacilli and more proportion of strict anaerobes including *Prevotella, Atopobium, Megasphaera,* etc. Interestingly, the function of lactic acid production was conserved in all the five types by the presence of *Lactobacillus, Megasphaera, Streptococcus,* and *Atopobium* [36].

Human virome is an emerging concept and comprises all the prokaryotic and eukaryotic viruses whether they are colonizing or pathogenic, acute or latent. Eukaryotic viruses though less common are important in terms of disease causation e.g. *Papillomaviridae* and *Herpesviridae*.

3.7 Vaginal Microbiome in Pregnancy

During pregnancy, there is a decrease in the diversity and richness of the vaginal microbiome. The microbiome is more stable as compared to nonpregnant females and a predominance of Lactobacillaceae, Clostridiales, Bacteroidales, and Actinomycetales has been reported [37]. *Lactobacilli* become less abundant and increase in alpha diversity has been noted in post-partum women.

Studies have evaluated the association of alterations in vaginal microbiome with preterm birth. As per the data by the integrative Human Microbiome Project, Fettweis and colleagues reported significantly reduced *L.crispatus* and more abundant BV-associated bacterium 1, *Sneathiaamnii*, TM7-H1, *Prevotella* species were noted in vaginal microbiome of women who had pre-term deliveries [38]. Many other studies have also reported an association of predominance of *L. crispatus* with a lesser risk of preterm birth [39]. Ascending infections from vaginal microbiome can also contribute to premature rupture of membranes and intra-amniotic infections.

3.8 Uterine Microbiome

The existence of a uterine microbiome in normal healthy women has been questionable for long. The development of advanced techniques like next-generation sequencing has helped in identifying microorganisms beyond what could be detected by culture-based methods. In a study by Franasiak and colleagues, *Lactobacillus* and *Flavobacterium* were predominant flora of the endometrial microbiota during embryo transfer [40]. Researchers have put forward various theories of a possible origin of the uterine or endometrial microbiome which include possible extension of vaginal or cervical microbiota or spread from gastrointestinal tract into peritoneal cavity and further migration through the fallopian tubes or hematogenous spread [41].

The uterine microbiota consists of bacteria belonging mainly to Firmicutes with *Lactobacillus* being most commonly reported, Bacteriodetes, Proteobacteria, and Actinobacteria. *Lactobacillus* and *Streptococcus* spp. have been commonly reported as a part of the uterine and endometrial microbiota, however, both the genera are also a part of the vaginal microbiome and a possible contamination in sample collection methods is plausible [42].

A healthy endometrium is important for successful implantation. The presence of microorganisms in the uterus has been linked with poor reproductive outcomes and endometriosis. Swidsinski and colleagues demonstrated a polymicrobial *Gardnerella vaginalis* endometrial biofilm in 50% of the women with bacterial vaginosis in their study [43]. Studies have linked uterine microbiome to endometriosis, endometrial cancer, and success of implantation in in-vitro fertilization.

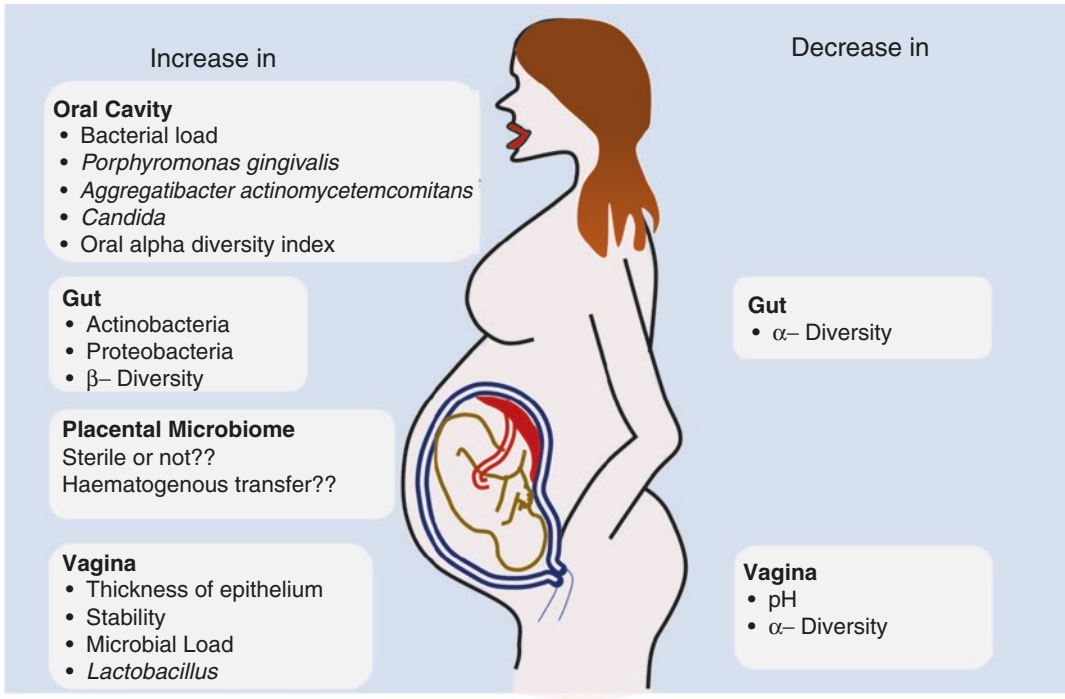

Fig. 3.2 Microbiome changes in pregnancy (Compiled and modified from Nuriel-Ohayon et al. [29] and Bagga et al. [35])

3.9 Conclusion

With the changes in hormones, metabolic processes of the body during pregnancy, changes in microbiome are also noted (Fig. 3.2). The changes in the microbiota at different sites can in turn affect the host metabolism and immunity. These host and microbiome interactions are complex and are still understudied. The advances in technology have provided insight into how alteration in the microbiome can result in diseases and adverse fetal outcomes. However, further studies are warranted to study how dysbiosis or specific changes in microbiome can predict poor reproductive outcomes or indicate disease-like states. Better understanding of these processes can result in better management and improved maternal and fetal outcomes.

Conflicts of Interest None declared.

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Part II

Respiratory Infections in Pregnancy: Management and Challenges

Bacterial and Fungal Pneumonia

4

Karan Madan

4.1 Introduction

The diagnosis and clinical management principles of pneumonia in pregnancy are essentially similar to those in non-pregnant adults. However, there are physiological changes in the respiratory system during pregnancy [1]. Based on available data from the USA, pneumonia was diagnosed in 30% of pregnant women with severe sepsis [2]. Pneumonia is associated with adverse fetal and maternal outcomes, including maternal mortality [3]. The overall approach to pneumonia in pregnancy may be subdivided into a diagnostic plan and a management approach. During the evaluation, a decision is required to differentiate between Community-acquired Pneumonia (CAP) or Nosocomial Pneumonia that includes Hospital-Acquired Pneumonia (HAP) and another subset of patients who may be receiving mechanical ventilation, Ventilator-Associated Pneumonia (VAP). Another terminology, HCAP (Healthcare-associated Pneumonia), was used previously but has recently fallen out of favor.

Essentially, CAP and Nosocomial pneumonia management principles differ primarily due to the differing underlying microbiological profile of the causative pathogens [4]. The empiric antimicrobial treatment, therefore, needs to be carefully chosen. Inappropriate antimicrobial therapy may be associated with adverse outcomes. The treatment's potential adverse effects on the fetus need to be considered when selecting the treatment drugs. In this chapter, we primarily discuss the diagnostic and management principles of bacterial pneumonia. Other clinically relevant conditions in pregnancy include aspiration pneumonia. The issues related to viral pneumonia and COVID-19 are covered elsewhere.

4.2 Definitions

4.2.1 Community-Acquired Pneumonia (CAP)

CAP may be defined depending on the presence or the absence of a chest radiograph. When a chest radiograph is not available, CAP is defined as (a) symptoms of an acute lower respiratory tract illness (cough with or without expectoration, breathlessness, pleuritic chest pain) of less than a week duration; and (b) at least one systemic feature (temperature > 37.7 °C, chills, and rigors, and/or severe malaise); and (c) new focal chest signs (bronchial breath sounds and/or crackles); with (d) no other explanation for the illness [5]. With a chest radiograph available, CAP is defined as:

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symptoms and signs as above with new radiographic shadows (with no other explanation like pulmonary edema or lung infarction) [5]. The radiographic shadows may include appearances like a lobar consolidation, patchy consolidation, silhouette sign, or interstitial opacities without an alternative explanation.

4.2.2 Hospital-Acquired Pneumonia (HAP)

HAP is defined as pneumonia developing at least after 48 h of hospital admission. HAP is the second most common nosocomial infection with a high attributable burden of mortality [5, 6]. HAP is associated with significantly increased costs of treatment and increased duration of stay in the hospital. The risk of developing HAP/VAP is greatest early during the hospital stay.

4.2.3 Ventilator-Associated Pneumonia (VAP)

VAP is pneumonia that develops after 48 h of endotracheal intubation. Approximately 50% of the episodes of VAP occur within 4 days of initiation of mechanical ventilation. VAP leads to increased ICU treatment costs and is associated with increased hospital stay duration and mortality (up to tenfold increased risk of death). The diagnosis of VAP may be considered on clinical grounds or in integration with microbiological sampling. One of the commonly used clinical definitions of VAP as proposed by the ACCP (American College of Chest Physicians); A diagnosis of pneumonia is defined as the presence of new, persistent pulmonary infiltrates not otherwise explained, appearing on chest radiographs. Moreover, at least two of the following criteria are required: (1) Temperature of >38 °C, (2) Leukocytosis >10,000 cells/mm^3, (3) Purulent respiratory secretions. Pneumonia is ventilator-associated when it occurred after intubation and judged not to be incubating before insertion of an artificial airway [7].

4.3 Clinical Profile

4.3.1 History

The pneumonia symptoms in pregnancy are similar to non-pregnant patients, and typical symptoms include fever, cough, expectoration, chest pain, and breathlessness. The onset is typically acute, with symptoms developing over hours to days. Some patients may also complain of streaky hemoptysis. However, significant hemoptysis is uncommon. The signs and symptoms of pneumonia are due to the exudation of fluid and leucocytes in the alveolar space. With extensive lung involvement, hypoxemia may occur due to impairment of gas exchange. The symptom severity is variable. Some patients demonstrate a mild illness, while the other extreme may be ARDS, sepsis, and multiorgan dysfunction. Few important risk factors for pneumonia in pregnancy include anemia, bronchial asthma, smoking, and immunosuppression.

In TB endemic settings like India, a high TB suspicion index may be kept if the clinical profile is atypical. This is especially important if the onset of illness is subacute, and there are clinical features like poor weight gain, loss of appetite, and other constitutional symptoms. Rarely, TB may present with an acute illness mimicking bacterial CAP, and ARDS has also been reported [8]. Many patients with tubercular pleural effusion have an acute illness that may mimic pneumonia [9]. Therefore, a radiological investigation is always preferred to confirm a diagnosis and exclude alternative conditions.

In patients receiving mechanical ventilation, a diagnosis of VAP is usually suspected in the setting of acute clinical worsening along with increasing radiological infiltrates on the chest radiograph. However, it is essential to note that all new chest radiographic opacities in mechanically ventilated patients do not represent VAP.

4.3.2 Clinical Examination

The role of clinical examination findings alone for the diagnosis of pneumonia is debatable.

Bronchial breath sounds may not be evident, and their absence does not exclude the diagnosis. Some patients with pneumonia may develop a parapneumonic pleural effusion, and in this situation, a reduction in the intensity of breath sounds may be evident on clinical examination [10].

Typically, the patients are tachypneic, and tachycardia may be evident. Hypoxemia is common, and the severity of hypoxemia depends on lung involvement and underlying physiological status. Patients with infection with atypical organisms may show clinical symptoms, but typical radiological findings of consolidation may be absent. The clinical examination should also focus on examining other organ systems to exclude alternative diagnoses or coexistent conditions. Other potential causes during pregnancy need to be considered as differential diagnoses in patients with acute respiratory failure. These include pulmonary edema, asthma exacerbation, preeclampsia and eclampsia, aspiration, pulmonary embolism, transfusion reactions, amniotic fluid embolism, and others.

4.4 Epidemiology and Microbiology

The incidence of pneumonia in pregnancy may be similar to the general adult population (reported rates 0.2–8.5 per 1000 deliveries) [11]. Based on a review of the available data, the most common bacterial etiological agents of CAP (Indian Pneumonia guidelines) include Streptococcus pneumonia, Staphylococcus aureus, Klebsiella pneumonia, Haemophilus influenza, Mycoplasma pneumonia, and Legionella pneumophila [5]. Streptococcus pneumoniae is the most common etiology for CAP. A microbiological diagnosis in CAP is possible in up to 40–70% of patients. In many patients, a definite etiology is not established, and empiric antimicrobial therapy is continued. One possible reason for the low incidence of microbiological diagnosis is the early initiation of empiric antimicrobial therapy. The risk factors for Pseudomonas aeruginosa as the causative organism for CAP include underlying chronic respiratory disease, immunosuppressive treatment or immunocompromised states, nasogastric tube feeding, and chronic neurological disorders.

In the context of HAP and VAP, the onset of pneumonia's timing is associated with possible microbiology and outcomes. Following hospitalization (or endotracheal intubation), Early-onset HAP (and VAP) is defined as pneumonia occurring within the first 4 days. The microbiological profile in this setting primarily includes drug-sensitive bacteria, and the prognosis is better. On the other hand, multidrug-resistant (MDR) pathogens predominate in late-onset HAP and VAP (day five or after that). Understandably, the morbidity and mortality associated with late-onset VAP/HAP are greater. The microbial etiology of HAP/VAP is broad, and infections with multiple bacteria are common. The primary causative bacteria include aerobic Gram-negative bacilli (P. aeruginosa, E. coli, K. pneumoniae, and Acinetobacter) and Gram-positive cocci (Staphylococcus aureus, particularly methicillin-resistant Staphylococcus. aureus). According to the available Indian literature, Gram-negative bacteria are the most common causes of HAP/VAP. The most commonly reported organisms are Acinetobacter species followed by Pseudomonas aeruginosa. The risk factors for acquiring infection with MDR pathogens are summarized in Table 4.1.

VAP may affect around a third of patients receiving mechanical ventilation; the incidence varies according to the clinical setting and

Table 4.1 Risk factors associated with the risk of infection with MDR pathogens [1]

Received antimicrobial therapy in the preceding 3 months
Current hospitalization of ≥5 days
High frequency of antibiotic resistance in the community/hospital unit
Hospitalization for ≥48 h in the prior 3 months
Home infusion therapy, including antibiotics
Home wound care
Chronic dialysis within 1 month
A family member with MDR pathogen
Immunosuppressive drug and/or therapy

Adapted from Hegewald MJ, Crapo RO. Respiratory physiology in pregnancy. Clinics in chest medicine 2011;32 [1]:1–13

increases with a longer invasive ventilation duration. The risk of developing VAP is the greatest early during mechanical ventilation (3% per day up to the first 5 days and reducing to 1% per day after the tenth day). Predictors and risk factors for VAP include severe illness, trauma, neurological, respiratory, cardiac conditions, aspiration, use of neuromuscular blockers, diabetes, alcoholism, hypotension, renal failure, enteral feedings, surgery, and malignancy. Routine change of ventilator circuits in mechanically ventilated patients may also increase the risk of developing VAP [5].

4.5 Diagnosis

4.5.1 Chest Radiograph

The diagnosis of pneumonia usually requires integrating clinical findings and demonstrating an infiltrate on the chest radiograph. A chest radiograph should always be obtained when pneumonia is suspected. A hesitancy to get a chest radiograph when pneumonia is suspected may lead to a delay in diagnosis, treatment delay and may be associated with adverse outcomes. The physician's clinical judgment alone had insufficient sensitivity for the diagnosis of pneumonia than a chest radiograph [12]. In the presence of the following findings, a chest radiograph should not be delayed in the clinical setting of pneumonia: breathlessness and/or cough with fever, tachycardia, tachypnea, reduced oxygen saturation, or bronchial breath sounds on clinical examination. An abdominal shield must be used when obtaining a chest radiograph in a pregnant patient. The fetal absorption of radiation with a chest radiograph is much below the doses known to be associated with radiation exposure adverse effects. Lateral chest radiographs are often underutilized, and most recommendations suggest obtaining both posteroanterior and lateral chest radiographs.

In typical cases, the chest radiograph may demonstrate evidence of lobar consolidation. This is indicated by the observations of air bronchograms within a localized opacity corresponding to a lobe. A diffuse white opacification may indicate extensive bilateral involvement and ARDS in the presence of significant arterial hypoxemia. In many patients, the appearance may suggest a bronchopneumonia picture that is characterized by multiple patchy opacities. A blunted costophrenic angle may indicate the presence of a pleural effusion. Certain organisms can cause significant parenchymal lung necrosis, leading to cavitation findings, referred to as necrotizing pneumonia. The interobserver reliability for the interpretation of chest radiographic findings is good [13].

In any hospitalized patient with signs and symptoms of pneumonia, HAP/VAP should be suspected. A chest radiograph should be obtained early for detection. The findings that support a diagnosis of HAP/VAP include new or progressive radiologic infiltrates along with two of the following: new onset fever, purulent secretions, leukocytosis, and decline in oxygen saturation.

The resolution of chest radiographic abnormality may lag behind the clinical response in pneumonia. Therefore, a slow radiological improvement is not a reason for extensive clinical evaluation if clinical recovery has occurred. With a persistent clinical and radiological abnormality persistent beyond 4–6 weeks, alternative etiology should be investigated and excluded. According to the Indian guidelines on pneumonia, a chest radiograph should be obtained routinely in patients suspected of pneumonia. Treatment may be administered even if a chest radiograph is not available. In patients who improve clinically, routine chest radiographs for follow-up are not warranted.

4.5.2 Computed Tomography (CT)

The role of CT scanning in the diagnosis of pneumonia is unclear. The CT scan does not add to decision-making in initial presentations with a typical clinical profile, and CT appearance does not correlate with the microbiological etiology. Keeping in view the significantly high radiation exposures with a CT scan, the role of CT scan for the evaluation of pneumonia in pregnancy is limited. CT features of pneumonia include consoli-

dation (with the demonstration of air bronchograms), ground-glass opacification, nodules, and bronchial wall thickening. However, there is a subset of patients with a CT-only pneumonia, and decisions on such a clinical profile in pregnancy must be undertaken as a part of a multidisciplinary team [14].

4.5.3 Thoracic Ultrasound

Point of care ultrasonography (POCUS) is increasingly being utilized to make on-site care decisions in emergency and critical care settings. With experience, operators who routinely use POCUS can use it to diagnose pneumonia with good sensitivity. The particular advantage of POCUS includes lack of radiation exposure and rapid assistance towards decision making. It is a repeatable and versatile modality in the evaluation of acute respiratory conditions. Pneumonia may be suggested by the presence of various lung ultrasound findings that include localized B-lines, dynamic air bronchograms, reduction in lung slide, shred sign, and pleural effusion [15, 16]. Chest radiograph remains the standard of care investigation for a diagnosis of pneumonia in pregnancy. However, the role of POCUS for pneumonia in pregnancy needs further research.

4.5.4 Microbiological Investigations

Microbiological investigations must always be sent in a patient with pneumonia. Blood cultures and sputum gram staining, and culture must be obtained in all patients. Although the diagnostic yield of blood cultures in pneumonia is low, the specificity is high. In patients with suspicion of TB, sputum smear examination for acid-fast bacilli and cartridge-based nucleic acid amplification test (like GeneXpert) may be performed. In patients with severe pneumonia, urine antigen testing for Legionella may be preferably obtained [17]. There is no need to test for atypical microorganisms routinely as these diagnostic techniques are cumbersome with variable diagnostic yield.

Although a VAP diagnosis is commonly made on clinical grounds for antimicrobial therapy initiation, many clinicians believe that a microbiological diagnosis is ideal for optimizing management. Microbial cultures from the lower respiratory tract may be obtained using bronchoscopic or non-bronchoscopic techniques. These techniques may improve the yield of establishing a microbiological diagnosis with a drug sensitivity pattern. The bronchoscopic approach relies on a flexible bronchoscope (reusable or disposable scopes), which is negotiated through the endotracheal or tracheostomy tube in ventilated patients. The lower airways may be visualized, and samples like bronchoalveolar lavage (BAL) and protected specimen brush (PSB) may be obtained. Quantitative cultures should be requested. The specimen sampling site is decided based on the pattern of radiological involvement or the abnormal appearance on a bronchoscopic examination. Non-bronchoscopic techniques for the diagnosis of VAP are mini-BAL and blind protected specimen brushes. A non-bronchoscopic approach is performed in most centers, as these do not require an experienced bronchoscopist. A microbiological approach for VAP diagnosis may limit antibiotic use and prevent the emergence of drug resistance and adverse effects. In all patients wherein a diagnosis of HAP/VAP is suspected, lower respiratory tract samples and blood cultures should be requested before antibiotic initiation. However, antibiotic initiation should not be delayed.

4.5.5 Ancillary Investigations

Pulse oximetric saturation must be monitored in these patients. Any hypoxemic pregnant patient with pneumonia requires inpatient management. Other investigations to be performed include a hemogram, liver and renal biochemistry, including urea, blood glucose, and serum electrolytes. Estimating inflammatory markers like Procalcitonin and C-Reactive protein need not be performed as part of pneumonia's routine diagnostic workup.

4.6 Severity Assessment and Site of Care Decision

The physiological changes during pregnancy may predispose patients to develop a more severe illness. The critical contributing factors include an elevated diaphragm, reduced functional residual capacity, increased oxygen demands, and increased lung water. These factors contribute to a reduced tolerance to hypoxia. Regardless of the severity assessment criteria used in non-pregnant adults, there should be a low threshold to admit pregnant patients with pneumonia for inpatient care.

Specific severity assessment criteria are used in adults for pneumonia. The most commonly used criteria include the Pneumonia Severity Index (PSI), CURB-65, and CRB-65 scores. PSI is more extensively validated. The PSI predicts prognosis and defines illness severity based on predicted 30-day mortality. Twenty prognostic variables are included, and the risk of death due to CAP is stratified into five classes [18]. The CURB-65 is a 6 point score comprising (Confusion, Urea ≥7 mmol/L, Respiratory rate ≥30 breaths/min, low Blood pressure [diastolic blood pressure (DBP) ≤60 mmHg or systolic blood pressure (SBP) ≤90 mmHg], age ≥65 years). The CRB-65 score that excludes urea (as biochemical investigations may not be available or there may be a delay in obtaining) also performs well with illness severity. The CURB-65 and CRB-65 scores are more widely used and recommended as part of the initial severity assessment. A CRB score <1 may be used as a criterion for outpatient management.

In patients admitted, a decision needs to be taken regarding the site of care, i.e. ward versus Intensive care unit (ICU). Criteria are given by the ATS-IDSA (American thoracic society-Infectious disease society of America) to decide regarding the site of care. These criteria include two major and nine minor criteria [19]. The presence of any of the major criteria or at least three of the minor criteria qualify for an ICU admission (Table 4.2). A prompt decision regarding the site of care translates into appropriate healthcare resource utilization and may optimize patient outcomes. Many patients with pneumonia are hypoxemic and may require vasopressor or ventilatory support, and are optimally managed under monitoring in the ICU.

Table 4.2 ATS-IDSA criteria for deciding level of care for admitted patients with pneumonia [19]

Major criteria
Invasive mechanical ventilation
Septic shock with the need for vasopressors
Minor criteria
Respiratory rate of ≥30 breaths/min
PaO2/FiO2 ratio of ≤250
Multilobar infiltrates
Confusion/disorientation
Uraemia (BUN level ≥20 mg/dL)
Leukopenia (WBC count <4000 cells/mm^3)
Thrombocytopenia (platelet count <100,000 cells/mm^3)
Hypothermia (core temperature <36 °C)

Source: Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44 Suppl 2(Suppl 2):S27–72

Pneumonia may increase the risk of preterm labor, low birth weight and pulmonary edema [20]. In pregnancy, tolerance to hypoxia is reduced, and respiratory alkalosis may occur due to increased respiratory rate. This may lead to a reduction in uterine blood flow. The authors suggest that there should be a low threshold for ICU management of pregnant patients with severe pneumonia so that they may receive close fetal-maternal monitoring.

4.7 Treatment

4.7.1 Supportive Management

Supportive treatment should be promptly initiated. Intravenous hydration may be required, and fever should be treated with paracetamol. Close monitoring of fluid and hemodynamic status is required. Overhydration may increase the risk of pulmonary edema. The patient should be nursed

in a semi-recumbent position to minimize the risk of aspiration. Steroids should not be routinely administered in non-severe pneumonia. Low-dose hydrocortisone may be administered if the patients' septic shock is poorly responsive to fluid and vasopressors [21].

4.7.2 Oxygen Therapy

Oxygen therapy is the cornerstone to the management of hypoxemic patients. The modality of oxygen delivery may be chosen based on the response. Initially, oxygen may be given via a venturi mask or nasal cannula. In patients with severe respiratory distress, a trial of non-invasive ventilation (preferably using a critical care ventilator) or high flow nasal cannula (HFNC) may be given under close observation [22]. The response is assessed by observing the saturation and respiratory rate along with general clinical status.

In contrast to the general adult population, higher oxygenation (saturation ≥ 95% or an arterial PaO2 of >70) is desirable in pregnant patients as this ensures fetal oxygenation. Patients with failure to respond to initial oxygen therapy or those who present with severe hypoxemia and impending respiratory arrest should be promptly intubated and mechanical ventilation initiated. Principles of mechanical ventilation in pregnant patients with severe pneumonia and ARDS include low tidal volume ventilation with minimization of airway pressures, a conservative fluid strategy, prophylaxis for stress ulcer, and deep venous thrombosis unless contraindicated. A detailed discussion on the principles of management of ARDS is beyond the scope of the current chapter.

4.7.3 Antibiotic Therapy

Prompt initiation of antibiotic therapy is crucial. A delay in antibiotic administration is associated with increased mortality in the setting of sepsis. The antibiotic treatment principles cover the likely causative organisms, considering the clinical setting and the community prevalence of the microbial data. Following clinical improvement, antibiotics may be switched from the parenteral to enteral route (if parenteral therapy was initially chosen).

4.7.4 CAP

The treatment in CAP should be primarily targeted towards the most common etiological agent, namely Streptococcus Pneumoniae [5]. Regardless of antibiotics' choice, these must be administered in an appropriate dose and duration to prevent the emergence of drug resistance. Tetracycline, Clarithromycin, and Fluoroquinolones may be avoided in pregnancy.

4.7.4.1 Non-Severe Cases Without Comorbidities for Outpatient Management

The recommended antibiotic in non-pregnant adults is a combination of oral macrolides (e.g. azithromycin) or oral β-lactams (e.g., amoxicillin or amoxicillin-clavulanate). The β-lactam may be substituted with Clindamycin if the patient has β-lactam hypersensitivity.

4.7.4.2 Hospitalized Non-ICU Cases

The antibiotic regimen recommended in this setting is a combination of a β-lactam plus a macrolide (azithromycin). The preferred β-lactams in this setting include cefotaxime, ceftriaxone, and amoxicillin-clavulanic acid. For hospitalized, non-ICU patients, the choice between oral and intravenous antibiotics may be taken based on clinical judgment.

4.7.4.3 Hospitalized ICU Cases

The first step in this setting is to assess whether the patient has any underlying risk factors for Pseudomonas aeruginosa. If no risk factors are present, the antibiotic regimen recommended is a β-lactam (cefotaxime, ceftriaxone, or amoxicillin-clavulanic acid) plus azithromycin. In patients

with risk factors for Pseudomonas aeruginosa, an antipseudomonal antibiotic should be administered. Some of these include ceftazidime, cefepime, cefoperazone, piperacillin-tazobactam, cefoperazone–sulbactam, imipenem, or meropenem. Combination therapy may be challenging due to the concerns with the use of fluoroquinolones and aminoglycosides in pregnancy. Decisions regarding the use of additional drugs for combination treatment may be taken on a case-to-case basis.

Once the results of microbiological investigations are available, the antibiotic regimen may be tailored accordingly. The patient must be closely monitored for clinical response. In case there is a failure to respond within 2–3 days, the patient should be reevaluated for issues like complications (parapneumonic pleural effusion, lung abscess, necrotizing pneumonia), alternative etiology, or drug resistance [5].

4.7.5 Hospital-Acquired Pneumonia/Ventilator-Associated Pneumonia (HAP/ VAP)

Antibiotics should be promptly initiated once a diagnosis of HAP/VAP is suspected. Samples should be obtained for microbiological investigations. The choice of antibiotics is tailored according to VAP onset and the risk of infection with MDR pathogens. According to the Indian guidelines on pneumonia, every ICU/hospital should have their empiric antibiotic policy for HAP based on local microbiological resistance profiles and patterns [5]. Treatment with an antipseudomonal antibiotic is required in all; also in all patients except those with low mortality risk/no risk factors, additional MRSA coverage is needed. These decisions are usually required as part of multidisciplinary management. As soon as culture results are made available, the treatment should be de-escalated. A longer duration of antibiotic therapy (14 days) may be required in patients with VAP due to Pseudomonas, Acinetobacter, and MRSA. In other patients who have clinically improved, a 7-day course of antibiotics may suffice.

4.8 Fungal Pneumonia

There is no evidence to indicate that pregnancy is a risk factor for the development of invasive fungal pneumonia. Fungal pneumonia should be considered as a differential diagnosis if specific risk factors for fungal infection are present. The diagnosis and management are on similar lines as non-pregnant adults.

Various fungi can cause pneumonia and mostly the setting is underlying immunosuppression. The common underlying conditions include uncontrolled diabetes, hematologic malignancies, hematopoietic cell transplantation, or solid organ transplantation. One important feature of pulmonary infection is vascular invasion and this leads to a rapid spread of infection and hemoptysis is an important clinical feature. Most invasive fungal pneumonias are caused by Aspergillus fumigatus species. Others include Mucormycosis and other fungi like fusariosis and scedosporiosis. The important risk factors include: severe neutropenia, treatment with high dose glucocorticoids, immunosuppressive drugs, and AIDS. Clinical features of fungal pneumonia may be indistinguishable from bacterial pneumonia. Many times, the clinical features may be minimal. Radiologically, the disease may be characterized by consolidation, nodules, and cavitation. (Fig. 4.1) HRCT scanning of the thorax is often an indicator pointing

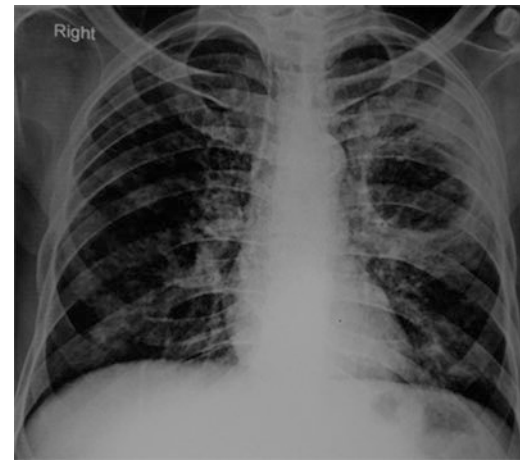

Fig. 4.1 A posteroanterior chest radiograph showing a large thick-walled cavitary lesion in the left upper and mid zone. Sputum examination demonstrated aseptate hyphae suggestive of Mucormycosis

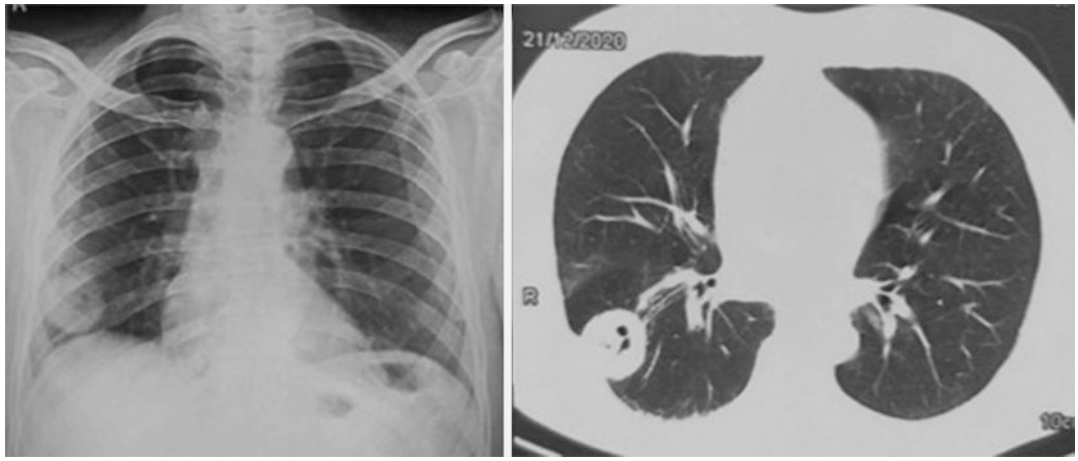

Fig. 4.2 Chest X-ray PA view (left panel) showing a nodular opacity in the right lower zone. CT scan showed a thick-walled lesion with central cavitation. Biopsy was suggestive of pulmonary Aspergillosis

towards a possible diagnosis of fungal pneumonia. Imaging findings on the CT scan may include consolidation, nodules, cavitation, halo sign, and pleural effusion. (Fig. 4.2) However, none of the radiological features is sensitive and specific enough for a particular fungal infection or differentiation from other causes of pneumonia. Disseminated disease may also occur.

In the setting of pregnancy, fungal pneumonia may be considered as a differential diagnosis if a specific underlying risk factor for fungal infection is present as highlighted above. This may also be considered in patients with non-resolving pneumonia wherein an initial consideration is bacterial pneumonia that fails to improve. Imaging investigations and bronchoscopy have a key role in the diagnosis and management of invasive fungal pneumonia.

4.8.1 Management of Fungal Pneumonia

The management of fungal pneumonia depends on the type of fungal infection. The anti-fungal therapy essential for treatment is embryotoxic but in critical cases of unresolving pneumonia in pregnancy, the treatment is life saving. The management principals of common fungal infections are discussed.

4.8.1.1 Candida

The principles of management include antifungal therapy and management of any localized focus if obvious. Blood cultures should be obtained daily. The patient should also be evaluated for any metastatic foci like endophthalmitis, endocarditis, abscess, and osteoarticular foci if fungemia is suspected. The preferred initial therapy is Echinocandin (Caspofungin, Micafungin, Anidulafungin). Echinocandin therapy is of similar efficacy as compared with Amphotericin B/Liposomal Amphotericin in this setting and the adverse event profile is more favorable. Azole treatment (Fluconazole) may be an acceptable alternative in patients who are not critically ill and are unlikely to have a fluconazole-resistant strain. Testing for azole susceptibility is recommended. Initial therapy with Echinocandin may be continued for 5–7 days and stepped down to fluconazole in clinically stable patients and negative repeat blood cultures following initiation of antifungal therapy. In patients with suspected Azole and Echinocandin-resistant Candida infections, lipid formulation of Amphotericin is recommended. The duration of treatment should be a minimum of 2 weeks after culture negativity. The treatment in neutropenic and non-neutropenic patients is usually on similar lines.

4.8.1.2 Invasive Aspergillosis

Invasive aspergillosis can involve the lung. The primary recommended treatment is with voriconazole. Isavuconazole may be used in patients who are intolerant to Voriconazole. Liposomal Amphotericin B is considered as the alternative first-line therapy. Combination antifungal therapy with Voriconazole and Echinocandin may be considered in selected patients but a primary therapy with an Echinocandin is not recommended. Echinocandins can be used in settings in which azole and polyene anti-fungal are contraindicated. The duration of treatment is usually a minimum of 6–12 weeks. A reduction in the dose or elimination of immunosuppressive agents, when feasible, is advised as a component of anti-aspergillus Therapy.

4.8.1.3 Pulmonary Mucormycosis

In Mucormycosis, a combination of surgical debridement and antifungal therapy is usually recommended. This is especially relevant in setting of operable sites and may also need to be considered with extensive pulmonary disease and complications like massive hemoptysis. Intravenous Amphotericin B is the drug of choice for initial therapy. Posaconazole or Isavuconazole may be used as step-down therapy for patients who have responded to Amphotericin B.

Key Points

- The diagnosis and management of pneumonia in pregnancy is essentially similar to the general adult population.
- Viral and bacterial etiologies are the most common causes of pneumonia in pregnancy.
- A chest radiograph should always be obtained when pneumonia is suspected and an abdominal shield used.
- The resolution of chest radiographic abnormality may lag behind the clinical response in pneumonia.
- In suspected pneumonia, microbiological investigations (blood cultures and sputum gram staining, and culture) must be obtained in all patients ideally before initiation of antibiotic treatment.
- Antibiotic administration must not be delayed awaiting microbiological investigations.
- There should be a low threshold for ICU management of pregnant patients with severe pneumonia.
- In CAP, it is important to assess whether the patient has any underlying risk factors for Pseudomonas aeruginosa.

4.9 Conclusion

The diagnosis and management of pneumonia in pregnancy presents a challenging clinical scenario. Management is similar to that in other non-pregnant adults. However, patients require close monitoring and there should be a low threshold for ICU admission in pregnant females with pneumonia. A prompt initiation of appropriate antimicrobial treatment and close monitoring for response may lead to optimal outcomes.

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5 Influenza and Influenza-Like Illness

Shiva Narang and Tanmay Diliprao Laxane

5.1 Introduction

Influenza is an acute, viral respiratory infection caused by influenza viruses [1]. Influenza viruses are Orthomyxoviridae family of viruses which has distinct genera and subtypes responsible for outbreaks of influenza almost every year depending on multiple factors varying from viral mutations to demographic factors. Symptoms of influenza can be mild upper respiratory to a severe lower respiratory symptom with complications often accompanied by symptoms like fever, headache, myalgias, and fatigue. Flu-like syndrome/symptoms is a medical diagnosis of all possible illnesses including influenza with abrupt onset of symptoms such as fever, shivering, chills, nausea, malaise, body aches, dry cough, and loss of appetite [2]. The term Influenza-like illness (ILI) though used casually in day-to-day practice has very strict criteria for definition when used for surveillance of a case of influenza. Case definitions for influenza-like illness (ILI) and severe acute respiratory infections as given by WHO global influenza surveillance standards are as follows [3].

5.1.1 Definitions

5.1.1.1 ILI Case Definition [3]

An acute respiratory infection with:

- Fever of ≥38 °C
- Cough
- With onset within the last 10 days.

5.1.1.2 SARI Case Definition [3]

An acute respiratory infection with:

- History of fever or measured fever of ≥38 °C
- Cough
- With onset within the last 10 days
- Requires hospitalization.

The normal physiologic changes occurring during pregnancy such as rise in the heart rate, increase in oxygen consumption, a decrease in the lung capacity, and alteration of immune responses subject the pregnant and postpartum women to increased severity of the disease and greater risk for mortality.

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5.2 Causes

ILI can be caused by various diseases and drugs. The most common cause of ILI is influenza, a group of RNA viruses belonging to Orthomyxoviridae family. Other causes include

• Self-limiting infections	• Emerging new infections
– Gastroenteritis	– SARS
– Rhino viral disease	– COVID-19 virus
• Respiratory Syncytial Virus	• Hepatitis C
• Malaria	• Lyme disease
• Acute HIV/AIDS infection	• Rabies
• Q fever	• Measles
• Poliomyelitis	• Dengue fever
• Herpes Simplex	Pharmaceutical agents*

*Pharmaceutical agents such as interferons, and monoclonal antibodies, chemotherapeutic agents, antitubercular drugs, bisphosphonates, and levamisole can cause flu-like syndrome [4–8].

5.3 Clinical Manifestations

Clinical manifestations of influenza in pregnant and postpartum patients are no different than general population. They include fever (usually 37.8–40.0 °C [100–104 °F]), headache, nonproductive cough, sore throat, rhinorrhea, myalgia, shortness of breath, and malaise. These clinical features have a significant overlap with other respiratory viral illnesses, and there is no way to distinguish between them without diagnostic evaluation [9].

5.4 Diagnosis

In pregnant and postpartum patients it is important to initiate the treatment promptly; therefore, the diagnosis should be made clinically and should not await laboratory testing. Diagnostic influenza laboratory tests are the same as those for other high-risk patients. Table 5.1 shows various tests that can be done for a respiratory specimen [10–13].

5.5 Clinical Course in Pregnancy

5.5.1 Maternal Effects

Adverse clinical outcome for Influenza and ILI and risk of developing SARI is decidedly more in pregnant and postpartum group as this group falls in a high-risk category. During the 2009 H1N1 pandemic, it was observed that the severity of the disease and risk of mortality was higher in pregnant patients as compared with nonpregnant patients. Preexisting comorbidities such as pulmonary disease, diabetes mellitus, chronic cardiac, chronic renal disease, malignancy, and immunosuppression further increased the possibility of adverse outcomes due to influenza (seasonal or pandemic) during pregnancy and postpartum period [14–17].

5.5.2 Fetal Effects

The fetal effects of influenza have not been evaluated in detail. Transplacental transmission of influenza virus is rare apart from a single case report of

Table 5.1 Influenza diagnostic test for respiratory specimens [10–13]

• Conventional RT-PCR (gel-based PCR, real-time RT-PCR, and multiplex PCR) and other molecular assays (influenza viral RNA or nucleic acid detection)
• Rapid molecular assays (influenza viral RNA or nucleic acid detection)
• Digital immunoassay (rapid immunochromatographic antigen detection test)
• Direct and indirect immunofluorescence
• Rapid influenza diagnostic tests (antigen detection tests)
• Viral culture – Shell viral culture – Isolation in cell culture
• Serologic tests (hemagglutinin inhibition, ELISA, complement-fixation, and neutralization)

fatal avian influenza (H5N1) in a pregnant patient. However, even in the absence of transplacental transmission, an increased risk for spontaneous abortion, preterm delivery, low birth weight, birth of a small for gestational age infant, and fetal death has been observed in pregnancy [18–21].

5.6 Management

5.6.1 Symptomatic Patients

In outpatient settings, patients should be screened for respiratory symptoms and signs and triaged appropriately. All precautionary measures should be followed at all times [22]. The American College of Obstetricians and Gynecologists considers pregnant and postpartum patients with the inability to retain fluids, signs of dehydration, difficulty in breathing, chest pain or pressure, mental status changes, comorbidities, obstetric complications, worsening symptoms after previous improvement, or inability for self-care as moderate or high risk. These patients should be attended immediately [21]. Pregnant patients who come to the hospital for delivery with confirmed or suspected influenza infection should be isolated in a separate room. All necessary infection control precautions for influenza that are used for other patient populations should be practiced for them also [23]. Appropriate antiviral therapy should be initiated immediately while awaiting the results of diagnostic testing.

5.6.2 Healthy Term Newborns of Symptomatic Mothers

CDC guidelines for management of asymptomatic, healthy newborns of mothers with confirmed or suspected influenza infection are as follows:

- Consider them as exposed not infected
- Temporary separation of the mother and the baby is recommended
- The newborn is cared for in the nursery using standard precautions and observed for signs of infection
- Feeding during separation is provided by the care giver. If the mother is keen to breastfeed her child, then expressed breast milk is given to the newborn
- The length of temporary separation is decided on a case-to-case basis.

At present there is no definite recommendation due to paucity of data regarding the length of separation but CDC suggests to follow the guidelines formulated post 2009 H1N1 epidemic. They suggest that the mother should be separated from the infant until three criteria in the mother are met.

- Received antiviral medications for 48 h
- Afebrile for >24 h without antipyretics
- Cough and respiratory secretions are under control.

If temporary separation is not possible or acceptable, then the mother and baby should be separated by either placing the newborn crib >6 ft away from the infected or suspect mother, or creating a physical barrier like a screen. Appropriate unidirectional airflow system should be in place and the caregiver should use standard infection control practices.

Oral Oseltamivir is not approved for use in children less than 1 year of age by the US Food and Drug Administration (FDA). Emergency Use Authorization (EUA) of the drug for use in infants less than 1 year was made during the 2009 H1N1 pandemic, which expired in June 2010, but the guidelines for use in children <1 year are available. It can be used for chemoprophylaxis in persons 1 year of age and older and treatment of acute uncomplicated influenza within 2 days of illness onset in persons 14 days of age and older. The American Academy of Pediatrics and CDC recommend use of oral oseltamivir for chemoprophylaxis in infants 3 months to 1 year of age and treatment of influenza in infants less than 14 days old but still if a child is younger than 3 months old, use of oseltamivir for chemoprophylaxis is not recommended unless the situation is judged critical, given limited data of safety and efficacy in this age group. Influenza vaccines are recommended for children ≥6 months of age [24, 25].

5.6.3 Infant Caregivers and Household Contacts

Vaccination against influenza is recommended for all individuals who live with or provide care for infants younger than 6 months of age. Caregivers and household contacts should be vaccinated before the infant is discharged home from the hospital. Otherwise, those who are unvaccinated and eligible for vaccination (i.e., >6 months of age) should be strongly encouraged to be vaccinated in a timely way. Infant caregivers and household contacts of the infant who have significant contact with an individual with influenza should be considered for post-exposure prophylaxis [26].

5.7 Breastfeeding

Antiviral drug oseltamivir and its active metabolite are poorly excreted into breast milk and pose no harm to their infants as per the limited data available. However we have not come across any research data on safety of antiviral medications—zanamivir, baloxavir, or marboxil during breastfeeding [27–29].

The following guidelines are suggested for breastfeeding

- Suspected or confirmed influenza in mother who is breast feeding—encouraged to continue breastfeeding if possible
- Suspected or confirmed influenza infection in mother who is in isolation and intends to breastfeed should be encouraged to express her breast milk, which a healthy caregiver can use to bottle feed the newborn.

5.8 Protection of Pregnant Healthcare Workers

The same infection control practices are to be followed for pregnant health care workers as for other health care personnel. Considerations can be made to avoid duties involving aerosol-generating procedures on patients with suspected or confirmed influenza to prevent potentially high-risk exposures [30].

5.9 Therapeutics

Decisions about antiviral therapy should be based on the clinical picture and information on local influenza activity in the community. It should be remembered that influenza vaccine is not 100% effective. Therefore, any individual who meets the current case criteria for defining a suspect or a case should be treated with appropriate influenza antiviral medications as early as possible without awaiting laboratory reports; regardless of vaccination status, and treatment should not be withheld while awaiting results of diagnostic testing or in situations in which testing is not performed.

For pregnant and postpartum patients (within 2 weeks of delivery or pregnancy loss), who meet current case definitions for suspected or confirmed influenza, it is recommended that empiric treatment with appropriate influenza antiviral medications should be initiated irrespective of the vaccination status. Furthermore, during periods when influenza viruses are circulating in the community, a negative test cannot rule out infection, especially if the test used does not have high sensitivity to detect influenza viruses or if the specimen was collected more than 4 days after illness onset [31–34].

A study from the 2010 to 2014 influenza seasons demonstrated a markedly shorter median length of hospital stay among patients with severe influenza receiving early antiviral treatment compared with those who received treatment >2 days after symptom onset [33]. The best results of antiviral therapy are seen when it is initiated within the first 48 h following onset of symptoms. But treatment should be administered to patients even if they present >48 h after onset of illness and are not showing improvement. The risk of treatment is believed to be low, and there may be some benefit even after a prolonged delay, particularly in severely ill pregnant and postpartum patients [35]. Antiviral treatment can be prescribed over the phone or in person for patients with mild symptoms and no medical or obstetric comorbidities, but this decision should take individual circumstances into account. All other patients should be seen promptly for evaluation, and those with respiratory compromise or com-

plications should be admitted for treatment as detailed in previous section. Health care providers can facilitate early treatment by informing pregnant and postpartum patients about signs and symptoms of influenza, emphasizing the need to contact their health care provider for early treatment, and ensuring rapid access to telephone consultation and clinical evaluation [36].

5.9.1 Antiviral Medications

The prevalence of a virus in a community decides the treatment protocols especially in disease where empirical treatment is given. It has been evaluated that the most of the currently circulating influenza viruses are susceptible to neuraminidase inhibitors—oseltamivir, zanamivir, and peramivir. There is limited data regarding the safety of the neuroaminidase inhibitors in pregnancy (especially the first trimester) but the benefits of treatment outweigh the potential risks. Oseltamivir is the drug of choice because of lower systemic absorption, greater clinical experience using this drug in pregnancy and because the prevalence of oseltamivir resistance is low among circulating influenza viruses. Therefore, it is preferred over inhaled zanamivir and intravenous peramivir but pregnancy is not a contraindication to use of zanamivir or peramivir. Zanamivir is relatively contraindicated in patients with asthma or chronic obstructive pulmonary disease. The dose of antiviral therapy for treatment of influenza during pregnancy is the same as in nonpregnant adults:

- *Oseltamivir 75 mg twice daily (preferred) or*
- *Zanamivir 10 mg (two 5 mg inhalations) twice daily*

The treatment is prescribed for 5 days usually. The treatment courses are extended for patients who remain severely ill after 5 days of treatment. Some isolated recommendations suggest that severely ill patients be treated with double-dose oseltamivir (i.e., 150 mg twice daily); however, no data are available to suggest that higher doses are more effective. In critically ill patients or those who are on parenteral therapy, can be given oral formulation of oseltamivir as it can be adequately absorbed following nasogastric administration [37–39].

5.9.2 Antipyretics

Febrile episodes during first trimester are associated with neural tube defects and other congenital defects. In labor, it has been observed to be a risk factor for neonatal seizures, encephalopathy, cerebral palsy, and neonatal death. Treatment of fever is, therefore, important. Acetaminophen is the drug of choice as other antipyretics (e.g., aspirin, ibuprofen) have been associated with adverse pregnancy and infant outcomes [40, 41].

5.9.3 Symptomatic Therapy

Many pregnant patients will seek advice about symptomatic therapy for cough, rhinorrhea, sore throat, headache, and myalgia. Symptomatic therapy is similar to that for the common cold [42].

5.9.4 Role of Antibiotics

Antibiotics are indicated only for bacterial complications of acute influenza, such as bacterial pneumonia, otitis media, or sinusitis. Treatment is similar to that in nonpregnant adults, except for avoidance of antibiotics with potentially harmful effects in pregnant patients or the fetus [43].

5.9.5 Management of ARDS

Pregnancy poses a unique problem in management as we have two circulatory systems to be ventilated simultaneously. The limitations to an adequate ventilation during pregnancy include difficult intubation due to gravid uterus, prone ventilation not possible, sustained paralysis not possible due to risk of arthrogryposis to the fetus and need for a higher FiO2 to maintain normaxia for satisfactory oxygen transfer gradient, need to

avoid causes physiological changes that make respiratory management more difficult. Airway pressure release ventilation (APRV) may be used as an alternative to conventional mechanical ventilation modes as it allow spontaneous ventilation while recruiting collapsed lung areas [44].

5.10 Obstetrical Management

There are no published guidelines for monitoring the fetus during or after maternal influenza infection. The type and frequency of fetal surveillance should be guided by the health care provider's judgment on a case-to-case basis [45].

5.11 Prevention

5.11.1 Vaccination

The Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices recommendations:

- Yearly influenza vaccination for all individuals more than 6 months of age including pregnant and postpartum females in the absence of any contraindications.
- Live-attenuated influenza vaccine is to be avoided in pregnant patients due to concerns about its safety during pregnancy.
- Postpartum women can safely be administered live-attenuated influenza vaccine.
- During an influenza season all women who might be pregnant, are pregnant, and postpartum should be administered any age-appropriate, licensed, recommended inactivated influenza vaccine (IIV) or recombinant influenza vaccine quadrivalent (RIV4), irrespective of trimester.
- Pregnant women are safe if they come in contact with people who have recently received a live-attenuated influenza vaccine [46].

Despite recommendations for influenza vaccination of pregnant patients, coverage rates have remained low for many years; in 2017–2018, influenza vaccination coverage was only 49% among pregnant and postpartum patients. In one study among pregnant patients in the United States, the most commonly reported primary reason for not receiving influenza vaccination was believing the vaccine is not effective [47, 48]. Indian figures would be much lower if assessed at a widespread level as we are still fighting much more basic issues such as nutritional inadequacies and so forth.

5.11.1.1 Benefits of Vaccination

- Reduction in maternal influenza illness: Influenza vaccination plays a key role in reducing the risk of maternal influenza illness. Multiple clinical studies and surveillance data have demonstrated the benefits of influenza vaccination for pregnant patients, including those with HIV infection. Pregnant patients achieve seroprotection at rates similar to non-pregnant patients [49–51].
- Reduction in maternal influenza hospitalization: A study done in hospitals in Australia, Canada, Israel, and the United State between 2010 and 2016, showed influenza vaccine was 40% effective (adjusted vaccine effectiveness 40%, 95% CI 12–59%) against laboratory-confirmed influenza-associated hospitalization during pregnancy [52].
- Improvement in pregnancy outcome: In a 2016 systematic review and meta-analysis of observational studies on the effect of maternal influenza immunization on stillbirth and miscarriage, influenza vaccination was associated with a reduction in risk of stillbirth. Others have reported influenza vaccination is associated with a reduced risk for small for gestational age infants and preterm delivery and an increase in birth weight [53, 54].
- Infant protection: In addition to protecting the pregnant patient, influenza vaccination during pregnancy protects the infant for several months after birth. Antenatal maternal immunization induces substantial levels of anti-influenza-specific serum immunoglobulin G (IgG), which are actively transferred across the placenta to the fetus, and anti-influenza-

specific IgA in breast milk, which is transferred to the infant during lactation. Thus, antenatal maternal vaccination is an effective strategy for reducing influenza-related morbidity and mortality among infants, who are at increased risk for severe influenza illness and not eligible for vaccination until 6 months of age because they fail to mount an adequate immune response. However, passive protection afforded by maternal influenza vaccination appears to decline significantly before the infant is eligible for vaccination [55–58]. It is possible that maternal immunization in the third trimester would improve passive protection for the newborn, as with Tdap; however, delaying maternal immunization places the mother and child at risk for influenza and its sequelae [59].

5.11.1.2 Safety of the Vaccine

Concerns regarding safety of vaccines are maximum when administering it to pregnant patients as it is indirectly related to the health and wellbeing of the fetus. Various studies have not shown an increased risk of complications associated with administration of IIVs to pregnant patients compared with the general population. Although rare, all vaccines, including influenza vaccine, have some background risk of adverse effects, such as Guillain–Barré syndrome [60]. Although influenza vaccines that contain adjuvants (substances that enhance the immune response and provide longer-lasting protection against antigenically-drifted viruses) are approved only in the United States for use in individuals ≥65 years of age experience from Europe provides limited but reassuring data on the safety of adjuvant-containing influenza vaccines in pregnant patients [61–63].

5.11.2 Antiviral Prophylaxis [12]

5.11.2.1 Candidates

Before starting antiviral prophylaxis it is important to take into consideration whether the exposure was significant and the host's risk for developing a complicated infection. Antiviral prophylaxis within 48 h of the most recent exposure is a reasonable option for pregnant and postpartum patients with a significant exposure up to 2 weeks post-delivery (including those who have had a pregnancy loss). Early empiric treatment, once signs or symptoms of influenza develop, is an alternative to prophylaxis.

5.11.2.2 Drug Regimen

For chemoprophylaxis in pregnancy, the recommended doses of influenza antiviral medications for chemoprophylaxis of influenza A and B are:

- *Zanamivir 10 mg (two 5 mg inhalations) once daily*
  or
- *Oseltamivir 75 mg orally once daily*

The recommended duration of prophylaxis is 7 days after the last known exposure [63].

In long-term care centers or hospitals, CDC recommendations for control of outbreaks are by providing long-term chemoprophylaxis. Antiviral Zanamivir or Oral oseltamivir is given for a minimum of 2 weeks and up to 1 week after the most recent known case was identified is suggested. Zanamivir is to be used via inhalational route. It may be a good choice given its limited systemic absorption but respiratory complications may arise and should be considered, especially in patients at risk for respiratory problems, such as those with asthma [23]. Oral oseltamivir is an alternative agent. No adverse events have been associated with oseltamivir or zanamivir among patients who received these drugs during pregnancy or among infants exposed in-utero or through breast milk.

5.12 Infection Control Measures

5.12.1 Precautions

Precautions are advocated to prevent contact, droplet, or airborne infections. Table 5.2 depicts various precautionary measures to be taken to prevent spread of infection.

Table 5.2 Precautions for preventing transmission of infection [64]

Precautions category	Description
Standard	• Hand hygiene before and after every patient contact • Wear gloves, gowns, eye protection as per requirement • Safe disposal and cleaning of linen and instruments • Cough etiquette: – Patients and visitors should cover their nose or mouth when coughing, – Prompt disposal of used tissues – Practice hand hygiene after contact with respiratory secretions
Contact	*In addition to standard precautions:* • Isolation in private room; cohorting allowed if necessary • Gloves to be worn upon entering room. Change gloves after contact with secretions • Gown to be worn if clothing may come into contact with the patient or environmental surfaces or if the patient has diarrhea • Minimize risk of environmental contamination during patient transport (e.g., patient can be placed in a gown) • Noncritical items should be dedicated for single use if possible
Droplet	*In addition to standard precautions:* • Private room preferred; cohorting allowed if necessary • Wear a mask when within three feet of the patient • Mask the patient during transport • Cough etiquette to be followed
Airborne	*In addition to standard precautions:* • Place the patient in a monitored negative pressure room with at least 6–12 air exchanges per hour • Room exhaust must be appropriately discharged outdoors or passed through a HEPA filter before recirculation within the hospital • A certified respirator must be worn when entering the room of a patient with diagnosed or suspected tuberculosis • Transport of the patient should be minimized; the patient should be masked if transport within the hospital is unavoidable • Cough etiquettes to be followed

Source: https://www.cdc.gov/infectioncontrol/guidelines/isolation/index.html. CDC. 2019;1–232

5.13 Conclusion

The risk of Influenza like illness (ILI) and developing SARI subsequently is more in pregnant and postpartum women due to their immunocompromised state. Transplacental transmission of influenza virus is rare, but an increased risk for spontaneous abortion, preterm delivery, low birth weight, and fetal death has been observed in pregnant women with influenza. The American College of Obstetricians and Gynecologists suggests inpatient care for high risk pregnant and postpartum women who show signs of dehydration, have difficulty in breathing, chest pain or pressure, mental status changes, co-morbidities, obstetric complications, worsening symptoms after previous improvement, or inability for self-care. Apart from symptomatic management, Oseltamivir is the antiviral drug of choice due to its safety profile in pregnancy. No specific change in management is suggested during delivery. Prevention of ILI in pregnancy can be aimed at by promoting vaccination, antiviral prophylaxis, and encouraging infection control measures.

Key Points

- Influenza infection causes a clinical syndrome not easily distinguished from other respiratory infections.
- Using one common case definition of ILI and SARI will give true burden of disease both nationally and globally which cannot be overemphasized in light of recent COVID-19 pandemic.
- Preventive measures and widespread awareness for vaccination is essential.
- Maternal and fetal outcomes can be adverse in influenza and ILI, so an early recognition of symptoms, isolation of patient, prompt diagnosis and treatment are mandatory.

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Tuberculosis in Pregnancy

6

Jai Bhagwan Sharma and Vikas Yadav

6.1 Introduction

Tuberculosis is an important cause of mortality and morbidity globally. TB in pregnancy affects the pregnant women both physically and mentally. It still continues to be the most significant cause of death from a single infectious microorganism. Although recently we have witnessed increased efforts in the fight to end TB, some basic gaps are hampering these efforts, particularly in resource constrained settings and in settings with a high burden of disease. The World Health Organization(WHO) estimates that close to 54 million TB deaths were averted between 2000 and 2017 because of improved disease prevention and management, but nevertheless up to ten million people continue to fall ill with TB every year [1]. The wide spectrum of opinion among medical practitioners on tuberculosis in pregnancy reflects the health significance of the condition. The physiological changes that occur during pregnancy may make it more difficult to confirm the diagnosis. About one-third of the world population is infected with tubercle bacilli. Most of them are within the age group of 15–54 years. Tuberculosis is also seen to be on the rise in tandem with HIV/AIDS due to weakened immune system.

6.2 Epidemiology

Tuberculosis (TB) in one of the leading causes of death worldwide. *Mycobacterium tuberculosis* is also the foremost single infectious agent responsible for deaths all over the world, ahead of HIV/AIDS. It accounted for 1.4 million deaths worldwide in 2019. According to WHO estimates, in 2019, ten million people from all over the world were diagnosed with tuberculosis. Of these, 5.6 million were males, 3.2 million females, and 1.2 million children. The disease is one of the three leading causes of death among women between 15 and 45 years [2].

The global burden of the disease has been divided according to the incidence of the disease in different countries. Countries with an incidence of <10 cases per 100,000 population per year are classified as low burden countries. In 2019, 54 countries of the WHO region of Americas, European, Eastern Mediterranean, and Western Pacific region were identified as low burden countries. 30 countries with 150–400 cases per 10,000 population per year have been classified as high TB burden countries. They account for 87% of all the cases of tuberculosis worldwide. Eight countries—India, Indonesia,

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China, Pakistan, Philippines, Bangladesh, Nigeria, and South Africa contribute to two-thirds of the total global burden, with India leading the count. Uniformity in diagnosis and treatment of the disease has brought down the incidence by 2% and cumulative reduction in the number of cases by 9% from 2015 to 2019. But due to the emergence of multidrug resistance, tuberculosis still remains a public health burden and a threat to the health of the society [3].

India accounts for around 30% of the global burden of the disease. Incidence is around 185 cases per lac population in 2015 with mortality of around 26 per 1 lac population. TB still continues to be one of the severest health crises faced by India. An estimated 1400 people die every day and about 4.8 lac every year due to tuberculosis, in India [1]. It is also one of the leading causes of infertility in developing countries.

Prevalence of active TB among pregnant women is 0.06–0.25% in low burden countries and between 0.07 and 0.5% in high burden countries [1]. Exact data on the proportion of antenatal women harboring TB during pregnancy is scanty [4]. Schaefer et al in 1975 reported an incidence of 18–29/100,000 during pregnancy, which matched the incidence reported from the city of New York—19–39/100,000 [5]. A recent study from United Kingdom study, quoted an incidence of 4.2 per 100,000 in pregnant women [6], thus suggesting a decline in the current global fall incidence of the disease [2]. However it is well established that TB in pregnancy is associated with significant obstetric morbidity [7].

6.3 Etiology and Risk Factors

Tuberculosis was discovered by Robert Koch in 1882. The causative organisms form the *Mycobacterium tuberculosis* complex which includes several species of mycobacteria such as *M. tuberculosis*, *M. africanum*, *M. bovis*, *M. caprae*, *M. microti*, *M. canettii*, *M. pinnipedii. Mycobacterium tuberculosis* is an aerobic, non-spore forming, non-motile bacilli. *Mycobacterium tuberculosis* is identified in 99% of the culture confirmed cases [8].

Tuberculosis affects almost every organ in human body, with a predilection for the lungs. After inhalation through the respiratory tract, Mycobacterium bacilli is internalized by macrophages. The processed antigens are presented to the T-helper cells ,which then release different cytokines (including TNF and interferons) and lead to granuloma formation. The persistence of mycobacteria (in the dormant stage) within the granuloma, without a disease outbreak is referred to as latent tuberculosis infection. Infection is caused by inhalation of infectious droplets released by coughing, sneezing, or talking. Aerosolized bacilli are then carried to terminal air spaces where multiplication of tubercles occurs. Pulmonary macrophages phagocytize bacilli forming granulomas. The bacilli are present in the granulomas in a dormant state.

6.3.1 Risk Factors for TB

- Close contact with infectious disease
- Living in, travel to, or receiving visitors from TB high burden countries
- HIV or other medical conditions associated with immunocompromised state
- Chronic nutrition and poor health due to of lifestyle problems such as homelessness, alcoholism, or drug abuse
- Living in poor or crowded housing conditions.

6.4 Clinical Features

Clinical features of tuberculosis during pregnancy are no different. Apart from non-specific symptoms of fever, night sweats, weight loss, the other clinical features are specific to the organ of affection.

6.4.1 Pulmonary Tuberculosis

Tuberculosis is a disease that sets in gradually. Persistent non-remitting cough is the most frequently reported symptom affecting 95% of the

patients [9]. Both productive and non-productive cough have been associated with tuberculosis. The sputum may be mucoid, mucopurulent, or blood stained. Cavitary formation in lung parenchyma or rupture of aneurysm of long standing dilated bronchial vessels can present as massive hemoptysis. The characteristic triad defined of fever, night sweats, and weight loss affects 75, 45, and 55% of patients, respectively [9].

- Persistent fever: fever typically develops in late afternoon or evening and usually low grade in feature<38.5 degrees
- Heavy sweating at night: it is a very non-specific symptom
- Loss of appetite and weight loss: plasma leptin concentrations are increased in TB and theoretically this may be the reason for loss of appetite and the resultant weight loss.

Acute onset of symptoms is seen in children and immunocompromised individuals. Other symptoms can be chest pain and dyspnea in subpleural involvement. Approximately 20% of active TB cases in the USA are exclusively extra-pulmonary (EPTB), with an additional 7% of cases being concurrent pulmonary and EPTB [10].

Endobronchial TB is a specific form of pulmonary TB affecting the trachea and major bronchi. Additional symptoms specific to it are wheezing and dyspnea. Differential diagnosis includes bronchial asthma or bronchial malignancy. This form of tuberculosis has a female preponderance (2:1) and if untreated can result in stricture formation. Bronchoscopy is an efficient tool in its diagnosis [11].

6.4.2 Pleural Tuberculosis

Incidence of tubercular pleuritis ranges between 3–25% in patients of tuberculosis. In high burden countries it is the leading cause of pleural effusion. The incidence is higher in HIV-infected individuals. Its presentation includes acute onset of fever, cough, and localized pleuritic chest pain.

It usually follows primary infection or reactivation of latent infection. The effusion is unilateral and is self-limiting if it is a part of primary infection.

Occurrence during pregnancy as reactivation of latent infection has potential risk to the fetus and may result in occult dissemination. Parenchymal lesions are diagnosed in 20% of cases on chest X-ray, but on chest CT 80% parenchymal affection can be picked up [12].

6.4.3 Extra-Pulmonary Tuberculosis

1. Extra-thoracic lymph node disease

   Tubercular lymphadenitis was commonly known as "Scrofula" in the past. It accounts for 40% cases of extra-pulmonary tuberculosis and is the most common extra-pulmonary presentation of tuberculosis in the USA [13]. The organisms responsible for tubercular lymphadenitis belong to the *Mycobacterium* complex—*Mycobacterium bovis, Mycobacterium scrofulaceum, Mycobacterium avium-intracellular complex, Mycobacterium malmoense, Mycobacterium fortuitum, Mycobacterium chelonae, and Mycobacterium kansasii* [14]. The bacteria enter either through the oropharyngeal mucosa, tonsils, or abraded skin. It presents as a palpable mass (lymph node) of more than 2 × 2 cm in the cervical region either in the supraclavicular, jugular or posterior triangle with formation of fistulous tract or sinus. Other common sites include mediastinal, axillary, hepatic, portal, peripancreatic, and inguinal lymph nodes. The mass is generally not tender unless it is associated with secondary bacterial infection. The disease may manifest as cold abscess. Generalized constitutional signs and symptoms are generally absent but are commonly reported in infected individuals [13].
2. Central nervous system tuberculosis

   Tubercular meningitis (TBM) is the commonest presentation. CNS tuberculoma, tubercular encephalopathy, tuberculous radic-

ulomyelitis are rare but known entities. TBM is common in patients with associated HIV infection and children with miliary tuberculosis. It is one of the most lethal affections of the disease. It is responsible for mortality in 50% of HIV co-infected patients and one third of only TBM patients. 50% of the survivors suffer from neurological deficits [15]. Clinical features can be non-specific. Fever, night sweats, weight loss, headache are some symptoms which are commonly associated. TBM should be ruled out if the patient has fever and headache of more than 5 days duration. In advanced stage altered sensorium, reduced consciousness, hemiplegia, and paraplegia may result.

Cerebral nerves can be affected—VI nerve (in 40% cases), III nerve, and VII nerve. Seizures are seen in 5% of adults and in 50% of children with TBM [16]. Sixth nerve involvement is considered pathognomonic.

3. Spinal tuberculosis

The affection of the spine results in deformities due to which the disease is commonly termed as "Pott's disease." Hematogenous spread of the tuberculous bacilli initially infects one vertebrae, but further progression of the disease results in subligamentous spread to the adjacent vertebrae. The disease causes softening of the vertebrae, resulting in wedging or collapse of the vertebral body [17]. This results in kyphosis, or gibbus formation. In severe cases cold abscess can form acute spinal angulations resulting in neurological deficits or paraplegia. In rare circumstances, subarachnoid spread can result in meningitis.

4. Tubercular pericarditis

Tubercular pericarditis is an important cause of cardiovascular death in tubercular endemic areas, especially where the HIV infection is more prevalent. Fever of unknown origin and distinctive pericardial rub are the presenting features.

6.4.4 Other Extra-Pulmonary Tuberculosis

Tuberculosis arthritis: It presents as pain in the commonly involved joints—Knee/Hip joint. It almost always affects only a single joint. Diagnosis is made by microscopic examination of the synovial fluid and synovial tissue biopsy.

Gastrointestinal tuberculosis: It mimics Crohn's disease in its symptoms-reduced appetite, loss of weight, abdominal pain, bloating, nausea, diarrhea, signs of intestinal obstruction, and blood in stools. In endemic countries, diagnosis is generally made on clinical suspicion though biopsy is diagnostic.

Urogenital tuberculosis: It is usually asymptomatic. It may cause flank pain, or present with a renal mass. It is characterized by sterile pyuria.

Laryngeal TB: It is one of the most infectious forms of TB. Hoarseness, dysphagia are common presentations. It may present with chronic cough if associated pulmonary tuberculosis is present.

Laryngeal malignancy must be ruled out.

6.5 Diagnosis

Diagnosis of tuberculosis is a challenging task especially in the event of extra-pulmonary tuberculosis, emergence of multidrug-resistant tuberculosis, and growing population of immunocompromised individuals with HIV infection. The focus of diagnostic tests is according to the burden of the disease. In high burden states, it is more important to diagnose the active cases while in low burden states, identification of latent cases is of more relevance.

6.5.1 Hematological Changes

They are non-specific and suggest lymphocytosis and raised erythrocyte sedimentation rate.

6.5.2 Tests to Identify Tubercular Bacilli

Direct microscopy is still considered the first-line test in high burden countries.

The tests are classified as

- Direct tests to identify rapidly growing bacilli
  - Microscopy
  - Culture
  - Nucleic acid detection.
- Indirect tests to identify immune response against the bacilli
  - Tuberculin skin testing
  - Interferon-gamma release assay (IGRAs).

6.5.2.1 Microscopy

Sputum smear microscopy is an inexpensive, fast, and specific test for identification of tubercular bacilli in high incidence areas. The Z-N (Zeil-Neelsen) staining was first discovered by Earlich in 1881 and modified by Zeil and Neelsen. It is a differential staining. The mycobacteria are acid-fast, i.e. have high content of lipids, fatty acids, and higher alcohols especially mycolic acid. The high lipid content along with integrity of the cell wall ensures the acid fastness. This prevents decolorization and counter staining with methylene blue dye. The test involves staining of the acid-fast mycobacterium with carbol fuchsin. According to the Revised National Tuberculosis Control Program (RNTCP), a 2 ml early morning sample of sputum is submitted for evaluation on 2/3 consecutive days. The first specimen generally can detect 85.8% cases and 11.9% additional are detected in the second sample [18]. But of concern are the 17% sputum negative patients after first sample who are falsely negative but still infective [19].

Advantages

- Highly specific
- Easy to perform with limited resources in outreach areas
- Cost-effective especially in high burden countries.

Disadvantages

- Requires at least 10,000 bacilli for identification
- It has varying sensitivity of 20–80% depending on the training of the technician, quality of smear [20]
- Sensitivity is low (20%) in children and immunocompromised individuals—HIV infected [21]
- The direct microscopy cannot differentiate between live and dead bacteria hence cannot be used for follow-up of the patient post treatment.

Smear testing is done at 3 months of starting treatment. Positive smear warrants a culture and drug sensitivity testing to identify multidrug-resistant tuberculosis. Patients with necrotic lung cavities, can cough up dead bacilli for long even while they are on treatment and are non-infective. As the smear has the disadvantage of picking up both live and dead bacilli, these patients are wrongly labelled as positive.

A positive smear after 5 months of treatment implies treatment failure (Fig. 6.1).

The other methods for microscopy include:

- Fluorescent microscopy with light-emitting diodes
- It is a modification of the direct microscopy using light emitting diodes (LED) recommended by WHO in 2009. It has the advantage

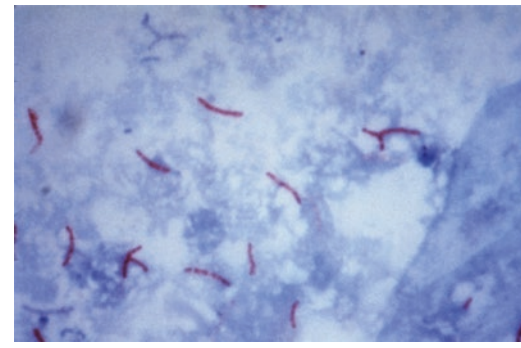

Fig. 6.1 ZN staining showing acid-fast bacilli

of use in outreach areas as they are more sustainable than halogen bulbs with longer battery life, do not require dark room, and increase sensitivity by allowing sixty slide evaluations at one time [22]. In 2009, WHO had recommended this technique. RNTCP has also adopted LED microscopy to replace ZN staining in microscopy centers in India.

- Fluorescein diacetate testing in addition to microscopy
- Fluorescein diacetate is a fluorescent viability marker used in combination with smear microscopy. It has the advantage of staining only cultivable, living bacteria [23]. Thus is a useful addition to microscopy in follow-up of patients to observe treatment responsiveness.
- Newer microscopic technologies
- Automated microscopic technology by TBDx (Signature Mapping Medical Sciences, USA) uses robotic loading of stained slides and their interpretation by automated high resolution digital images. This system has a capacity of handling 200 slides, thus saving time and effort. Studies regarding its performance are under way in Nigeria, and South Africa [24, 25] (Fig. 6.2).

6.5.2.2 Culture

It is still the gold-standard for diagnosis of tuberculosis infection. Culture has a 30–50% higher sensitivity than smear as it can detect up to 100 bacilli/ml.

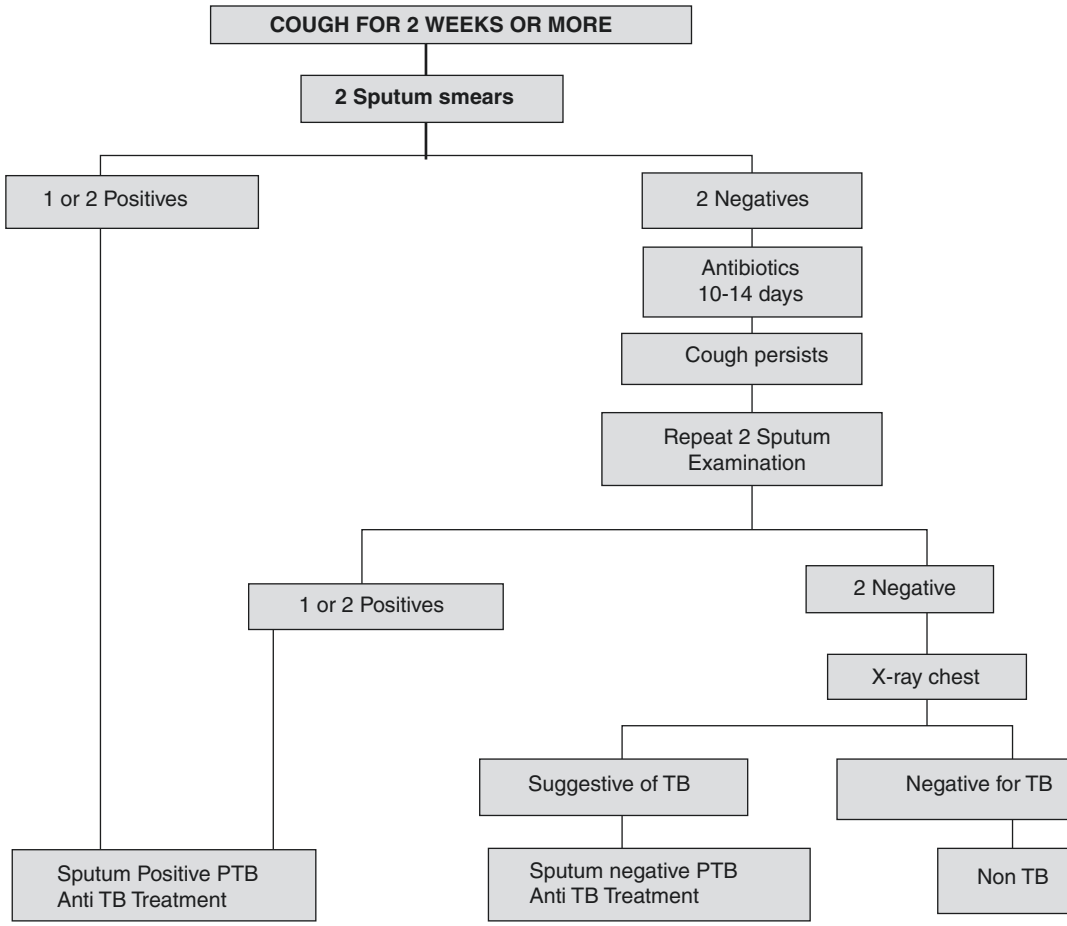

Fig. 6.2 Algorithm for diagnosing TB with sputum sample

Culture is used for

- Diagnosis of tuberculosis infection
- Species identification
- Drug susceptibility testing (DST)
- Genotyping
- To monitor patients response to treatment.

The culture mediums traditionally used are egg based—Lowenstein—Jenson and agar based—Middlebrook 7H10/11. Culture takes 4–8 weeks and drug testing takes additional 4–14 weeks. In 2007 WHO endorsed the liquid based culture medium—Middlebrook 7H9 broth—the mycobacterium growth indicator tube (MGIT) [21]. This method has also been validated by RNTCP. It utilizes non-radiometric detection of oxygen consumption by measuring the fluorescence. Liquid culture takes lesser time than solid culture. It takes 9 days for smear positive and about 16 days for smear negative. But negative reports are given for the culture only after 6 weeks [26]. Automated systems reduce the workload of technicians, provide standardization of reading samples, and give 100% sensitivity and specificity. Studies have shown that both automated and manual systems are efficient in detection of isoniazid and rifampicin susceptibility, but not for ethambutol and streptomycin [27]. For diagnosis of tubercular meningitis, liquid culture is the gold-standard which can detect in 65% of the TBM cases in 2–4 weeks. WHO currently recommends this PCR based test for the diagnosis of TBM (Table 6.1).

6.5.2.3 Molecular Detection: Nucleic Acid Amplification Tests

Molecular method validated by WHO are those which detect nucleic acid-DNA of mycobacterium, irrespective of it being live or dead. Nucleic Acid Amplification Tests (NAAT) initially approved by US-FDA included Polymerase Chain Reaction, Transcription-mediated amplification (Gen-probe), and Geno Type Mycobacteria Direct Assay.

Advantages

- Rapid detection of *M. tuberculosis* complex
- High pooled sensitivity and specificity are 85% (36–100%) and 97% (54–100%) [20]
- Useful in diagnosis of tubercular meningitis [20]

Disadvantages

- Cannot differentiate *M. tubercular* complex from *Mycobacterium tuberculosis*
- Strict infrastructure required to prevent contamination of DNA

At present, three methods of NAAT are in use

- Cartridge-based NAAT (CB-NAAT)—WHO approved
- Line probe assay (LPA)—WHO approved
- Loop-mediated amplification (LAMP).

Cartridge-based nucleic acid amplification test—It is a semi-quantitative nested real-time PCR. It is used for detection of *Mycobacterium*

Table 6.1 Different culture techniques

Culture technique	MGIT (manual and automated)	MB/BacT (automated)	Versa TREK/ ESP (automated)	Micro colony detection (MODS)	TLA—thin layer agar	Nitrate reduction assay or colorimetric assay
Principle	Measurement of consumption of oxygen	Measurement of CO_2	Measurement of pressure	Liquid culture in micro plates	Middlebrook agar	Detect viable cells
Average reading time	9–16 days	13.7 days	15.5 days	9 days for culture 7 days for MDR	11–14 days	10–15 days
Comment	Endorsed by WHO 2007 for culture and DST	Endorsed by WHO for culture	Endorsed by WHO for culture	Endorsed by WHO in 2009		Endorsed by WHO in 2009

tuberculosis and rifampicin resistance directly from clinical samples. WHO in 2010 endorsed its usage in diagnosis of pulmonary and extra-pulmonary tuberculosis and for pediatric tuberculosis. RNTCP has validated its use for diagnosis of drug resistant-TB (DR-TB) in presumptive DR-TB and to diagnose tuberculosis in pediatric age group, in HIV-infected individuals and in extra-pulmonary cases. The test has a sensitivity of 99.8% in smear and culture positive patient and 90.2% in smear negative and culture positive patients. This test is currently the most popular test for diagnosing rifampicin resistance with a sensitivity of 99.1% and specificity of 100% [28].

This test has a disadvantage that it fails to pick up isoniazid mono resistance which has a prevalence of 7–11% in first-line treatment failures [29]. It also fails to distinguish live from dead bacilli, therefore is not used for follow-up testing. In the event of an indeterminate test result or suspected false positive rifampicin resistance, confirmation by culture + DST or LPA is recommended.

Line probe assay (LPA)—It is used to detect tubercular DNA and various genetic mutations related to development of drug resistance from smear-positive sputum specimens or culture isolates by DNA extraction and PCR amplification. WHO endorsed LPA for MDR-TB in 2009 and it has a sensitivity of 98.8% and specificity of 100% for detection of MDR tuberculosis. The sensitivity, specificity of Rifampicin resistance, and INH resistance were 98.9%, 99.4% and 97.9% and 99.7% respectively [30].

Loop Mediated Amplification (LAMP)—It is a specific, simple, rapid, and cost-effective nucleic acid amplification method developed by Eiken Chemical Co., Ltd, Japan [31]. LAMP amplifies the DNA 109–1010 times within 16–60 min. It permits visual detection of the amplification, thus it can be used at outreach areas with minimal technical expertise. It can detect *M. tuberculosis* complex but does not detect resistance.

6.5.2.4 Tuberculin Skin Testing (TST)

It was first developed by Kochs in 1890 and later modified by Charles Mantoux in 1912. This test has been popularly named as Mantoux test after Charles Mantoux [32]. The test works on the principle that introduction of a small amount of tubercular protein into the body of the infected person with normal immune response will generate an antibody response. 2 ml of WHO approved purified protein derivative of *Mycobacterium tuberculosis* is injected in the forearm. The test is read after 48–72 h. An induration at the site of injection of 10 mm or more is considered as a positive test result. The International Standard Tuberculin is in the custody of the Laboratory of Biological Standards, Staten, Serum Institute, Copenhagen, Denmark.

Advantages

- Simple
- Easy to perform
- Cost effective.

Disadvantages

- Only detects presence or absence of the infection
- Cannot differentiate latent from active disease
- False positive in BCG vaccinated children and repeat tuberculin testing
- False negative in immunocompromised individuals.

6.5.2.5 Interferon-Gamma Release Assay (IGRA)

This test works on the principle that T cells sensitized with *Mycobacterium* generate interferon gamma (a THN1 cytokine) when in contact with a mycobacterial antigen [33]. The previous generation IGRA required 16 h incubation. But newer IGRA require (T-spot) requires only 8 h of incubation. But they are expensive and technically complex to do than the TST. WHO, in 2011, recommended against the use of IGRAs to replace TST in high burden countries for mass usage and RNTCP also discourages its use for diagnosis in adults in high burden countries.

6.5.2.6 Chest X-ray

Chest X-ray is one of the basic tests available in low resource settings to identify pulmonary

tuberculosis. It is at times the only report on the basis of which treatment may be started in the event of sputum smear negative cases. Typical chest X-ray findings include focal upper lobe opacities, diffuse opacities, consolidation, reticulonodular opacities, cavities, nodules, miliary pattern, intrathoracic lymphadenopathy, pleural effusion (Figs. 6.3 and 6.4). In HIV-infected patients, smear yield is lower and even the radiological abnormalities may be less typical.

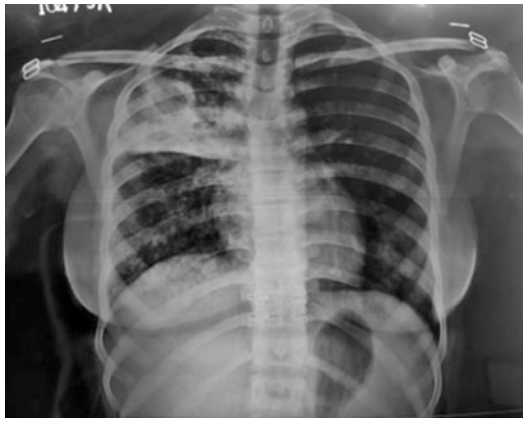

Fig. 6.3 Consolidation seen in right upper zone with cavitation

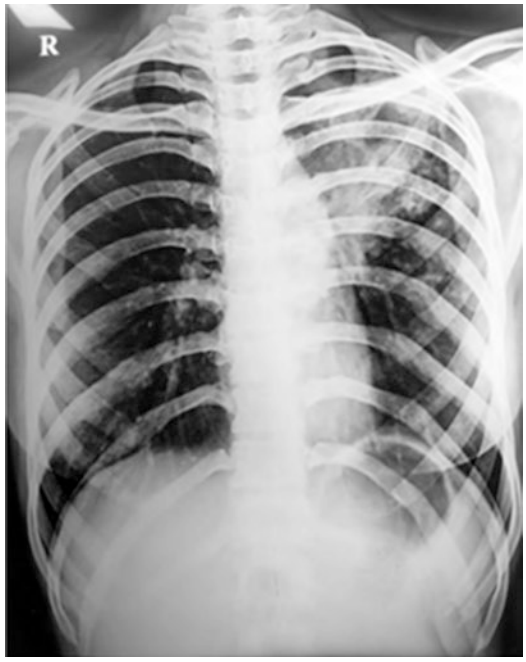

Fig. 6.4 Fibroinfiltrative lesion in left upper mid zone with area of breakdown

Ionizing radiation (X-ray) is made up of high energy photons that are capable of causing damage to the DNA by generating caustic free radicals. Radiation induced teratogenesis (calculated on the survivors of Hiroshima atomic bomb exposure) is estimated as 40% with 100 rad exposure at 10–17 weeks, resulting in microcephaly and mental retardation. Risks of childhood malignancies like leukemia have been found to increase with as little as 1–2 rads exposure. Minimum harmful dose calculated is 5 rads. The estimated two-view chest X-ray exposure to fetus is 0.00007 [34]. The number of views required for a cumulative 5 rad dose is 71,429. As per recommendations of American College of Obstetricians and Gynecologists single X-ray exposure does not result in any increase in fetal loss or anomalies [35].

6.5.2.7 Tissue Diagnosis

The characteristic feature of tubercular disease on histopathology specimen is the presence of the caseating granulomatous inflammation with Langhans giant cells. In 60–80% cases, a positive culture has been reported from biopsies. Fine needle aspiration biopsy (FNAB) reports even higher rates of positive diagnosis and has replaced the more invasive biopsies as the diagnostic procedure of choice.

6.5.2.8 Magnetic Resonance Imaging of Brain

Used to evaluate TBM and spinal tuberculosis. MRI features in TBM are basal meningeal enhancement, hydrocephalus, and presence of solitary or multiple tuberculoma. MRI brain is not contraindicated during pregnancy.

6.5.2.9 ECG and Echocardiogram

They are the most important investigation to clinch the diagnosis of tubercular pericarditis. Cardiac

tamponade is the most predictive sign which suggests constrictive pericarditis.

6.5.2.10 CSF Examination

Cerebrospinal fluid examination shows presence of lymphocytosis, raised protein content, and moderately raised lactate (3–8 mmols/l) in TBM as compared to bacterial meningitis in which the lactate levels are higher. As TBM is paucibacillary, AFB in CSF smear is seen only in 20% cases.

6.6 Effect of TB Infection on Pregnancy

During pregnancy, the maternal immune system undergoes changes crucial for preventing fetal rejection. These changes are mediated by the estrogen and progesterone hormones. Cellular immunity is suppressed and humoral immunity is augmented with TH1-/TH2 phenotype shift. This immunosuppressed situation acts as a risk for reactivation of a latent tuberculosis infection in a pregnant woman. The increase in the regulatory T cell during pregnancy results in reduction of multi-functional CD4+T cell production of Th1 cytokines in response to MTB antigens. This results in increased incidence of progression of latent to active TB . Among other factors there is significant decrease in secretion of tumor necrosis factor (TNF) from natural killer cells (NK cells). These changes tend to occur gradually over the course of pregnancy and are more pronounced in second and third trimester. Several factors such as the type, site, extent of disease, and trimester of pregnancy effect the development of the disease. It also depends on nutritional status of mother, presence of other medical comorbidity, immune status, and co-existence of HIV infection [36]. Pulmonary and extrapulmonary TB affects pregnant women in the same way as any other patient [37]. It is seen that TB in pregnancy is associated with increased chances of abortions, preterm labor, fetal prematurity, low birth weight babies, pre-eclampsia, and PPH (ninefold increase). Maternal outcome associated with TB depends on which gestation ATT is begun. Early initiation of ATT will reduce the obstetric morbidity [38]. In a meta-analysis by Sobhy et al. [39] TB in pregnancy was associated with increased chances of maternal morbidity, anemia (OR 3.9, 95% CI 2.2–6.7), cesarean section (OR 2.1, 95% CI 1.2–3.8), preterm birth (OR 1.7, 95% CI 1.2–2.4), low birth weight (OR 1.7, 95% CI 1.2–2.4), birth asphyxia (OR 4.6, 95% CI 2.4–8.6), and perinatal death (OR 4.2, 95% CI 1.5–11.8).

6.7 Effect of Pregnancy on TB

There is physiological collapse of basal pulmonary cavity due to rise of diaphragm. Although some studies hypothesize that TB gets flared up by the immune-deficient state mimicked by pregnancy, many studies also refute this theory [40]. Consecutive pregnancies may lead to reactivation of latent tuberculosis. Diagnosis of TB in pregnancy is more challenging due to masking of symptoms due to physiological changes occurring in pregnancy. Nonspecific symptoms and signs common to both include malaise, fatigue, dyspepsia, tachycardia, anemia, and raised ESR [41].

6.8 Fetal Effects of Maternal TB

Congenital TB is very rare. It can spread either by hematogenous route via the umbilical vein to fetal organs or by ingestion of infected amniotic fluid. The presentation of congenital TB is characterized by poor feeding, irritability, fever, abdominal distension, lymphadenopathy, and hepatosplenomegaly [42]. Demonstration of caseating hepatic granuloma on percutaneous liver biopsy either at birth or first week of life is characteristic [43]. An abnormal chest X-ray and CT scan are found in most of these cases (Figs. 6.5 and 6.6). Overall mortality of congenital TB is as high as 35% if left untreated [44]. The Cantwell's diagnostic criteria (mentioned below) is used for defining congenital TB [45].

Cantwell criteria of congenital TB include a proven tuberculous lesion plus one of the following:

1. Lesions present in the first week of life

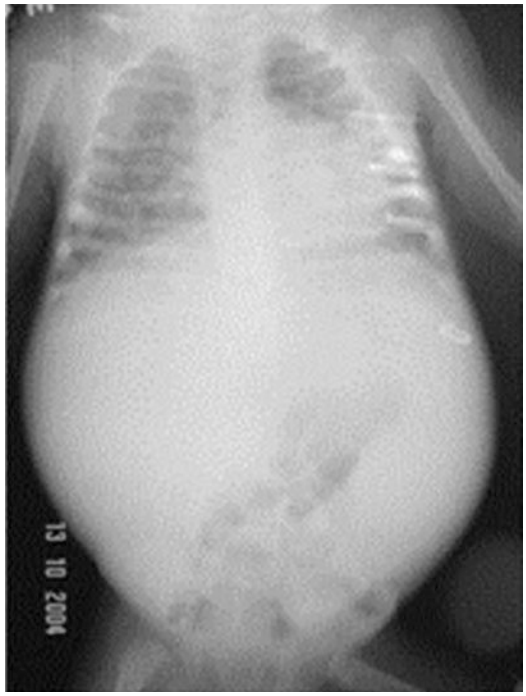

Fig. 6.5 Consolidation in left lung with hilar lymphadenopathy on X-ray

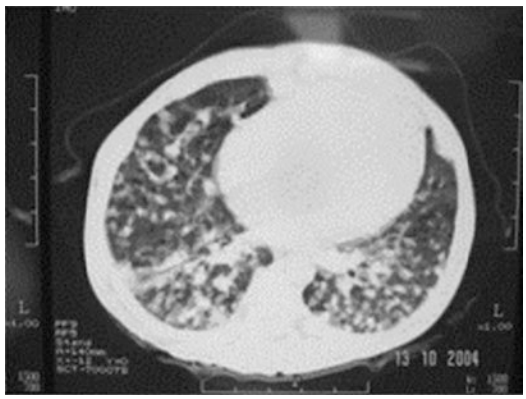

Fig. 6.6 CT scan in congenital TB with multiple low attenuation areas

2. Primary hepatic complex or caseating hepatic granulomas
3. Mother has genital tract or placental TB
4. Infection of the neonate by the contacts has to be excluded by their thorough investigation.

When there is no evidence of congenital tuberculosis, Isoniazid (10 mg/kg/day) is commenced at birth and continued for 6 months. Full course of antitubercular treatment is given depending on the clinical features and tuberculin test. Tuberculin skin test and chest X-ray are done at 6 weeks, 12 weeks, and 6 months. The baby is vaccinated with BCG at 6 months if these tests are negative. If any of these tests comes out to be positive, baby is started on multidrug therapy.

6.8.1 HIV and TB Coinfection

HIV coinfection is the strongest known risk factor for progression of latent TB infection to active TB disease. Immune response to TB bacilli increases HIV replication leading to rapid progression of HIV disease [14]. Over 50% of maternal mortality occurring in mother with tuberculosis is due to coinfection with HIV. Efavirenz is contraindicated before 13 weeks of gestation while the risk of toxicity from use of didanosine and stavudine is significantly increased in pregnancy. Rifampicin can reduce the serum concentration of efavirenz and nevirapine by as much as 50%. To curtail this problem rifabutin may be used in place of rifampicin as it has less effect on CYP3A. Optimal access to DOTS will significantly reduce morbidity and mortality. Due to drug interactions between rifampicin and antiretroviral drugs, policy is to start antiretroviral drugs after completing anti-TB treatment [45].

6.8.2 Classification of Tuberculosis

Center for Disease Control has classified tuberculosis on the basis of pathogenesis of the disease in 1999 (Table 6.2). This classification has been endorsed by the American Thoracic Society and the Council of the Infectious Disease Society of America.

Table 6.2 CDC classification of tuberculosis

Class	Type	Description	Intervention
0	No TB Not Infected	• No history of exposure • A negative reaction to the tuberculin skin test (TST)	
1	Tuberculosis exposure, no evidence of infection	• History of exposure • A negative reaction to the tuberculin skin test	If significant exposure within 3 months, retest with TST at 10 weeks after the last exposure In the interim, treatment of latent tuberculosis considered, for children < 15 years of age and HIV infection
2	Latent tuberculosis infection, no disease	• A positive reaction to the tuberculin skin test (indicate mm in duration) • Negative bacteriologic studies (if done) • No clinical, bacteriological, or radiographic evidence of active tuberculosis	Treatment of latent tuberculosis infection may be indicated for some persons in this group
3	Tuberculosis, clinically active	• *M. tuberculosis* cultured (if performed) • Clinical, bacteriological, or radiological evidence of current disease	A person remains in Class 3 until treatment for the current episode of disease is completed
4	Tuberculosis not clinically active	• History of episode (s) of TB/ abnormal but stable radiographic findings • Positive TST • Negative bacteriologic studies (if done) *And* • No radiological evidence of current disease	If current clinically active disease has not been ruled out, especially in persons not adequately treated in the past, consider as Suspect (Class 5) until diagnostic evaluation permits classification as Class 3 or Class 4
5	Tuberculosis suspect	• Diagnosis pending • TB disease should be ruled out within 3 months	

Source: Diagnostic Standards and Classification of Tuberculosis in Adults and Children. Am. J. Respir. Crit. Care Med., Volume 161, Number 4, April 2000, 1376–1395

6.9 Treatment of TB in Pregnancy

Pregnant woman with pulmonary TB is managed by multidisciplinary team comprising of obstetrician, chest physician, infectious disease specialist, bacteriologist, and neonatologist [47].

WHO Treatment Guidelines Treatment of tuberculosis is not to be restricted or deferred in pregnancy, as the disease can cause poor pregnancy outcomes. Treatment should be carried out as per the regimens laid out for the different categories. Excepting Streptomycin, which has been associated with fetal ototoxicity, all other first-line drugs are found to be safe in pregnancy. Pyridoxin supplements should be given to women on isoniazid.

6.9.1 CDC Recommendations for Treatment of Tuberculosis in Pregnancy

Untreated tuberculosis (TB) disease—is more detrimental to both the pregnant woman and the fetus than the treatment per se. Timely initiation of the treatment is essential when the probability of TB is moderate to high.

- It has been seen that pregnant women with TB have an increased incidence of low birth weight infants as compared to those without TB. Rarely the newborn may be born with tuberculosis.
- The anti-tubercular drugs used in the initial phase of the treatment cross the placental barrier but they have not been documented to cause any harmful effects on the fetus.

Latent TB Infection

- To avoid unnecessary medication during pregnancy, the treatment of latent TB infection may be deferred till 2–3 months post-partum.
- Treatment for latent TB infection should not be delayed on the basis of pregnancy alone, even during the first trimester. This is especially those women who have come in recent contact of someone with infectious TB disease and are at a high risk for progression from latent TB infection to TB disease.
- Treatment to be given is
  - 4-month daily regimen of Rifampicin (RIF) (4R)
  - 3-month daily regimen of Isoniazid (INH) and RIF (3HR)
  - 6- or 9-month daily regimen of INH (6H or 9H) , with pyridoxine (vitamin B6) supplementation
  - During pregnancy or for women expecting to become pregnant it is not recommended to administer 3-month weekly INH and Rifampicin (3HP) regimen as its safety during pregnancy has not been studied.

TB Disease

- Initial treatment regimen is INH, rifampin (RIF), and ethambutol (EMB) daily for 2 months, followed by INH and RIF daily, or twice weekly for 7 months (for a total of 9 months of treatment).
- Streptomycin should not be used because it has been shown to have harmful effects on the fetus.
- Pyrazinamide (PZA) is not recommended to be used because its effect on the fetus is unknown.

Indian Guidelines—Revised National Tuberculosis Control program was launched in 1997. It has adopted the internationally recommended Direct Observed Treatment Short Course (DOTS) [46]. Management of TB cases in pregnancy is also according to the Revised National Tuberculosis Programme (RNTCP) and follows the directly observed treatment short course which is in accordance with recently issued WHO guidelines on prevention of tuberculosis. RNTCP is responsible for carrying out 5-year TB national strategic plans under the government of India. Under RNTCP, sputum examination is the preferred modality for diagnosing pulmonary TB [47, 48].

RNTCP in 2008 recommended changes in diagnostic criteria and also specified that the number of sputum specimens required for diagnosis is two. Two samples of sputum (one is random and one is taken early morning) are to be collected and examined for acid-fast bacilli with ZN stain. Even if one specimen is positive out of the two, it is enough to declare a patient smear positive pulmonary TB. Pregnant women with TB are categorized as new cases. Revised guidelines have introduced daily TB treatment regimen and also a new anti-TB drug bedaquiline for the management of drug resistant TB (Table 6.3).

Table 6.3 RNTPC treatment category of TB in pregnancy

Treatment group	Intensive phase	Continuation phase
New	(2) HRZE (for 2 months)	(4) HRE (for 4 months)
Previously treated	(2) HRZES + (1) HRZE	(5) HRE (for 5 months)
MDR TB	6–9 (Km Lfx Eto Cs Z E) (for 6–9 months)	18 (Lfx Eto Cs E) (for 18 months)
XDR TB	(6–12) Cm, PAS, Mfx, High dose-H, Cfz, Lzd, Amx/Clv	(18) PAS, Mfx, High dose – H, Cfz, Lzd, Amx/Clv

Source: Revised National Tuberculosis Control Program. Training module for medical practitioners. New Delhi: Ministry of Health and Family Welfare; 2010
H, isoniazid; R, rifampicin; Z, pyrazinamide; E, ethambutol; S, streptomycin; Km, kanamycin; Lfx, levofloxacin; Eto, ethionamide; Cs, cycloserine

Table 6.4 Different drugs and their side effects in pregnancy

Name of drug	Dosing	Side-effect in pregnancy	Recommendations in pregnancy
Isoniazid	5–10 mg/kg	Hepatotoxicity	LFT fortnightly in first 2 months of treatment and then monthly Pyridoxine supplementation
Rifampicin	10 mg/kg	Hypoprothombinemia	Vitamin K for both mother and infant
Ethambutol	15–25 mg/kg	Retrobulbar neuritis	
Pyrazinamide	20–30 mg/kg	No animal studies available	If not used in pregnancy—9 month regimen to be followed
Fluoroquinolones	750–1000 mg once daily	Category C—risk of damage to articular cartilage and resulting in juvenile arthritis	Category C
Streptomycin	15 mg/kg/day	Nephrotoxic and ototoxic to the fetus	Category D
Capreomycin	20 mg/kg/day	Animal studies show teratogenicity	Category C
Ethionamide, Cycloserine, PAS[a]	500–750 mg/day in divided dose [a]8 g/day in 2 divided dose	Animal studies show teratogenicity	Category C

Source: Revised National Tuberculosis Control Program. Training module for medical practitioners. New Delhi: Ministry of Health and Family Welfare; 2010

Dose regimens, side effects, and teratogenicity are described in detail in Table 6.4.

Following are the salient features of ATT treatment during pregnancy:

1. Pyridoxine should be supplemented in dose of 20 mg/day for the entire course of ATT to counter the effect of isoniazid associated neuropathy
2. MDR TB cases need isolation and neonate may need to be segregated from mother
3. Cautious use of medicine due to drug interactions
4. CDC does not endorse the use of pyrazinamide in pregnancy due to absence of detailed teratogenic data
5. First-line ATT drugs except streptomycin are safe
6. A higher cure rate was seen with the daily administration of antituberculosis therapy as compared with the thrice weekly regimen. It also prevented acquired rifampicin resistance.
7. Follow up of ATT drugs can be combined with antenatal checkups.

Antitubercular drugs contraindicated during pregnancy are:

- Streptomycin
- Kanamycin
- Amikacin
- Capreomycin
- Fluoroquinolones
- Ethionamide and PAS.

6.10 Breastfeeding

There is no contraindication for breast feeding in women on first-line antitubercular drugs because concentration of these medications in the breastmilk is very less to cause any adverse effect in the nursing newborn. In severe cases of pulmonary TB or MDR-TB breastfeeding may be interrupted and breastmilk expressed [49]. As per the recommendations of the American Academy of Pediatrics, a woman diagnosed with TB who has been appropriately treated for 2 weeks or more is considered non-contagious, and should be allowed to breast feed [50]. RNTCP recommends

breastfeeding of neonates irrespective of the mothers TB status and if mother is diagnosed TB recently she should be started on anti-tubercular therapy right away without delay and under no circumstances TB should be a prohibiting factor for mother to breastfeed her baby [51].

Precautions in breastfed infants on anti-tubercular treatment:

- Reduce dose of INH by 20% as it is the most excreted anti-tubercular drug.
- To reduce the possibility of high plasma levels in the neonates, the mother on anti-tubercular treatment should take her medication after breastfeed, and substitute the breast milk with formula feed for the next feed. Thereafter the mother can follow her usual routine.

6.10.1 Pyridoxine Supplementation

The two most drugs which are the mainstay of anti-tubercular treatment are isoniazid and rifampicin. A well-recognized adverse effect of isoniazid is peripheral neuropathy as a result of pyridoxin deficiency. Pyridoxin supplementation is generally prescribed in certain groups affected with tuberculosis, i.e. diabetics, renal failure, chronic liver disease, alcoholics, associated HIV infection and pregnant women and breastfeeding mothers. Pyridoxine deficiency related to isoniazid is rare in children, with an incidence of 0.7% as per studies [52, 53]. Two case reports of pyridoxin responsive seizures have been reported in literature. Whether breastfed infants of mothers on isoniazid require pyridoxine supplementation remains controversial. World Health Organization (WHO), National Institute for Health and Clinical Excellence (NICE), British National Formulary (BNF), and The Italian Pediatric Tuberculosis Study Group do not suggest pyridoxine supplementation but recommend monitoring of these infants for isoniazid toxicity [54–57]. The American Thoracic Society and Electronic Medicines Compendium (eMC) recommends pyridoxine supplementation to breastfed infants of nursing mothers [58, 59]. Paucity of evidence based studies in this area has led to inconsistencies in recommendations. Regular monitoring of these infants breast fed by mothers who are on treatment with isoniazid is recommended to look for both short- and long-term side effects.

6.11 Multidrug-Resistant TB (MDR-TB) in Pregnancy

The criteria to define multidrug-resistant TB (MDR-TB) is unresponsiveness of the tubercular disease to the two most powerful anti-TB drugs—isoniazid and rifampicin. Another rare type of multidrug-resistant tuberculosis is extensive drug resistant TB (XDR TB), in which the disease shows resistance to isoniazid and rifampin, along with any fluoroquinolone and at least one of the three injectable second-line drugs (amikacin, kanamycin, or capreomycin). The overall incidence of multidrug resistance is less than 1% of all TB cases and it is associated with a high mortality rate. Management needs to be individualized. It must be treated with second-line ATT drugs after prognosticating about fetal implications of the drugs [60]. Para-aminosalicylic acid (PAS) has been used in combination with isoniazid without any significant teratogenic side effect. All non-pregnant women receiving drug resistant treatment should be advised contraception, as the teratogenic potential of second-line drugs is still not well defined. Obstetrical complications like spontaneous abortion, preterm labor, oligoamnios, fetal growth restriction, and increased neonatal mortality are also found to be more in such patients. TB is not an indication for termination and second-line drugs like (kanamycin, levofloxacin, ethionamide, cycloserine, PAS, capreomycin) should be used judiciously. MDR kanamycin and ethionamide are omitted before 12 weeks gestation and added after 12 weeks of gestation. Therapeutic abortion has been suggested in cases with severe respiratory distress with patients in the first trimester of pregnancy but the treatment may be delayed to the second trimester if the case permits. The standard treatment for such patients is of 18–24 months duration [61, 62].

6.12 Prevention of Tuberculosis

As tuberculosis is still a disease of poverty and overcrowding, improvement in the standard of living and population control go a long way in reduction of prevalence of the disease. Good nutrition and access to health facilities help in reduction of morbidity and mortality associated with it. Certain other preventive measures include:

Vaccination—Many high burden countries like India, Pakistan, Bangladesh, Nigeria have included BCG vaccination into the national immunization policy. These countries aim to confer active immunity from childhood. Certain countries like Austria, Germany, United Kingdom, Finland, France, United States have stopped universal immunization and opted for BCG vaccination for selective high risk individuals including those who traveling to high burden countries. 16 countries recommend additional booster vaccination. These include Armenia, Belarus, Croatia, Czech Republic, Fiji, Kazakhstan, Macedonia, Nigeria, Tunisia, etc. Countries like Kazakhstan, Belarus, Uzbekistan, and Turkmenistan recommend three doses of vaccination [63]. Vaccination is also recommended for non-immune women travelling to tuberculosis endemic countries. Vaccination during pregnancy is contraindicated.

Primary prevention of HIV/AIDS—In 2009 1.1 million people were diagnosed with coinfection of HIV/AIDs and Tuberculosis. Susceptibility of pregnant women infected with HIV in developing tuberculosis is greater due to immunocompromised state. It is recommended to screen all pregnant women living with HIV for active tuberculosis even if obvious symptoms are not present.

Isoniazid preventive therapy (IPT)—The prevalence of latent tuberculosis in the community is about 50%. Isoniazid Preventive Therapy is being promoted to bring about a reduction in the cases of latent tuberculosis progressing to active tuberculosis by giving INH especially to HIV-infected individuals. This strategy is recommended by World Health Organization. Isoniazid is an effective bactericidal, anti-tubercular drug. It provides protection against reactivation as well as tubercular reinfection after exposure to an open case of TB. IPT has been shown to decrease the overall risk of developing tuberculosis by 33% (relative effect 0.67; CI 0.51–0.87). It also reduces the incidence of tuberculosis and mortality rates in HIV-infected patients [64]. It is administered as 10 mg/kg/day (maximum up to 300 mg) for 6 months along with Pyridoxin 50 mg/day. WHO guidelines strongly recommends that pregnancy should not exclude women living with HIV from symptom-based TB screening and receiving IPT.

6.13 Conclusion

Tuberculosis is a significant cause of mortality and morbidity with TB in pregnancy affecting the pregnant women both physically and mentally. TB in pregnancy is associated with an increased risk of abortions, preterm labor, fetal prematurity, low birth weight babies, pre-eclampsia, and PPH. Early initiation of ATT will help to reduce the obstetric complications. Diagnosis of TB in pregnancy is more challenging due to masking of symptoms by the physiological changes in pregnancy. Guidelines by WHO or RNTCP should be followed for management of TB cases in pregnancy. A multidisciplinary approach with obstetrician, chest physician, infectious disease specialist, bacteriologist, and neonatologist as a team should together plan the management for pregnant women with pulmonary TB .

Key Points

- Tuberculosis is a significant cause of mortality and morbidity in both developed and developing countries.
- Prevalence of active TB is 0.06–0.25% among pregnant women belonging to low burden countries and between 0.07 and 0.5% in high burden countries.
- The gold-standard for diagnosis of tuberculosis infection is culture of the mycobacterium.

- During pregnancy there is decline in cellular immunity and augmentation of humoral immunity with TH1-/TH2 phenotype shift thus increasing risk of reactivation of a latent tuberculosis infection.
- TB in pregnancy increases the risk of abortions, preterm labor, fetal prematurity, low birth weight babies, preeclampsia, and PPH.
- Management of pulmonary TB during pregnancy requires a multidisciplinary approach with a team of obstetrician, chest physician, infectious disease specialist, bacteriologist, and neonatologist.
- Treatment of tuberculosis is not to be restricted or deferred in pregnancy, as the disease can cause poor pregnancy outcomes. Treatment should be carried out as per the regimens laid out for the different categories.
- There is no contraindication for breast feeding in women on first-line antitubercular drugs because concentration of these drugs is too small to produce any effect in the nursing newborn.

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7 Pregnancy and COVID-19: Management and Challenges

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7.1 Introduction

Pregnancy has been categorized under the "increased risk" category by CDC and ICMR. Although the risk of becoming infected is the same in this subgroup as that of the general population, the illness course is more severe and it is associated with an increased risk of ICU admission, mechanical ventilation, and death. This risk is further enhanced if associated with comorbidities like gestational diabetes, hypertension, multiple gestations, and heart disease. Hence, prevention of disease transmission and its prompt management in pregnancy is crucial.

Infection control measures like social distancing, hand hygiene, and the use of masks are imperative to prevent the spread of COVID-19. Nevertheless, its management in pregnancy still remains a significant challenge as this virus is novel and research is still ongoing. Limited literature is currently available on its management and the probable effects of this virus on the mother and baby, let alone the risk of treatment-associated teratogenicity. Henceforth, pregnancy with COVID-19 should be managed by a multidisciplinary approach and individualized care should be preferred.

This chapter highlights the current principles being followed for the prevention and management of COVID-19 during the antenatal, intrapartum, and postpartum period including the care of newborn of infected mothers.

7.2 Testing and Triage

According to the current ICMR guidelines, testing should be done in the following cases:

1. Travel history
2. History of exposure to positive cases of COVID-19
3. If a woman is residing in a hot spot area
4. Symptoms of COVID-19 (fever with a respiratory symptoms such as cough, congestion, sore throat, or shortness of breath)
5. Immunocompromised conditions and/or associated comorbidities.

The patient should be treated as a confirmed case until the test results are negative, in an appropriate labor/delivery room as per institutional protocols. However, obstetric management should not be delayed while the test results are awaited. It is recommended that within 7 days of illness RT-PCR should be performed and after 7 days of illness antibody test should be performed

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which if found to be negative is confirmed by RT-PCR [4].

Asymptomatic direct and high-risk contacts (defined as those living in the same household, traveling together by any conveyance, working together in close proximity [same room], or healthcare workers providing direct care) of a confirmed case should be tested once between day 5 and day 14 of coming in his/her contact. However, universal testing with a rapid COVID-19 test can be done on presentation to the hospital, if testing is available. Patients undergoing planned induction or cesarean delivery can also have screening 24–72 h before the planned procedure in an attempt to have results available before admission, if testing is available.

7.3 Antenatal Management

Various guidelines have been issued by the American College of Obstetricians and Gynecologists (ACOG), the Society for Maternal-Fetal Medicine (SMFM), World Health Organization (WHO), Federation of Obstetric and Gynaecological Societies of India (FOGSI), and Indian Council of Medical Research (ICMR) for providing appropriate antenatal care to women during this pandemic while also limiting the exposure to the virus by restricting the number of hospital visits. The main strategy to achieve this is by modifying the protocols formerly followed by clubbing the antenatal visits for examination with ultrasounds and laboratory investigations. Video and tele-consultations play a major role in this regard and have been particularly publicized in the current times. The modifications for antenatal USG monitoring if the patient is suspected/ confirmed case of COVID-19 are given in Table 7.1.

Health care workers examining these patients and performing the ultrasounds and laboratory investigations should wear appropriate PPE and should ensure precautions like frequent hand washing and maintaining a physical distance of at least 1 m wherever possible. The patient along with the attendants should also be encouraged to wear face masks.

Table 7.1 USG monitoring in suspected/ confirmed COVID-19 patients

Scan	Outpatient	Inpatient
11 + 0 to 13 + 6 weeks (also for dating)	Combined test to be rescheduled in 2 weeks (if patient still in the gestational age window) Offer NIPT/ serum screening and detailed scan 3–4 weeks after recovery	Offer NIPT screening Perform bedside if available
18 + 0 to 19 + 4 weeks	Reschedule in 3–4 weeks after recovery	Perform bedside
Fetal growth scan (third trimester)	Reduce frequency with first scan 2–4 weeks after recovery	Follow up growth every 4 weeks or earlier based on findings

Source: http://www.fogsi.org/fogsi-gcpr-on-pregnancwit-covid-19-infection-version-2/

The examination room should have minimum furniture and equipment to prevent fomite-related transmission and the room along with the equipment (mobile phones, electronic devices, pens, measuring tapes, stethoscopes, and BP apparatus) need to be frequently sanitized to prevent the spread. Ideally, confirmed/ suspected patients should be kept in a well-ventilated, single-occupancy room with a closed door and dedicated bathroom. Also, aerosol-generating procedures (AGP) should be performed in a room with negative pressure ventilation.

In 2016, WHO increased the recommended number of antenatal visits from four to eight for a positive pregnancy experience particularly in LMICs. But, in view of the current pandemic, the focussed antenatal care model (FANC) (visits at 8–12 weeks, 24–26 weeks, 32 weeks, and 36–38 weeks) that was followed prior to 2016 can be adopted again to limit exposure. FOGSI also recommends the timing of antenatal visits with ultrasounds at 12–13 weeks, 18–22 weeks, and then at 30–32 weeks. ICMR complies with these principles and recommends reduced number of antenatal visits (that is at 12, 20, 28, and 36 weeks). It further adds that visits should be deferred for 7 days in case the female develops respiratory symptoms/fever and for 14 days in case any

household member has tested positive and testing for COVID-19 should be done in such cases. On the other hand, in developed nations like Australia, antenatal visits are clubbed with immunization schedules (first visit with delivery of influenza vaccine, second at 28 weeks along with pertussis vaccine, and the third visit between 34 and 37 weeks which also includes a growth scan). Similar approach has been followed in hospitals in America with an initial prenatal visit, an anatomy ultrasound, and then at 28 weeks, 36 weeks, and at 39-weeks along with blood investigations.

Home BP monitoring, weight measurement, and daily fetal movement count are advised in all pregnant females and are asked to report to hospital in case of any worsening of respiratory symptoms or development of obstetric symptoms such as pain abdomen, leaking per vaginum, bleeding per vaginum or decreased fetal movements.

COVID-19 pandemic may be associated with new onset or exacerbation of subsyndromal psychiatric symptoms as well as full-blown psychiatric disorders, including anxiety disorders, depressive disorders, post-traumatic stress disorder, or substance use disorders. Hence, all pregnant females should undergo counseling at antenatal visits to provide psychological support to patients.

If the patient is found to be uninfected, counseling regarding the risks of COVID-19 in pregnancy and infection control measures must be done during her visits or consultations.

If COVID-19 infection is confirmed during pregnancy, the patient can be isolated either at home or in a health care facility depending on the clinical status, for the purpose of preventing infection transmission and further monitoring. If they remain asymptomatic the period of isolation is 14 days. However, in symptomatic cases, the management depends on the severity of illness, underlying medical comorbidities or coexistent pregnancy complications along with measures to prevent the spread of disease. Admission to the hospital is required in the following case scenarios:

1. Mild signs and symptoms
   (a) Fever, cough, sore throat, malaise, headache, muscle pain without shortness of breath, dyspnea, or abnormal chest imaging AND
   (b) Comorbidity like poorly controlled hypertension or diabetes, chronic kidney disease, chronic cardiopulmonary disease, immunosuppressive states [intrinsic or medication-related]
2. Fever >39 °C not responding to acetaminophen
3. Moderate or severe signs and symptoms
   (a) Oxygen saturation <95% [when pulse oximetry is available] on room air and while walking
   (b) Respiratory rate >30 breaths per minute
   (c) Rapidly escalating supplemental oxygen requirement
4. Critical cases
   (a) Respiratory failure
   (b) Hypotension despite appropriate hydration AND/OR
   (c) New end-organ dysfunction (e.g., mental status changes, hepatic or renal insufficiency, cardiac dysfunction).

Mild/moderately ill cases can be managed with supportive measures and monitoring for signs and symptoms of deterioration. Counseling should be done regarding the need for ambulation, plenty of fluid intake, home BP monitoring, and daily fetal movement count and to report immediately to the hospital in case of development of medical/obstetric symptoms. The US Food and Drug Administration (FDA) has provided expanded approval for use of non-invasive fetal and maternal monitoring devices at home to limit hospital visits for the same.

In severely ill/ critical cases, multidisciplinary management is required and early decision should be taken regarding the need for ICU admission. The principal guidelines for the management of ARDS in confirmed COVID-19 cases provided by FOGSI are:

1. Conservative Intravenous fluid strategies
2. Empirical early antibiotic for possible bacterial pneumonia
3. Early invasive ventilation may be needed
4. Lung protective ventilation strategies

5. Place the patient in lateral decubitus position
6. Extracorporeal membrane oxygenation where needed.

7.3.1 Medical Management

The following treatment strategies are currently reported to be effective in the management of pregnancy with COVID-19:

1. *Supportive treatment*: Patients with mild symptoms can be managed with supportive treatment which includes adequate hydration, rest in left lateral position, and frequent ambulation along with over-the-counter medications like acetaminophen (preferred over NSAIDs).
2. *NSAIDs and acetaminophen***:** ACOG, WHO, and European Medicines Agency (EMA) have recommended using NSAIDs in the lowest effective dose, ideally for less than 48 h in cases of fever or pain. Low-dose aspirin for the prevention of preeclampsia is safe throughout pregnancy. However, due to the risks of fetal toxicity (oligohydramnios, premature closure of ductus arteriosus) acetaminophen is preferred analgesic and antipyretic. However, acetaminophen is used cautiously in cases of liver disease due to the risk of hepatic toxicity. Doses less than 2 g/day are considered safe in the absence of severe or decompensated hepatic disease.
3. *Monoclonal antibodies:*
   (a) Bamlanivimab: It can be used in mild to moderate cases that are at high risk of progression to severe or critical disease. Since it is an IgG1 neutralizing monoclonal antibody, it can cross the placental barrier; however, the benefit or risk to the fetus is not yet proven.
   (b) Casirivimab-imdevimab combination: This is another monoclonal antibody that can be used in mild cases of COVID-19. However, pregnancy implications are not yet proven and should be used cautiously if necessary.
4. *Maternal respiratory support*—The main goal is to maintain maternal peripheral oxygen saturation (SpO_2) ≥95% or a maternal PaO_2 >70 mmHg to facilitate adequate diffusion of oxygen via the placenta to the fetus. World Health Organization (WHO) suggests maintaining maternal SpO_2 ≥92–95% once the patient is stable. This can be achieved either by supplemental oxygen (using masks/nasal prongs) or by mechanical ventilation [in critically ill patients with acute respiratory distress syndrome (ARDS)]
5. *Venous thromboembolism (VTE) prophylaxis:* Pregnancy in itself is a hypercoagulable state and the risk of thromboembolism is further enhanced in case of COVID-19 infection. Although anticoagulant prophylaxis is currently not recommended in asymptomatic or mild-moderate symptoms, it must be started in patients who are severely ill/ critical (if not otherwise contraindicated). Moreover, if a patient is already started on anticoagulant therapy due to obstetric reasons, it must be continued as before. Therapeutic doses need to be given in case VTE has already manifested. Low molecular weight heparin (LMWH) is appropriate if delivery is not expected within 24 h and after delivery. On the other hand, unfractionated heparin (UFH) is used if faster discontinuation is needed (eg, if delivery, neuraxial anesthesia, or an invasive procedure is anticipated within approximately 12–24 h or at 36–37 weeks of gestation). Intermittent pneumatic compression devices should be used along with medical management for VTE prophylaxis.
6. *Steroid therapy***:** Dexamethasone can be used in critically ill patients on ventilator support and in cases of refractory shock (dose of 6 mg daily for 10 days or till the day of discharge, whichever is earlier). Additionally, in women in whom preterm delivery (<34 weeks) is anticipated, dexamethasone four doses of 6 mg intramuscular 12 h apart should be given for fetal lung maturity. Some studies have also suggested using methyl-

prednisolone or hydrocortisone for maternal benefit due to less fetal exposure.

7. *Antiviral drugs*:
   (a) Lopinavir-ritonavir—This is the first antiviral combination to be used in the treatment of COVID-19 in the dose of 400/100 mg twice daily for 14 days. But based on further studies, its benefit remains controversial.
   (b) Remdesivir—It is a novel nucleotide analog found to be effective against COVID-19 in vitro. Fetal toxicity has not been reported when it is used in pregnant women with Ebola and Marburg virus disease, hence its use has been currently extended to treat only severe cases of pregnancy with COVID-19. However, no randomized trials are currently available for its use during pregnancy and breastfeeding.
   (c) Ribavirin—Its use is still experimental for COVID-19. Moreover, it is a teratogenic drug and should be avoided during pregnancy.
   (d) Baricitinib—It is a JAK (Janus Kinases, non-receptor tyrosine kinase) inhibitor that can be used for emergency use in combination with remdesivir for treatment of severely ill patients. It should only be used if benefits of its use are more than the associated fetal risks after assessing the severity of maternal status, underlying risk factors, and gestational age, as it can cross the placental barrier and safety data report is limited. Embryo-fetal toxicity, such as skeletal anomalies and reduced fertility, have been observed in animals when doses in excess of the maximum human exposure are used.
8. *Hydroxychloroquine or chloroquine*—Recent randomized controlled trials have reported no benefit of hydroxychloroquine or chloroquine with or without azithromycin for prophylaxis or in confirmed COVID-19 cases. Moreover, adverse effects like abnormal heart rhythms (QT interval prolongation and ventricular tachycardia), especially in patients taking other drugs associated with QTc prolongation have been reported. It also crosses the placenta and can get accumulated in fetal ocular tissue thus increasing the risk of fetal ocular abnormalities, but this effect has not been observed in humans when used in pregnancy with systemic lupus erythematosus or for prevention of malaria.
9. *Convalescent plasma therapy*—It can be used in severe or critical cases in combination with supportive care and medical management. However, its use is still limited under clinical trial settings.
10. *Antibiotics*—The use is ideally recommended if there is suspicion of secondary bacterial infection. However, antibiotics that are considered safe during pregnancy can be used for prophylaxis in critically ill patients.

7.3.2 Fetal Monitoring

Non-reassuring fetal status has been reported to be associated with COVID-19 infection, especially in cases with respiratory compromise. Monitoring is done at home by daily fetal movement count and home fetal monitoring devices (recently approved by FDA). For hospitalized patients, continuous fetal heart monitoring is recommended, if available, otherwise a nonstress test should be done once or twice daily.

7.3.3 Monitoring for Preterm Labor

COVID-19 infection is found to be associated with spontaneous as well as iatrogenic preterm birth. Therefore monitoring for signs and symptoms of preterm labor is essential and patients should be counseled regarding the neonatal risks involved. Steroid cover with dexamethasone for fetal lung maturity should be given when preterm delivery (<34 weeks) is anticipated.

7.3.4 Discharge and Follow-Up

Patient can be discharged if she remains asymptomatic and vitals remain stable for 24 h and sat-

uration is more than 94%. Home isolation can be discontinued if she remains afebrile for 72 h without antipyretics, at least 7 days after the onset of symptoms and no other symptoms are present.

Maternal follow-up should be done preferably within 1 week of recovery at the same hospital where she underwent treatment to look for any medical/obstetric symptoms either by in-person visit or by tele/video consultation. If patients in home isolation develop any new symptom, they should visit the nearest health facility. Since COVID-19 infection is found to be associated with uteroplacental insufficiency thereby leading to fetal growth restriction, fetal monitoring is recommended by at least one ultrasound assessment of AFI, beginning in the third trimester and at least 14 days after symptom resolution. For those with first or early second-trimester infection, a detailed fetal morphology scan at 18–20 weeks of gestation is indicated. Antepartum fetal monitoring with nonstress test and biophysical profile is reserved only for obstetric indications after recovery.

7.4 Labor and Delivery

Termination of pregnancy by is not recommended in confirmed COVID-19 cases other than for obstetric indication. However, this decision can be individualized in critically ill patients between 32 and 34 weeks (under steroid cover for fetal lung maturity) to aid maternal resuscitation or to prevent worsening of the clinical status of mother. This is because, after 32 weeks, the risk of decompensation increases due to decreased functional residual capacity of lungs caused by distended uterus. It is further exacerbated in patients with multiple gestations and polyhydramnios (causing over-distension of the uterus). On the other hand, before 32 weeks, maternal-fetal monitoring is preferred over the termination of pregnancy (as long as maternal condition is stable) due to increased risk of perinatal morbidity and mortality.

Induction of labor can be done on an outpatient basis, wherever feasible, after appropriate counseling of patients to return to the facility in case of any medical/obstetric symptoms. Moreover, for inpatient induction, a combination of two methods like mechanical and misoprostol or mechanical and oxytocin can be used to decrease the induction to delivery time. Care should be taken while using oxytocin in such patients to minimize the risk of fluid overload and cardiovascular decompensation, especially in critically ill patients. Induction can be performed safely even in intubated patients. Care of severe or critically ill cases should be done under the guidance of a multidisciplinary team which includes consultant critical care, consultant obstetrics or maternal-fetal medicine, consultant neonatology, and nursing support from obstetrics.

Respectful maternity care should be offered to all suspected/confirmed COVID-19 patients and informed consent should be taken before performing any procedure. One birth attendant can be allowed in the labor and delivery room with the patient only if no symptoms suggestive of COVID-19 are present within the last 14 days like. Birth attendants must wear face masks throughout labor and delivery.

Tocolysis is contraindicated in cases of preterm labor in such patients in accordance with the general principles of avoiding any such intervention in patients with systemic disease. The decision should however be individualized depending on the severity of the disease. The use of betamimetic agents should be avoided in cases with respiratory symptoms. *Dexamethasone* should be administered for fetal lung maturity before 34 weeks gestation if preterm birth is anticipated.

Intrapartum fever (especially when associated with respiratory symptoms and reduced oxygenation) should be evaluated with testing for COVID-19 along with other fever-related investigations.

Separate delivery room and operation theatres should be arranged for suspected/ confirmed COVID-19 cases equipped with a neonatal resuscitation corner located at least 2 m away from the delivery table.

Second stage of labor should be managed taking all appropriate infection control precautions as COVID-19 virus can be present in feces

and hence using birthing pools is currently not recommended. Evidence also suggests that active pushing can cause deep breathing and hence increased risk of exposure to patient's respiratory secretions, but delay in active pushing is not recommended. Decision to cut short the second stage of labor has to be individualized and instrumental delivery is performed after informed consent from the patient or relatives in a symptomatic woman who is becoming exhausted or hypoxic.

Active management of third stage of labor and management of PPH is done similar to that of uninfected patients. However, tranexamic acid (increased risk of thrombosis) and methylergometrine(increased risk of respiratory failure and severe vasoconstriction) should be used with caution especially in severe/critically ill patients.

Delayed cord clamping is currently recommended by the American Academy of Paediatrics (AAP) and *umbilical cord blood banking* can be performed in cases of suspected/confirmed COVID-19 cases as it is unlikely to increase the risk of vertical transmission. Skin to skin care is permitted but the use of masks and hand hygiene has to be stressed upon.

PPE should be worn at all times during the management of COVID-19 cases by all the health care workers. If any such patient requires cesarean section, the operating team, anesthesiologist, and neonatologist should be informed in advance to allow the time of donning of PPE. There remains a challenge in communication (hearing is reduced) along with PPE and tactile sensation is reduced (increased operating time). Therefore, the operating team should be proficient with the standard operative steps of a particular procedure. Air-conditioning has to be switched off to prevent the spread of the virus into the atmosphere and the heat, perspiration, and humidity especially with PPE can be particularly tricky.

Low threshold should be kept for starting antibiotics keeping a possibility of another coexisting infection even in confirmed cases of COVID-19.

7.4.1 Maternal and Fetal Monitoring During Labor

Hourly vital and saturation monitoring must be done along with strict input-output charting to maintain a neutral fluid balance (decrease the risk of sudden cardiopulmonary compromise).

Supplemental oxygen is started if saturation falls below 94% and arterial blood gas analysis should be done in such a scenario. Signs of decompensation includes:

- Increase in O_2 requirement
- FiO_2 >40%
- RR >30/min
- Reduction in urine output
- Drowsiness (even if saturation normal)

Continuous electronic fetal monitoring is recommended in labor monitoring. This virus has not been reported in vaginal secretions or amniotic fluid, so rupture of fetal membranes and internal fetal heart rate monitoring may be performed if indicated.

7.4.2 Labor Analgesia and Anaesthesia in Patients with Known or Suspected COVID-19

Neuraxial anesthesia is not contraindicated in patients with known or suspected COVID-19 as it reduces cardiopulmonary stress from pain and anxiety and it is available in case an emergency cesarean is required, thus obviating the need for general anesthesia.

However, in case of respiratory compromise, general anesthesia is preferred. The patient is first preoxygenated for 5 min followed by rapid sequence induction (RSI) and intubation. Video laryngoscopy is preferred wherever facilities are available to improve the chances of success and reduce the risk of aerosolization. A high-efficiency hydrophobic filter is placed between the facemask and breathing circuit or between the facemask and reservoir bag to avoid contamina-

tion of the surrounding atmosphere. The use of Entonox is not considered to be an aerosol-generating procedure.

7.4.3 Use of Magnesium Sulfate in Patients with Respiratory Compromise

In COVID-19 confirmed cases with features of respiratory compromise, magnesium sulfate for seizures prophylaxis and/or neonatal neuroprotection is started with caution and under strict monitoring for signs and symptoms of magnesium toxicity (deep tendon reflexes, respiratory rate, urine output, and magnesium levels)since it can cause respiratory paralysis. Senior obstetricians and critical care specialists should always be involved in the decision-making.

7.5 Postpartum Management

The following principles are followed in postpartum management of confirmed COVID-19 cases:

1. *Maternal monitoring*:
   (a) *Asymptomatic suspected/confirmed cases*: routine maternal monitoring is performed
   (b) *In case of mild symptoms*—vitals and input-output monitoring is done every 4 h for 24 h after vaginal delivery and 48 h after cesarean delivery.
   (c) *In case with moderate illness*—continuous oxygen saturation monitoring is advised for the first 24 h or until improvement in signs and symptoms. Frequency of laboratory investigations and chest imaging should be guided by the clinical status of the patient
   (d) *In cases with severe or critical illness*—intensive monitoring in ICU is required
   (e) If there is any deterioration of clinical condition of the patient that is the development of breathing difficulty or reduced saturation, the differential diagnosis includes severe COVID-19, sepsis, influenza, cardiomyopathy, and pulmonary embolism.
2. *VTE prophylaxis*:
   (a) VTE prophylaxis that is started in severe/critical hospitalized cases of COVID-19 is stopped on discharge.
   (b) If previously on anticoagulants, thromboprophylaxis should be continued for 10 days post discharge which can be extended to 6 weeks in case of ongoing morbidity.
3. *Infection control precautions*—decision regarding temporary separation or rooming-in should be taken after counseling of the mother and family. Current guidelines allow rooming in with the infant with appropriate hand hygiene, frequent sanitization of the fomites, use of mask by the mother and a distance of 1 m to be maintained between the mother and the baby except while breastfeeding.
4. *Postpartum analgesia*—Acetaminophen is the preferred analgesic in postpartum period.
5. *Postpartum fever*—COVID-19 should be kept as a differential diagnosis along with other causes of postpartum sepsis and testing for COVID-19 should be done. Testing should be repeated in case of new-onset symptoms, even in case of a previously negative report. Acetaminophen is the preferred antipyretic agent.
6. *Permanent and reversible contraception*—Permanent contraception (tubal sterilization) can be done along with an uncomplicated cesarean of confirmed COVID-19 cases as it doesn't increase any associated risk. However, the decision of sterilization after vaginal delivery should be made depending on the availability of resources as it is considered to be an elective procedure. Alternatively, a reversible contraceptive method like immediate postpartum long-acting reversible contraception or depot medroxyprogesterone acetate is preferred after vaginal delivery of confirmed COVID-19 patients.

7. *Discharge from hospital*
   (a) Uninfected patients—Early discharge postpartum is recommended in such patients (1 day after vaginal delivery and 2 days after cesarean delivery) to limit their personal risk of acquiring infection in the hospital environment
   (b) Suspected/confirmed COVID-19—the decision for discharge depends on the clinical status and the requirement in patient monitoring. Patient is counseled regarding the warning signs and symptoms of deterioration (dyspnea, fever, altered mental status, decreased oxygen saturation) to severe or critical disease at the time of discharge and is asked to return to the hospital immediately in case of any such symptoms.
8. The number of postpartum visits should be reduced to limit the hospital-related exposure and video/teleconsultations are preferred for postpartum assessment. In-person visits should be planned at 12 weeks in patients with comorbidities.
9. *Screening for postpartum depression* should be performed at 4–8 weeks after delivery as COVID-19 is known to have psychological impact on patients which may include moderate to severe anxiety and appropriate support should be offered.
10. Good perineal and hand hygiene techniques should be explained.
11. Counseling should be done regarding breast engorgement and methods of increasing breastfeeding should be advised
12. *Dietary advice*—Although no particular diet has been recommended to cure COVID-19, but, dietary advice is to be given at discharge to help in recovery and build immunity (high protein diet, vitamins, and mineral supplementation). It is particularly useful in cases of associated comorbidities like diabetes mellitus and other metabolic abnormalities.
13. Advice regarding social distancing and warning signs and symptoms to be explained
14. After recovery they may face the stigma of the disease. Awareness regarding the disease and destigmatization should be done

7.6 Management of Newborn

Newborn of confirmed COVID-19 mothers should be treated as suspects and testing and isolation should be performed of all such newborns. However, newborn of suspected COVID-19 cases (either pending results or not tested) are not considered to be suspects (CDC guidelines).

Delayed cord clamping, skin-to-skin care, and rooming-in can be practiced in newborn of suspected/confirmed cases. They should be bathed after birth to remove the virus from the skin surface. Approximately 2–3% of newborn of confirmed COVID-19 mothers near delivery are found to be positive in the first 24–96 h after birth.

7.6.1 Newborn Testing

The American Academy of Paediatrics (AAP) recommendations for newborn testing are as follows:

- Test at approximately 24 h of age and, if negative, again at approximately 48 h of age (some infants have had a negative test at 24 h only to have a positive test at a later time)
- If a healthy, asymptomatic newborn will be discharged prior to 48 h of age, a single test at 24–48 h of age can be performed
- For infants who are positive at the first test, the test should be repeated after 48–72 h till two consecutive negative reports (to ensure clearance of bacteria from mucosa)
- Obtain either a single swab of the nasopharynx, a single swab of the throat followed by the nasopharynx, or two separate swabs from each of these sites, and submit for a single test. Some centers also take swabs of the anterior nares. Testing to be done according to the requirements of local testing platforms.

7.7 Breastfeeding and COVID-19 Infected Mother

Presently, there is no evidence that COVID-19 is secreted in breast milk. As breast milk is known to be the best source of nutrition and general immunity for the infant, WHO recommends that the benefits of breastfeeding are more than the risks of transmission and hence, early and exclusive breastfeeding is currently suggested in confirmed/suspected COVID-19. It not only also enhances mother-infant bonding but there exists a possibility of passive transfer of COVID-19 antibody via breast milk.

Nevertheless, the risk of transmission to the baby still remains due to infected fomites and airborne droplets if the baby is in close contact with the mother. Thereby, the following precautions are recommended by AAP to prevent the spread of infection to the baby:

- The baby should be kept at a distance of at least 1 m from the mother if roomed in with the infected mother, except at the time of breastfeeding.
- The mother should wash her hands before and after touching her baby.
- She should wear a mask (preferably an FFP3 or FFP2/N95).
- Masks or cloth face coverings should not be placed on neonates or children younger than 2 years of age.
- She should avoid coughing or sneezing while breastfeeding.
- Proper cleaning and disinfection of all surfaces should be done.
- Expressed breast milk can be given if the mother does not wish to feed the child directly. Expressing breast milk is also necessary to maintain the milk supply of the mother.
- Hand hygiene should be practiced before pumping the milk and cleaning and hygiene instructions of the pump should be followed. Ideally, a dedicated breast pump for each mother should be used.
- The expressed milk should be fed to the baby by another individual who is not infected and the need of infection control measures (e.g., wearing a mask, practicing hand hygiene) by the caregiver should be reinstated.
- In case of neonates at high risk of infection (e.g., preterm infants, infants with underlying medical conditions, infants needing higher levels of care), temporary separation from the mother and either expressed breast milk or formula feeding is advised.
- If mother is too unwell to feed the baby or express milk, formula feeding is needed and this should be provided with strict adherence to sterilization guidelines
- In case of separation of the baby from the mother, neonates of suspected/confirmed cases of COVID-19 should be kept isolated from other healthy neonates
- Pasteurized donor human milk—Holder pasteurization done in human milk banks appears to eliminate replication-competent COVID-19 virus.

The risk of transmission of infection from the mother to the child decreases and separation can be stopped based on the following strategies:

- *Symptom- and time-based strategies for discontinuing transmission precautions*
  - 10 days after the first appearance of symptoms or 20 days in case of severe or critical illness or immunocompromised status of mother.
  - At least 24 h have passed since the last fever without the use of antipyretics, and other symptomatic improvements.
  - For asymptomatic mothers identified because of routine COVID-19 screening upon hospital admission, at least 10 days should have passed since the positive test before discontinuing mother-newborn infection precautions.
- *Test-based strategies*
  - Not recommended as positive result of RT-PCR can persist for weeks although it doesn't indicate the presence of viable virus and risk of transmission is low in such cases.

7.8 Conclusion

Management of COVID-19 in pregnancy is complex owing to the severe course of illness and dubious effects on the mother and baby. Although management protocols are rapidly evolving with newer researches, meticulous implementation of infection control measures are pivotal till a definitive cure or vaccination is available. Finally, it is our responsibility that maternity care services are accessible to all pregnant females even during social restrictions to prevent any further morbidity or mortality.

Key Points

- Pregnant women with Covid-19 infection are categorised by CDC and ICMR as "Increased Risk".
- Various guidelines have recommended reducing number of antenatal visits during the pandemic to reduce hospital visits and exposure.
- US FDA has approved use of non-invasive fetal and maternal monitering devices at home to reduce hospital visists.
- Pregnant women with confirmed Covid-19 infection need hospitalization in mild cases with unresponsive fever or associated co-morbidities, moderate and severe cases.
- All infection control practices are to be followed as in other patients.
- During infection acetoaminophen is a preferred anti-pyretic over NSAIDS.
- Anticoagulant therapy and Steroid therapy is recommended only in critically ill patients.
- Limited data is available regarding benefit / risk of Monoclonal antibody use in pregnant patients.
- Anti-viral drugs though not recommended in pregnancy due to their possible teratogenic profile, may be used as a life saving measure.
- Termination of pregnancy is not recommended in confirmed cases of Covid-19 infection other than due to obstetric indication. In certain cases of severe disease at 32–34 weeks, termination of pregnancy may be done to improve the functional capacity of the lungs compromised by the distended uterus.
- Labor induction is not recommended during active infection.
- WHO recommends breast feeding with appropriate infection control practices in confirmed Covid-19 patients.
- Newborns born to Covid-19 positive mothers are tested with nasopharyngeal swab once at 24 hours and if negative at 48 hours again.

Suggested Reading

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Part III

Viral Infections

CMV Infection in Pregnancy: An Updated Overview

8

Juhi Bharti and Seema Singhal

8.1 Introduction

Cytomegalovirus (CMV) is a DNA virus and belongs to Human Herpesvirus family. It has similar biological properties of latency and reactivation as of other members of herpes family. It affects 0.2–2% of all live births and is the most common cause of intrauterine infection. It is the major non-genetic cause of sensorineural hearing loss (SNHL) and neurological disability in infants [1].

8.2 Epidemiology

The prevalence of CMV varies by population and various other demographic factors, ranging from 40 to 100%. A systematic review has estimated CMV seroprevalence in women of childbearing age to be as high as 86%, with the highest rates in the region of Eastern Mediterranean, Western Pacific, African, and Southeast Asian regions (approx. 90%) and the lowest rates in Europe (70%) and America (79%) [2].

The seroprevalence of CMV is higher in residents of developing nations and those with increased parity, lower socioeconomic strata, age more than 30 years, those working in day-care settings or parents of children less than 3 years [3, 4]. The rate of seroconversion in seronegative women during pregnancy ranges from 1 to 7% [5].

8.3 Classification of Maternal Infection

Cytomegalovirus infection in pregnancy can be classified as either primary or non-primary.

Primary Infection Primary maternal CMV infection occurs when the virus is first acquired in pregnancy. The incidence of primary CMV infection is 0.7–4.1% of all pregnancies [6]. The disease severity of primary infection is more than non-primary disease. Almost one-fourth of congenital CMV infections are due to primary maternal infection. The main causes of primary infection acquired in pregnancy are sexual transmission and contact with young children [7]. Horizontal transmission among children or from children to adults is highly prevalent in day-care settings where it spreads through saliva on hands or toys. Other routes of transmission are contact with secretions like vaginal, cervical, seminal, saliva, or fluids like blood or urine**.** It has not been shown to be transmitted via respiratory aerosols.

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Non-primary or Secondary Infection Secondary maternal CMV infection is defined as when the virus is first acquired before pregnancy and mother develops antibodies against CMV before pregnancy. After the infection has subsided, the virus becomes latent and resides in the host. In such cases, infection during pregnancy may be due to reactivation of the latent endogenous virus or reinfection with a new virus strain. There are reports of variable rates of viral shedding from multiple sites after primary or non-primary CMV infection. There is frequent reactivation of the latent virus in immunocompromised individuals.

8.4 Transmission to Fetus

The rates of congenital CMV infection is much higher in women with primary infection (up to 50%) than in women with non-primary infection (<2%) [1]. Vertical transmission of CMV infection can occur in-utero, intrapartum, or during postpartum period. The virus can cross placenta and is able to replicate in placental cytotrophoblasts and multiple embryonic or fetal tissues, including renal tubules. Transmission during delivery can occur through ingestion of secretions from cervix or vagina. Postnatal transmission can be because of breastfeeding or horizontal transmission. Rarely, ascending infection from genital tract can occur in antenatal period.

Intrauterine transmission carries risk of greatest sequelae as compared to intrapartum or postpartum transmission. The risk of in-utero transmission increases with advancing gestation from around 40% in the first and second trimesters to more than 60% in the third trimester of pregnancy [8]. However, the severity of sequelae decreases with advancing gestation with favorable outcomes for those infected in the third trimester. Also, non-primary maternal infection is associated with less severe fetal disease, suggesting partial protection from maternal antibodies.

8.5 Clinical Features

Primary cytomegalovirus infections in pregnant women are often asymptomatic in up to 75–95% of individuals. Others may show symptoms of mild mononucleosis or flu-like syndrome with non-specific symptoms like fever, malaise, fatigue, upper respiratory tract infections, headache, and enlargement of cervical lymph nodes. One-third of such patients may present with skin eruptions or rashes. Therefore, any non-specific illness during pregnancy could indicate primary CMV infection. These patients may have lymphocytosis and transaminitis (elevated alanine transaminase and aspartate transaminase) in approximately 40% of cases [9]. With advancing gestation, cervical shedding in pregnancy increases; from <5% in the first trimester to up to 30% in the third trimester [10].

8.6 Diagnosis of Maternal Infection

The gold standard for diagnosis of maternal primary CMV infection is serology. Routine prenatal screening is not recommended. Indications of testing a pregnant woman for CMV infection are as follows:

Symptomatic Cases Testing should be considered in cases with mononucleosis or flu-like syndrome with negative Epstein Barr and influenza virus tests or in cases with features of hepatitis with negative hepatitis A, B and C reports. This will detect only 10% of cases who are symptomatic as a majority of maternal CMV illnesses are asymptomatic.

Suspected Intrauterine Infection Testing is indicated in cases of fetal anomalies suggestive of CMV infection are detected on routine antenatal ultrasound. The features are listed below in the section "role of ultrasound".

Seroconversion of CMV IgG in paired acute and convalescent sera at an interval of 3–4 weeks

Box 8.1. Diagnosis of CMV Infection in Mother

1. Documented recent seroconversion of CMV-specific IgG
2. CMV IgM antibody with low IgG avidity

is diagnostic of new-onset acute infection (Box 8.1).

Unlike other viral infections, detection of IgM antibody is not diagnostic in CMV. This is so because IgM can remain positive for almost an year after an acute infection, is present in only 75–90% of acute infection, can become positive in cases of reactivation or reinfection with a new strain and can be false-positive in cases of other viral infections like EBV or parvovirus B [10]. Therefore, it is difficult to distinguish between cases of primary and non-primary maternal infections in the absence of documented recent seroconversion since IgM and IgG can be elevated in both.

Role of IgG Avidity IgG avidity can detect acute infections with high sensitivity (92–100%) and specificity (82–100%). Antibody avidity is a measure of the strength by which a multivalent antibody binds with an antigen. It can be helpful in having an idea about the timing of CMV infection. After recent primary infection, IgG antibody shows low affinity for antigen. Afterward, the antibody slowly matures and shows high avidity 3–4 months later and these high avidity antibodies can persist for many years. Avidity index is the percentage of IgG bound to the antigen following treatment with denaturing agents. An avidity index of more than 60% suggests past (>3 months) or secondary infection but an index of <30% is highly suggestive of recent infection (<3 months) [11]. The interpretation of serological testing in CMV is summarised in Table 8.1.

Table 8.1 Interpretation of CMV serological testing

Antibody status	IgG avidity testing	Result
Both IgM and IgG negative	Not required	Uninfected
IgM positive IgG negative	Not required	False-positive Repeat IgG in 2 weeks
Both IgM and IgG positive	Low (<30%)	Recent infection
Both IgM and IgG positive	High (>30%)	Past infection
IgM negative IgG positive	Low	Recent infection
IgM negative IgG positive	High	Past infection

8.7 Diagnosis of Fetal Infection

Amniocentesis Amniocentesis is offered in cases of confirmed primary maternal infection or suspected fetal infection based on ultrasound findings. The demonstration of cytomegalovirus or viral genome in the amniotic fluid is diagnostic of fetal infection [5]. The timing of amniocentesis is very crucial to avoid false-negative tests. It should be done at least 7 weeks after the onset of maternal infection and after 21 weeks of pregnancy. The fetal urinary system matures after 20 weeks and is able to excrete virus through the urine into amniotic fluid [12]. Moreover, it takes around 6–8 weeks for virus to infect placenta, replicate, transmit to fetus, viral replication in fetal kidneys and excretion into urine. Diagnosis of fetal CMV infection is made by culture and polymerase chain reaction (PCR) testing of amniotic fluid. Sensitivity of PCR is as high as 70–100%. In case of positive results, DNA viral load can be quantified which may have some role in predicting symptoms in the neonate. Some studies have found an association of high CMV viral loads (>10^5 genome equivalents) with a greater risk of sequelae [13, 14], whereas others have refuted this association [15, 16].

Rarely, there can be false-positive results in cases of maternal contamination of the amniotic fluid sample which can be reduced by discarding initial 1–2 ml of amniotic fluid. The risk of iatrogenic CMV transmission to the fetus during amniocentesis is insignificant.

Cordocentesis Cordocentesis for detection of CMV-specific fetal IgM is not recommended due to higher associated risks of fetal loss and because fetal IgM is not developed until late pregnancy leading to poor sensitivity of this test. There have been reports of anemia, thrombocytopenia, and elevated liver enzymes in fetal blood suggestive of disseminated CMV infection.

Ultrasound 2–4 weekly serial ultrasound examinations have to be done in a case of infected fetus. There can be a lag of 3 or more months for the development of ultrasound abnormalities after maternal infection. The ultrasound abnormalities suggestive of CMV infection have been summarized in Box 8.2. Echogenic bowel may be the first indicator of CMV infection on ultrasound, and it can be seen as early as 20 weeks (Fig. 8.1). The most characteristic finding of fetal CMV infection on ultrasound is bilateral periventricular calcifications. There are overlapping findings in cases of congenital CMV infection and congenital Zika syndrome. The features like microcephaly, fetal brain collapse, and evidence of contractures are the most characteristic of congenital Zika syndrome. The intracerebral calcifications are periventricular in congenital CMV infection whereas subcortical in congenital Zika syndrome. Ultrasound is a non-invasive method that helps to identify cases of suspected fetal CMV infection on the basis of structural or growth abnormalities. However, it has poor sensitivity that helps to identify only 20% of infected infants [17]. There are other features of congenital CMV infection like sensorineural hearing loss, chorioretinitis, petechiae, and neurodevelopmental defects which cannot be detected on antenatal ultrasound and so normal ultrasound findings do not exclude CMV infection. There are other features of congenital CMV infection like sensorineural hearing loss, chorioretinitis, petechiae, and neurodevelopmental defects which cannot be detected on antenatal ultrasound. Therefore, normal ultrasound findings do not exclude CMV infection.

Box 8.2. Ultrasound Abnormalities Suggestive of Fetal CMV Infection [18]

- Periventricular calcifications
- Microcephaly
- Ventriculomegaly
- Pseudocysts, periventricular or adjacent to occipital or temporal horn
- Large cisterna magna
- Polymicrogyria
- Cerebellar hypoplasia
- Fetal growth restriction
- Hyperechogenic bowel
- Hydrops
- Amniotic fluid abnormalities
- Hepatosplenomegaly
- Hepatic calcifications
- Placentomegaly >4 cm

MRI Fetal MRI can be added to ultrasound for better detection of neurological abnormalities in cases with normal ultrasound report. This may help in counseling parents regarding the prognosis, though complete role is yet to be established. A normal MRI report does not exclude the possibility of symptoms in neonates.

Placental Infection CMV infection in pregnancy interferes with normal placental development. The virus replicates in cytotrophoblast which then spreads to villous stroma and fetal capillaries. There could be fibrosis and other vascular changes at the uterine and placental interface leading to impaired placental function. This may cause fetal growth restriction [19]. Grossly the placenta may appear large and pale or small and fibrotic. The classic histopathological findings can be lymphoplasmacytic villitis, villous fibrosis and mineralization, chorionic vessel thromboses, and large intranuclear inclusions [20].

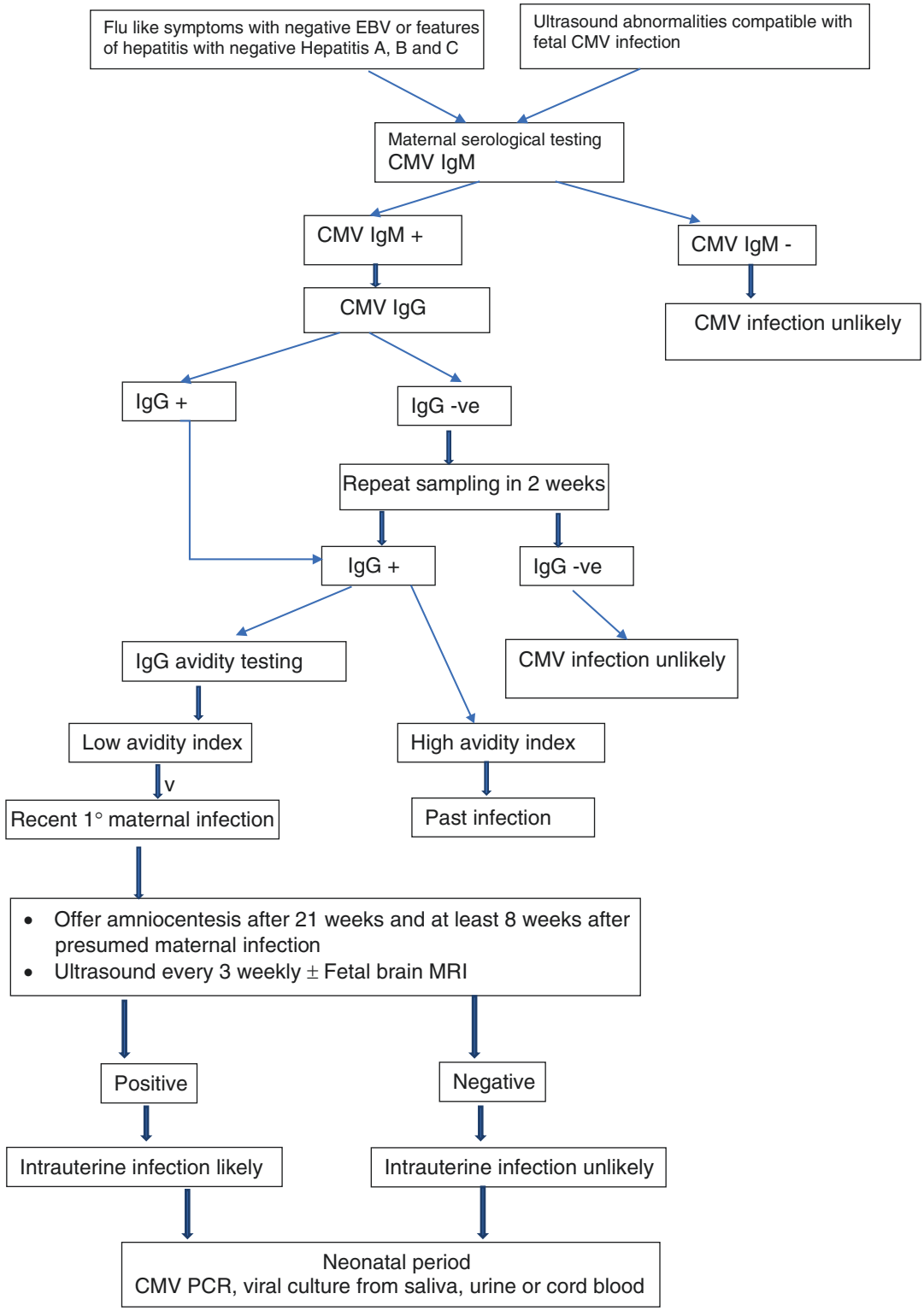

Fig. 8.1 Flowchart depicting diagnostic algorithm for maternal, fetal, and congenital CMV infection

8.8 Congenital CMV Infection

Cytomegalovirus is the most common nonhereditary cause of sensorineural hearing loss and causes significant morbidity, especially in symptomatic infants. Approximately 0.5% of congenital CMV infections may result in fetal/neonatal death [21]. Congenital CMV infections are frequently diagnosed after delivery in cases of SNHL detected on routine hearing assessment of newborns or in presence of other signs of congenital infections. Congenital CMV infection is the one with active infection detected within the first 3 weeks of life.

Symptomatic Newborns Of all the infected neonates, 10–15% will be symptomatic at birth and another 10–15% will develop symptoms later in childhood, predominantly hearing loss [22]. The most common manifestations in up to 75% of symptomatic neonates are jaundice, petechiae, hepatosplenomegaly, and neurological abnormalities like microcephaly and intracranial calcifications. Other less frequent signs are cataracts, microphthalmia, myocarditis, and cardiac abnormalities. They can also present with prematurity, fetal growth restriction, poor tone, lethargy, and feeding problems. On laboratory testing, there may be elevated liver enzymes, decreased platelet counts, or hyperbilirubinemia suggesting hepatobiliary involvement in up to 25–80% of symptomatic newborns which usually reverts to normal in a few weeks [23]. All these findings can be attributed to the cytopathic effects of virus and immune responses to the virus in various organs like salivary gland, lung, liver, kidney, adrenal gland, placenta, and central nervous system. Severe sequelae are more likely to occur in neonates born to mothers with primary infection in first trimester.

Approximately 5% of symptomatic newborns die and around 50–60% of those who survive to develop serious long-term sequelae. Symptomatic neonates with CNS involvement are most likely to have permanent sequelae like SNHL, mental retardation, motor deficits, seizures, and chorioretinitis.

Asymptomatic Newborns Around 85% of congenital CMV infections are asymptomatic at birth. However, 15% of these newborns develop neurodevelopmental problems later in life, within the first 3 years of life. A prospective study showed 50% of those who developed hearing loss later had bilateral deficit ranging from mild to severe impairment [24]. Out of these, around 50% had further worsening of hearing loss at around 18 months. Some of the asymptomatic ones (18%) showed delayed onset of symptoms at around 27 months.

8.8.1 Differential Diagnosis of Congenital CMV

- Rubella
- Toxoplasmosis
- Herpes simplex virus infection
- Syphilis
- Enterovirus infection.

8.9 Prenatal Treatment

Routine antenatal care has to be provided. Supportive therapy is offered for symptomatic relief. Antiviral therapy in immunocompetent pregnant women is not recommended as antiviral drugs have not been shown to reduce fetal transmission [25]. Sometimes, fetal interventions like paracentesis or intrauterine transfusions may be needed as a lifesaving procedure for the fetus. Timing and mode of delivery will depend on standard maternal and fetal indications.

Drugs Antiviral drugs are used in the prevention of CMV disease in immunocompromised patients like HIV, transplant recipients, or severe congenital CMV infection in neonates. Antiviral therapy is not proven to be effective and is currently not recommended in pregnancy for prevention of fetal transmission [26].

Antiviral drugs licensed for use in CMV infection in nonpregnant state are Valaciclovir,

Ganciclovir. Valganciclovir, cidofovir and foscarnet. Except valaciclovir, other drugs cannot be used in pregnancy because of teratogenic effects. Valaciclovir is a prodrug, its active drug is acyclovir which is formed in liver during first pass metabolism. As compared to acyclovir, Valaciclovir has higher oral bioavailability (55% vs. 10–20) [27]. A multicentric open-label phase II study was done to assess the efficacy of oral Valaciclovir in pregnancy associated with moderately infected CMV fetuses. Only the fetuses with extracerebral or mild cerebral symptoms on ultrasound were included. They excluded the fetuses with severe ultrasonographic abnormalities of brain and asymptomatic ones as drug therapy is not expected to have much role in these groups. The dose used was 8 g/day from the median gestational age of 26 weeks to either delivery or termination of pregnancy. They found that high dose valaciclovir in pregnancy resulted in significant increase in numbers of asymptomatic neonates from 43% without treatment to 82% with treatment**.** The drug was well tolerated, compliance was high (>90%) and no adverse effects on maternal and fetal parameters were noted [18]. A randomized controlled trial is required to further elucidate regarding its routine use in mild congenital CMV infection.

Hyperimmune globulin (HIG) is not routinely recommended for CMV infection in pregnancy. Its role in pregnancy is still unclear and can be used only for the purpose of research. There are some studies that have found beneficial role of CMV-specific HIG in pregnancy resulting in reduced mother-to-fetus transmission and severity of congenital infection [28, 29].

Subsequently, in a randomized controlled trial in 124 women, there was no significant difference in the rate of congenital infection in HIG versus placebo group (30% vs. 44%). Additionally, adverse obstetric events (preterm delivery, preeclampsia, and fetal growth restriction) were higher in the HIG group versus placebo (13% vs. 2%) [30].

8.10 Vaccine

Developing a vaccine for CMV infection is a priority due to the huge economical burden associated with prolonged treatment and care of the disabilities associated with CMV. At present, there is no suitable CMV vaccine. Development of CMV vaccine is a challenge as there are high rates of reinfection even in women with preconception immunity and it results in fetal transmission and other sequelae. However, vaccine-induced preconception immunity will help in reducing the burden of the disease by reducing the severity of sequelae.

Vaccines using live attenuated viruses have failed to provide wild-type immunity. CMV vaccines focus on surface glycoprotein gB which mediates attachment and entry of CMV into fibroblasts. A randomized controlled trial done in 400 women receiving either gB/MF59 or placebo showed 50% efficacy of vaccine. Among the vaccinated group, there was one case of congenital CMV infection whereas there were three cases of congenital CMV infection in the placebo group. Though the study was underpowered, the results were promising [31]. This subunit vaccine has also been studied in seronegative adolescent girls and solid organ transplant recipients.

Ideally, a CMV vaccine needs to be developed that induces high titers of cross-neutralizing antibodies and provides protection against various CMV strains.

8.11 Prevention

In the setting of non-feasibility of routine screening for CMV and unavailability of vaccine, it becomes highly important to develop strategies for CMV prevention. All pregnant women should be aware of good hygiene practices to reduce the risk of CMV infection. Educating them about CMV, virus transmission, the risks in pregnancy and sensitization regarding preventive measures remains the most important strategy to reduce the

risk of congenital CMV infections. This is especially important for those involved in care of young children in family, school, hospitals, or day-care settings. Good hygiene measures are as follows:

1. Frequent handwashing with soap and water after coming in contact with young children (diaper changes, bathing, feeding, or handling toys)
2. Avoiding intimate contact with young children (e.g., kissing on the mouth)
3. Avoid sharing food/drinks/utensils/toothbrush
4. Regular cleaning of toys/surfaces that may have come in contact with saliva/urine.

8.12 Conclusion

Congenital CMV infection is a predominant non-genetic cause of hearing loss and other mental disorders. IgG avidity test helps in facilitating the diagnosis of primary maternal infection. Counseling of parents is a challenging task as there are no reliable prognostic indicators or established therapies. However, routine CMV screening for pregnant women is not recommended.

Key Points

- Cytomegalovirus in pregnancy affects 0.2–2% of all live births and is the most common cause of intrauterine infection.
- It is the major non-genetic cause of sensorineural hearing loss (SNHL) in infants.
- Cytomegalovirus infection in pregnancy can be classified as either primary or non-primary.
- Primary maternal CMV infection occurs when the virus is first acquired in pregnancy. The disease severity of primary infection is more than non-primary disease.
- The rates of congenital CMV infection is much higher in women with primary infection (up to 50%) than in women with non-primary infection (<2%).
- The risk of in-utero transmission increases with advancing gestation from around 40% in first and second trimesters to more than 60% in the third trimester of pregnancy. However, the severity of sequelae decreases with advancing gestation with favorable outcomes for those infected in the third trimester.
- Primary cytomegalovirus infections in pregnant women are often asymptomatic in up to 75–95% of individuals. Others may show symptoms of mild mononucleosis or flu-like syndrome with non-specific symptoms.
- The demonstration of cytomegalovirus or viral genome in the amniotic fluid is diagnostic of fetal infection. The timing of amniocentesis is very crucial to avoid false-negative tests and it should be done at least 7 weeks after the onset of maternal infection and after 21 weeks of pregnancy.
- The most characteristic finding of fetal CMV infection on ultrasound is bilateral periventricular calcifications.

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Varicella, Rubella and Rubeola

9

Shikha Sharma

9.1 Varicella Zoster Virus Infection

Varicella Zoster virus (VZV) is one of the eight herpesviruses, that are DNA viruses, notorious for causing a highly contagious infection amongst humans worldwide. More than 90% of individuals over 15 years of age are seropositive for VZV immunoglobulin G (IgG) antibody indicating that it's a common childhood illness. Also, more than 95% of pregnant women are immune to varicella [1].VZV infection exhibits two clinically distinct forms of disease: Varicella (chickenpox) and Herpes zoster (shingles).

Varicella Primary VZV infection causes a diffuse vesicular rash. Adults older than 20 years of age, although exhibiting less than 2% prevalence for varicella infection, constitute almost 25% VZV-related mortality. Primary infection with VZV up to 20 weeks of gestation increases the risk of congenital varicella syndrome, characterized by limb hypoplasia, skin lesions, neurologic abnormalities, and structural eye damage. Maternal varicella during pregnancy can, subsequently, lead to infant herpes zoster. And, if occurs immediately before or after delivery, can also cause neonatal varicella, which can range from a mild rash to disseminated infection.

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Herpes Zoster The virus has the potentiality to stay dormant in the sensory nerve ganglia for years following a primary infection and can subsequently, get reactivated to cause a dermatomal vesicular erythematous skin rash known as herpes zoster or zoster or shingles. Maternal herpes zoster infection is not associated with a significant risk of congenital varicella syndrome [2].

9.1.1 Epidemiology

The introduction of varicella vaccine in 1995 caused a conspicuous fluctuation in the VZV infection rates, with the overall epidemiological trends being in a flux ever since then. The seropositivity rate amongst adults in temperate areas is over 95% as compared to around 50% in tropical areas [3, 4]. The fact that it is not a notifiable disease, makes it difficult to know the exact prevalence. As per United States data, the varicella incidence during pregnancy is estimated to be 1–5 cases/10,000 pregnancies [5]. Although the incidence remains unchanged, the severity appears to increase during pregnancy. Varicella pneumonia, in the present era, is estimated to complicate 10–20% of maternal infections as compared to the 20–45% in the pre-vaccine era [6]. The 10-year efficacy of the two-dose schedule is about 98% for prevention of infection and 100% for prevention of severity. Australian data from 2006 to 2009 projected the incidence of

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congenital varicella infection at 0.19 per 100,000 live births/annum and neonatal infections at 2 per 100,000 live births/annum representing an 85% reduction in varicella cases in the post-vaccination era compared to the pre-vaccination era [7].

9.1.2 Pathogenesis and Transmission

Primary varicella infection leads to viremia with spread to regional lymph nodes, tonsils, ductal tissue of salivary glands, and subsequently to other organs. Continued viral replication causes secondary viremia which invades cutaneous tissue resulting in VZV exanthem within 14–21 days. Maternal viremia infects the placenta with a subsequent affliction of multiple fetal organs with the culprit varicella DNA [8]. Infection of the dorsal root ganglia in-utero results in cell destruction in nerve tissue, leading to limb denervation changes as seen in congenital varicella syndrome. Placental histopathology demonstrates granulomas and acute inflammation. Varicella exposure has a higher risk of transmission than Zoster.

9.1.2.1 Transmission

Person to person—Patients are infectious from 1 to 2 days prior to the appearance of rash until the lesions have crusted over. Varicella is usually transmitted by droplets from infected nasopharyngeal secretions, by direct contact with infected fomites (e.g., hair, clothing, bedding), and rarely, by airborne route. Although, zoster has low transmission rate but close exposure to open cutaneous lesions can cause varicella infection [9].

Mother to infant—Both perinatal and postnatal routes of vertical transmission have been reported. Intrauterine or perinatal transmission is through transplacental spread while postnatal is through respiratory droplets or direct contact with an infected source. Fetal VZV transmission during herpes zoster infection is a rare entity either due to pre-existing maternal antibodies to VZV or to the generally lower levels of viremia seen with shingles as compared to the primary infection [10].

Incubation Period 10–21 days after exposure in both children and adults.

9.1.3 Clinical Features

Uncomplicated Varicella The prodrome of fever, malaise, and myalgia commences 1–4 days prior to the onset of rash. Lesions typically begin as pruritic macules, rapidly developing into papules followed by vesicles. Since, the lesions crop successively on the face, trunk, and extremities, the patient typically has lesions in different stages of development. Most lesions crust fully by day 6 in normal hosts [11].

Complicated Infection Varicella-related complications are more common in adults and include meningitis, encephalitis, cerebellar ataxia, pneumonia, glomerulonephritis, myocarditis, ocular disease, adrenal insufficiency, and death [12].

Varicella Pneumonia This is the most common complication of varicella infection during pregnancy presenting predominantly with cough, fever, dyspnoea, and tachypnoea seen in 0.7–3/1000 pregnancies [10]. Maternal pneumonia complicates about 10–20% of cases of chickenpox in pregnancy leading to higher mortality/morbidity compared to general population. The risk increases as the gestation advances which may be purely mechanical as the diaphragm is pushed by the gravid uterus. Smoking and presence of more than 100 cutaneous vesicles are risk factors for varicella pneumonia during pregnancy. X-ray picture shows a diffuse or nodular infiltrative pattern in the peri-bronchial region in both lungs.

Congenital Varicella Syndrome This exhibits multi-system involvement and was first described in 1947. Incidence of congenital abnormalities is 0.4% when maternal infection occurs before the

12 weeks of pregnancy rising to approximately 2% when occurring between 13 and 20 weeks [13]. Dermatological lesions occur in approximately 70%, limb hypoplasia in 46–72% and neurological abnormalities such as microcephaly, cortical atrophy, hydrocephaly and mental retardation are seen in 48–62% of cases [14]. Eye disorders such as microphthalmia, chorioretinitis, and cataracts are seen in 44–52% of cases while muscle hypoplasia, developmental delay, abnormalities of the gastrointestinal and genitourinary tracts and the cardiovascular system occur in 7–24% of cases. Long-term learning difficulties and developmental problems may also be seen, although studies do not suggest the same [15].

Congenital varicella syndrome (CVS) demonstrates a 30% mortality risk in the first few months of life and a 15% risk of developing herpes zoster in the first 4 years of life [16]. Primary VZV infection in the first two trimesters results in intrauterine infection in up to 25% of cases of which 12% display typical CVS anomalies. There are no cases reported following maternal chickenpox after 28 weeks of gestation [17].

Neonatal VZV Infection Neonatal chickenpox may be caused by transmission through transplacental route, ascending infection or via the neonatal respiratory tract. The mortality rate has reduced from 31% in the pre-vaccine era to 7% in the modern era. Neonates born within 5 days prior to 2 days after delivery, babies born at <28 weeks of gestation or <1000 g are at the greatest risk for severe disease and poor outcome [18]. All babies born to mothers with chickenpox rash 7 days before delivery will have detectable serum VZV antibodies.

9.1.4 Effect of Varicella on Pregnancy

It is not yet proven to cause abortions, preterm labor, or congenital fetal anomalies. However, it is definitely proven to cause vertical transmission which can lead to miliary calcified necroses in fetal organs [19].

9.1.5 Diagnosis

Maternal Varicella Varicella pneumonia must be considered whenever a pregnant woman presents with contact history, peculiar skin lesions, and respiratory symptoms. Viral DNA detected by PCR testing of scrapings from the base of the vesicle or through the detection of VZV antigen by immunofluorescence is a confirmatory test. Serologic testing is not utilized due to the considerable variation in sensitivity and specificity.

9.1.5.1 Congenital Varicella Syndrome

Prenatal diagnosis—The risk of congenital varicella syndrome can be estimated by polymerase chain reaction (PCR) testing of fetal blood or amniotic fluid for VZV DNA along with ultrasonography for fetal anomalies [6]. A detailed ultrasound evaluation should be done a minimum 5 weeks after maternal infection to assess fetal sequelae of congenital varicella syndrome (e.g., microcephaly, limb hypoplasia, intrauterine growth retardation) and interpreted as:

- Normal ultrasound as well as laboratory results- low risk of CVS
- Normal ultrasound with detectable VZV DNA- potential risk warranting repeat ultrasound at 22–24 weeks
- Repeat ultrasound normal suggests remote risk of CVS
- Repeat USG showing CVS peculiar anomalies suggests high likelihood of fetal effect [16].

Postnatal diagnosis—Diagnosis of Congenital varicella syndrome requires the following criteria [16]:

- Maternal varicella infection during the first or second trimester of pregnancy
- USG features of fetal abnormalities consistent with congenital varicella syndrome
- Intrauterine VZV infection proven by VZV DNA in the neonate, VZV-specific IgM antibodies in cord blood, persistence of VZV IgG beyond 7 months of age or appearance of clinical zoster infection during early infancy.

9.1.6 Management of Maternal VZV Infection

Uncomplicated Varicella Infection Oral acyclovir 800 mg five times per day for 7 days is the treatment of choice for all uncomplicated antenatal women. A randomized placebo-controlled trial has determined better efficacy of acyclovir in healing of skin lesions and a shorter duration of fever, if initiated within 24 h of symptom onset [20]. None of the available data suggests any evidence of teratogenicity.

Varicella Pneumonia Varicella pneumonia during pregnancy is a medical emergency that may require hospitalization for monitoring and initiation of antiviral therapy and up to up to 40% of them may eventually require mechanical ventilation. Observational data suggests that acyclovir therapy reduces maternal mortality [6]. It is recommended to start intravenous acyclovir within 24–72 h of rash in a dose of 10–15 mg/kg of body weight IV every 8 h for 5–10 days. Although, the drug crosses the placenta but neither any congenital malformations nor any fetal benefits with respect to CVS or chickenpox have been reported with its use [21].

Treatment of Herpes Zoster Infection Management of herpes zoster during pregnancy remains the same as that of general population.

9.1.7 Post-exposure Prophylaxis

Significant exposure to varicella infection, is defined as a household contact or face-to-face contact with an index case for at least five minutes, or sharing the same hospital room with a contagious patient. Herpes zoster which is much less contagious, requires close contact or exposure to open cutaneous lesions for significant transmission [3]. Ideally, a VZV serologic test should be done prior to administration of immune-prophylaxis. However, if results are not available within 10 days of exposure, post-exposure prophylaxis should be offered.

Immunoprophylaxis for the Prevention of Maternal Varicella Infection The US Advisory Committee on Immunization Practices recommends post-exposure prophylaxis with varicella-zoster immunoglobulin in all nonimmune pregnant women with history of VZV contact, intramuscularly, within 10 days of exposure.

Post-exposure prophylaxis is not for women who have history of having received the vaccine in the past. Those infected despite the prophylaxis should be treated for varicella infection. Pregnant women who could not receive timely varicella immunoglobulin, may either be administered a single dose of intravenous immunoglobulin (IVIG) at 400 mg/kg or be closely monitored for signs and symptoms of varicella infection and subsequently, started on acyclovir if illness occurs [12]. Immuno-prophylaxis to all VZV-exposed pregnant women primarily reduces the risk of maternal infection and subsequent mortality while there is no evidence to prove its role in the prevention of embryopathy.

Antiviral therapy—There is no post-exposure role of acyclovir.

9.1.8 Pre-exposure Prophylaxis

It requires the use of a live, attenuated vaccine, that stimulates production of endogenously produced antibodies with a seroconversion rate of approximately 82% in adults and 91% in children [8].

9.1.8.1 Dosage

Children 12 months to 12 years—2 doses, 0.5 ml each, subcutaneously, at least 3 months apart.

MMRV vaccine is approved for this age group.

People 13 years or older—2 doses, 0.5 ml each, subcutaneously, 4–8 weeks apart.

MMRV vaccine not approved for this age group.

Non-pregnant Females Varicella immunization prior to conception can considerably reduce the fetal, maternal, and neonatal burden of varicella infection [15]. Therefore, it is recommended that

all women of child-bearing age be assessed prior to conception for varicella immunity which is suggested by either history of previous vaccination or varicella infection or laboratory evidence of immunity [3]. Women who are not immune to VZ infection should be offered the standard two doses of VZV vaccine prior to conception and subsequently, pregnancy be avoided for 1 month thereafter to avoid the theoretical risk to the fetus [22].

Pregnancy Varicella vaccine, being a live vaccine, is contraindicated during pregnancy.

9.2 Rubella

9.2.1 Introduction

Rubella, also known as German measles, has significantly declined in incidence ever since the introduction of routine childhood rubella vaccination. Rubella virus is a member of the family Togavirus, genus Rubivirus, with humans being the only known reservoir. Transmission is facilitated by direct droplet contact from nasopharyngeal secretions followed by replication in the lymphatics of the upper respiratory tract, and hematogenous spread thereafter. It usually causes a self-limiting infection, but in case of transplacental viral spread, can lead to devastating fetal effects including congenital rubella syndrome. The dreaded congenital rubella syndrome (CRS) occurs mainly when the infection occurs in the first 8–16 weeks and is also associated with late-onset sequelae, including diabetes and possibly autism.

9.2.2 Epidemiology

The incidence of rubella declined from 0.45 per 100,000 in 1990 to 0.1 per 100,000 in 1999 [21]. However, Rubella outbreaks continue to occur in parts of the world, and CRS remains a concern even today. Ever since the introduction of the comprehensive vaccination program in 2004, CRS has been rarely reported in the United States and rubella is not considered endemic in the United States any longer [23, 24]. In countries with not such vigorous vaccination programs, cases of rubella infection and subsequent CRS are still witnessed [25]. Even in countries with competent rubella vaccination programs, the extent of vaccination is not always optimal. Among women living in or emigrating from resource-limited countries, a positive rubella screening test at the first prenatal visit suggests recent active infection, rather than an old infection or vaccination [26–28].

9.2.3 Clinical Manifestations

Acquired rubella is generally a mild, self-limiting illness with a characteristic exanthem and remains asymptomatic in 25–50% cases. Symptoms commonly appear 14–21 days after the initial inoculation and consist of low-grade fever, conjunctivitis, coryza, sore throat, cough, headache, and malaise lasting 1–5 days before the onset of rash. Generalized tender lymphadenopathy, commonly involving suboccipital, postauricular, and cervical nodes may also be seen, particularly during the rash. Approximately 20% of those infected develop discrete rose spots on the soft palate called *Forchheimer spots*, just before the onset of rash.

The typical rubella rash is erythematous, maculopapular and may be mildly pruritic evolving into pinpoint papules over time. It characteristically begins on the face spreading to the trunk and extremities within hours and lasts approximately 1–3 days. Polyarthritis and polyarthralgia are may develop 1 week after the rash and are more commonly seen in female adolescents and adults. Classically, the hands, knees, wrists, and ankles are affected in a symmetric pattern with associated pain and morning stiffness for 1–4 weeks. Tenosynovitis and carpal tunnel syndrome may also be associated. Chronic arthritis although, is rarely seen. Other rare complications are thrombocytopenia, post-infectious encephalitis, myocarditis, pericarditis, hepatitis, hemolytic anemia, and hemolytic uremic syndrome [29].

Congenital Rubella Syndrome An Australian ophthalmologist, Norman Gregg, was the first to establish the link between congenital cataracts and maternal rubella infection in 1941 after witnessing an unusual number of infants with cataracts following a rubella epidemic in 1940 [30]. Maternal-fetal transmission occurs trans-placentally and spreads through the vascular system of the developing fetus ensuing cytopathic damage to the blood vessels and ischemia in affected organs. Fetal infection rates can be as high as 80% in the first trimester, dropping to 25% in the late second trimester and increasing again in the third trimester from 35% at 27–30 weeks to nearly 100% for exposures beyond 36 weeks. However, congenital rubella syndrome occurs when the maternal infection is in the first 16 weeks of pregnancy. Little, if any, risk of congenital rubella syndrome (CRS) is associated with infection after 20 weeks' gestation while intrauterine growth retardation may be the only sequelae of third-trimester infection.

The following case definition for CRS was approved by the Council of State and Territorial Epidemiologists (CSTE) and published in 2009 [31].

Suspected An infant who does not meet the criteria for a probable or confirmed case but who has one or more of the following findings:

- Cataracts
- Congenital glaucoma
- Congenital heart disease (most commonly patent ductus arteriosus or peripheral pulmonary artery stenosis)
- Hearing impairment
- Pigmentary retinopathy
- Purpura
- Hepatosplenomegaly
- Jaundice
- Microcephaly
- Developmental delay
- Meningoencephalitis
- Radiolucent bone disease.

Probable An infant who does not have laboratory confirmation of rubella infection but has at least two of the following, without a more plausible etiology:

- Cataracts or congenital glaucoma
- Congenital heart disease
- Hearing impairment
- Pigmentary retinopathy

OR

An infant who does not have laboratory confirmation of rubella infection but has at least one or more of the following, without a more plausible etiology:

- Cataracts or congenital glaucoma
- Congenital heart disease (most commonly patent ductus arteriosus or peripheral pulmonary artery stenosis)
- Hearing impairment
- Pigmentary retinopathy

AND one or more of the following:

- Purpura
- Hepatosplenomegaly
- Microcephaly
- Developmental delay
- Meningoencephalitis
- Radiolucent bone disease.

Confirmed An infant with at least one of the symptoms clinically consistent with congenital rubella syndrome listed above, and laboratory evidence of congenital rubella infection demonstrated by:

- Isolation of rubella virus, or
- Detection of rubella-specific IgM antibody, or
- Infant rubella antibody titers that do not drop at the expected rate of a two-fold dilution per month, or
- A specimen that is PCR-positive for rubella virus.

Infection Only An infant without any clinical symptoms or signs of rubella but with laboratory evidence of infection demonstrated by:

- Detection of rubella virus, or rubella-specific IgM antibody, or
- Infant rubella antibody titers that do not drop at the expected rate of two-fold dilution per month, or
- A specimen that is PCR-positive for rubella virus.

There is no available evidence that rubella infection immediately prior to conception increases the risk of congenital infection. Maternal immunity, either vaccine or naturally derived, is protective against trans-placental rubella infection. However, CRS cases have been reported even after maternal reinfection. However, none were reported after 12 weeks gestation [32].

9.2.4 Effect of Rubella Infection on Pregnancy

Rubella infection in pregnancy is one of the most common vaccine preventable cause of birth defects. If the infection occurs before 16 weeks of gestation, the patient should be counseled regarding fetal transmission and offered pregnancy termination. Beyond 20 weeks, management should be individualized and parents should be counseled regarding the delayed consequences of rubella infection.

9.2.5 Diagnosis

Enzyme-linked immunoassays (ELISA) are sensitive, accurate, easily reproducible, and measure rubella-specific immunoglobulin IgG and IgM antibodies. Immunofluorescent antibody assays are also sensitive and rapid. Other serologic tests include passive hemagglutination antibody, latex agglutination, complement fixation, and hemagglutination inhibition. Immunoglobulin M (IgM), as in all infections, assists in diagnosing acute infection but unfortunately, IgM may persist for a long time after the acute episode and also, resurface in case of reinfection. Evaluation of RV-IgG avidity, in that case, is of value, as low avidity IgG suggests recent infection.

Acute rubella syndrome is best diagnosed by:

- Presence of rubella specific IgM antibodies
- Fourfold rise in IgG titers between acute (within 7–10 days of rash onset) and convalescent (2–3 weeks later) serum
- Positive rubella culture (from nasal, blood, throat, urine, or cerebrospinal fluid samples). The virus is generally isolated from the pharynx 1 week before to 2 weeks after the rash [33].

Rubella IgM can be falsely positive due to rheumatoid factor or other infections in which cases rubella specific avidity assay is beneficial. Because of issues of false-positivity, the Centre for Disease Control and Prevention discourages the use of rubella IgM for rubella screening in pregnancy [34].

9.2.5.1 Prenatal Diagnosis

Polymerase chain reaction (PCR) provides presumptive diagnosis of rubella infection and has been used extensively in clinical practice. A reverse transcription-nested PCR assay has also been studied for detection of rubella virus in chorionic villous samples (CVS) and amniotic fluid samples of affected pregnancies [35]. It has also been observed that PCR testing on CVS samples may be superior to standard serologic testing on fetal blood. In addition, CVS sampling at 10–12 weeks gestation allows for earlier detection.

It is extremely difficult to diagnose CRS fetal malformations on ultrasound given their nature. However, the workup of any fetus with intrauterine growth restriction should include evaluation for congenital viral infections including rubella.

9.2.6 Treatment

Treatment for acute infection mainly involves symptomatic relief using acetaminophen. Glucocorticoids, platelet transfusion, and other

supportive measures are reserved for complications such as thrombocytopenia or encephalopathy.

Use of immune globulin for antenatal women with acute infection is controversial with no consensus on whether IgG has any beneficial effect on the fetal response to disease. Centre for Disease Control and Prevention recommends limiting the use of immune globulin to women with known rubella exposure who decline pregnancy termination [36].

9.2.7 Prevention

The first rubella vaccine was introduced in 1969. RA 27/3, a live-attenuated vaccine, is currently used world over. Vaccination is recommended for all children at 12–15 months and then at 4–6 years in conjunction with measles and mumps (MMR). A single dose of the vaccine administered at age 1 year or more results in measurable antibody in almost 95% of susceptible population. Occasional side effects seen are arthritis, arthralgia, rash, adenopathy, or fever. It is a good clinical practice to screen childbearing age women, if not vaccinated, for RV-specific immunoglobulin G (RV-IgG) to identify susceptible women and offer them vaccination before pregnancy or after delivery, since the rubella vaccine cannot be administered during pregnancy.

Although rubella vaccine virus may cause trans-placental infection, inadvertent vaccination during pregnancy is not an indication for termination of pregnancy as no cases of vaccine-associated congenital rubella syndrome (CRS) have been reported. However, women are advised against conception for 28 days after the vaccine [37].

Contraindications to rubella vaccination include febrile illness, immunodeficiency disorder, history of anaphylaxis to neomycin, and pregnancy. Postpartum vaccination should be encouraged in all susceptible women as breastfeeding is not a contraindication to the same.

9.3 Rubeola (Measles)

9.3.1 Introduction

Measles (rubeola) is a highly contagious respiratory illness caused by a single-stranded, enveloped RNA virus, which is a member of the genus Morbillivirus within the family Paramyxoviridae. The virus has brief persistence in the environment and causes an acute viral illness with no known carrier states. It is clinically and genetically distinct from rubella (sometimes referred to as German or 3-day measles). Severe morbidity and mortality from measles is more common in infants, young children, and adults compared with older children and adolescents. Pregnant women, in various studies, have been shown to be at an increased risk of measles-associated adverse pregnancy outcomes. Therefore, it is essential that obstetric health care providers are aware of measles and its consequences on pregnancy.

9.3.2 Epidemiology

Measles was primarily a childhood disease, with the highest incidence noted amongst 5–9-year-olds who accounted for more than 50% of cases, prior to the introduction of the measles vaccine in 2000. Since then, however, the incidence amongst adults has risen to about 40% with about a quarter reported in the 20–39 years age group. According to a recent World Health Organization (WHO) report, approximately 110,000 people died from measles in 2017, mostly children under the age of 5 years, despite the availability of an effective vaccine [38]. Although majority of cases are witnessed in countries with weak health systems, large outbreaks have also been reported in developed countries with effective vaccination programs in place. These comebacks can be explained by immunity gaps in the population as well as vaccine refusal [39]. WHO has identified vaccine hesitancy as one of the top ten global health threats in 2019 [40].

9.3.3 Pathogenesis and Transmission

9.3.3.1 Transmission

Measles is highly contagious and is transmitted through infectious droplets or aerosols. Measles droplets can remain airborne for up to two hours, therefore making transmission possible in public spaces, even in the absence of person-to-person contact [41]. Large outbreaks can occur in areas of crowding such as schools and densely populated communities. About 90% of susceptible persons develop measles after exposure. Contact is defined as anyone who has shared the same airspace for any length of time with an infectious person OR who has been in a waiting area or consulting room previously occupied by the infectious person for a period of up to 30 min. Although, mostly seen in temperate areas during the late winter and early spring time, cases may be seen perennially with no apparent seasonal variation in a few areas.

Incubation Period The average incubation period of measles from exposure until prodrome onset is 10–12 days. Onset of the rash typically occurs about 14 days (range 7–21 days) after exposure. The period of contagiousness is estimated to be from 5 days before the appearance of rash to 4 days afterward [42]. It is most contagious during the late prodrome phase, when the patient is febrile and has respiratory symptoms. Patients who have measles-associated subacute sclerosing pan-encephalitis are not considered contagious [43].

Mother to Child Congenital measles is defined as the presence of rash at birth or within the first 10 days of neonatal life when mother has had measles within 10 days of delivery. Infants who develop congenital measles are at increased risk for mortality and for subacute sclerosing pan-encephalitis, which appears to be more severe, with a shorter latency and rapidly progressive course [44].

9.3.4 Clinical Features

Adults Infected persons typically present with high fever, malaise and the "three Cs" of cough, coryza, and conjunctivitis. This prodrome is followed by appearance of rash 3–4 days later. Koplik's spots, which look like small white lesions on an erythematous base, may appear on the buccal mucosa towards the end of prodrome. This phase is followed by a maculopapular rash that typically spreads from the head to the lower extremities and then gradually fades in the same manner [42]. Measles complications include pneumonia and encephalitis. Subacute sclerosing pan-encephalitis is another notable complication, which is a degenerative CNS disorder characterized by intellectual decline and behavioral changes followed by seizures, dementia, and death seen on an average 4–10 years after the acute measles illness.

Pregnant Women Although the presentation is similar to that of the general population, it has been observed that pregnant women are significantly more likely to be hospitalized, develop pneumonia, and to succumb to the illness. Fever and elevated liver enzymes are also more common. In a study from Namibia on 55 pregnant women with measles, diarrhea was observed in 60%, pneumonia in 40%, and encephalitis in 5% [45]. Of the 42 pregnancies with known outcomes, 60% had at least one adverse maternal, fetal, or neonatal outcome, and 12% of women died. Risk for low birth weight, spontaneous abortion, intrauterine fetal death, and maternal death was significantly increased. Another study noted an increased incidence of premature birth [46]. Alteration of immune response mechanisms could be responsible for adverse pregnancy outcomes. Overall, CD8 levels increase as a consequence of the interaction between T lymphocytes and infected cells. During the first trimester, the subpopulation of natural killer uterine cells (uNK) increases to comprise

approximately 70% of the leukocyte population in the endometrium. The fine regulation of the panel of cytokines produced by these cells finally determines the pregnancy outcome in such women [47].

Considering all the possibilities discussed above, it is imperative that any pregnant who is exposed to measles must report to her GP/ hospital as soon as possible.

Fetus/Newborn Congenital measles (defined by the appearance of measles rash within 10 days of birth) and postnatally acquired measles (defined as appearance of measles rash within 14–30 days of birth) are associated with a spectrum of illnesses ranging from mild to severe disease [48]. Neonates born to women with measles are significantly more likely to be born preterm, to be admitted to the neonatal intensive care unit, and to have longer intensive care unit stay than neonates born to women without measles. Rates of spontaneous abortion, intrauterine fetal demise, and neonatal mortality were also found to be higher among pregnant women with measles [46]. In children with impaired cellular immunity, the infection has an unfavorable course due to complications such as giant cell pneumonia or encephalitis.

9.3.5 Effect of Measles on Pregnancy

If a woman becomes infected in the absence of prior immunity to measles, there is risk of:

(a) Miscarriage
(b) Stillbirth
(c) Preterm labor
(d) Fetal growth restriction

Hence, it becomes essential that if a pregnant woman is exposed to measles, she must report to the health provider immediately.

9.3.6 Diagnosis

Measles should be considered in a patient presenting with a febrile rash compatible symptoms (eg, cough, coryza, and conjunctivitis), especially in the setting of recent exposure to an individual with a febrile rash illness or travel to an area of high measles prevalence, particularly in the absence of measles immunity. Patients being evaluated for measles should be isolated.

The difference in the presentation between varicella, measles, and rubella is shown in Table 9.1.

The approach to diagnosis differs depending on the regional prevalence of measles. Diagnosis of recent infection is based on presence of at least one of the following:

- Positive measles IgM antibody
- Significant rise in measles IgG antibody titers between acute and convalescent titers
- Isolation of measles virus in culture from peripheral blood mononuclear cells, nasopharyngeal secretions, conjunctival swabs, or urine. However, culture of the virus requires special facilities.
- Detection of measles virus RNA by reverse transcription-polymerase chain reaction (RT-PCR), either real-time reverse transcription-polymerase chain reaction (rRT-PCR) or conventional, endpoint RT-PCR [49]. Viral RNA is usually present for approximately 3 days after rash onset.

9.3.7 Treatment

Patients with suspected measles should be promptly isolated in an airborne infection isolation room. All health care staff and caregivers should have evidence of measles immunity and use appropriate personal protective equipment including N95 masks, especially around patients with measles.

Table 9.1 Characteristic features of Varicella, German measles, and Measles

Characteristics	Varicella	German measles (Rubella)	Measles
Causative virus	DNA virus, Herpes virus Invades regional lymph nodes, tonsils, ductal tissue of salivary glands	RNA virus, Togaviridae; Invades skin, eyes, and lymphnodes	RNA virus; Morbillivirus, Paramyxoviridae family Infects respiratory system
Spread	Respiratory droplets, fomites	Direct droplet contact	Direct droplet contact and airborne
Incubation Period	10–21 days	14–21 days	10–12 days
Symptoms	Fever, malaise, loss of appetite	Fever, headache, rash &joint pain	3 "C"; Conjunctivitis, coryza, cough
Rash	Self-limiting rash Begins as macules, progresses to papules to vesicles to crusting	Pink red macules and papules on the face and spread caudally Forschheimer's spots on soft palate	Red or reddish-brown rash which appears in hairline, spreads over neck and trunk and finally the upper and lower limbs; Koplik's spots appear 2 days before the rash
Fever	Fever in the range of 101–102 °F (38.3–38.8 °C)	Usually no fever	Associated with high fever
Maternal Prognosis	Usually with fever, malaise, dyspnoea Varicella pneumonia seen in 10–20% cases may be fatal	Usually self-limiting, benign or of mild nature	Higher hospital admission, complications and mortality
Fetal prognosis	CVS risk 0.4% ≤13 weeks; 2% if 13–20 weeks	CRS risk 80% in first trimester; 25% late second; 35% 27–32 weeks; 100% after 36 weeks FGR	Risk if within 10 days of exposure Sub-acute sclerosing pan-encephalitis Higher mortality
Neonatal prognosis	7% mortality rate Delivery within 5 days of maternal infection, <28 weeks, <1000 g highest risk	Multiple anomalies involving eye, heart, hearing	Spontaneous abortion, FGR, neonatal mortaltiy
Diagnosis	Viral DNA PCR from vesicular base/immunofluorescence Serological test has no value	ELISA for IgG/ IgM Immunofluorescence Prenatal-PCR of amniotic fluid/ CVS sample	IgM, IgG serology Culture, viral RNA RT-PCR
Treatment	Uncomplicated- Acyclovir Complicated- Hospital management	Symptomatic	Symptomatic

Pregnant women with measles should receive symptomatic care as no specific treatment is available. The management is mainly supportive consisting of antipyretics, fluids, and treatment of bacterial superinfections, such as pneumonia and otitis. Treatment of other complications, such as seizures and respiratory failure, may also be necessary. Antibiotic prophylaxis during measles epidemics may prevent complications although, further research is needed [50].

Vitamin A A deficiency of Vitamin A leads to delayed recovery and high rate of post-measles complications. In addition, measles infection may precipitate acute vitamin A deficiency and xerophthalmia [51]. Even in countries where measles is not usually severe, vitamin A should be given to all cases of severe measles.

Ribavirin Its use on a case-to-case basis, administered either intravenously or orally, significantly improves morbidity and mortality.

Treatment of Infant It is recommended that infants with exposure to measles receive measles

immune globulin intramuscularly at a dose of 0.5 ml/kg of body weight (max = 15 ml).

Prophylaxis Susceptible pregnant women exposed to measles are recommended to receive 1 g of human normal immunoglobulin (Ig) within 72 h and not more than 6 days of exposure to prevent or modify the course of the disease.

9.3.8 Measles/Rubella Vaccination

MMR vaccine is a live vaccine and the summary of use of MMR vaccine is given below.

9.3.8.1 Summary and Recommendations

1. Health care providers should review vaccination history as a routine part of a woman's general preventive health care
2. Acceptable evidence of measles immunity includes:
   (a) Written documentation of live measles virus-containing vaccine (two doses for adults at increased risk for exposure, such as students attending colleges, health care personnel, and international travelers; one dose for other adults aged 18 years or older)
   (b) Serological evidence of measles-specific immunoglobulin IgG antibody or
   (c) Birth before 1957 who are presumed to be immune.
3. Routine pregnancy testing of women of reproductive age is not recommended before MMR vaccine administration
4. MMR vaccine is a live vaccine, women who are pregnant or planning to become pregnant should not be vaccinated and those vaccinated should be advised against conception for the following 4 weeks.

   Despite the theoretical risk of congenital rubella syndrome associated with receiving a rubella-containing vaccine, MMR vaccination during pregnancy should not be considered a reason for pregnancy termination as studies have not shown an increased risk of adverse outcomes
5. Non-immune women should receive MMR vaccine post-delivery with reassurance that breastfeeding poses no risk to the newborns.

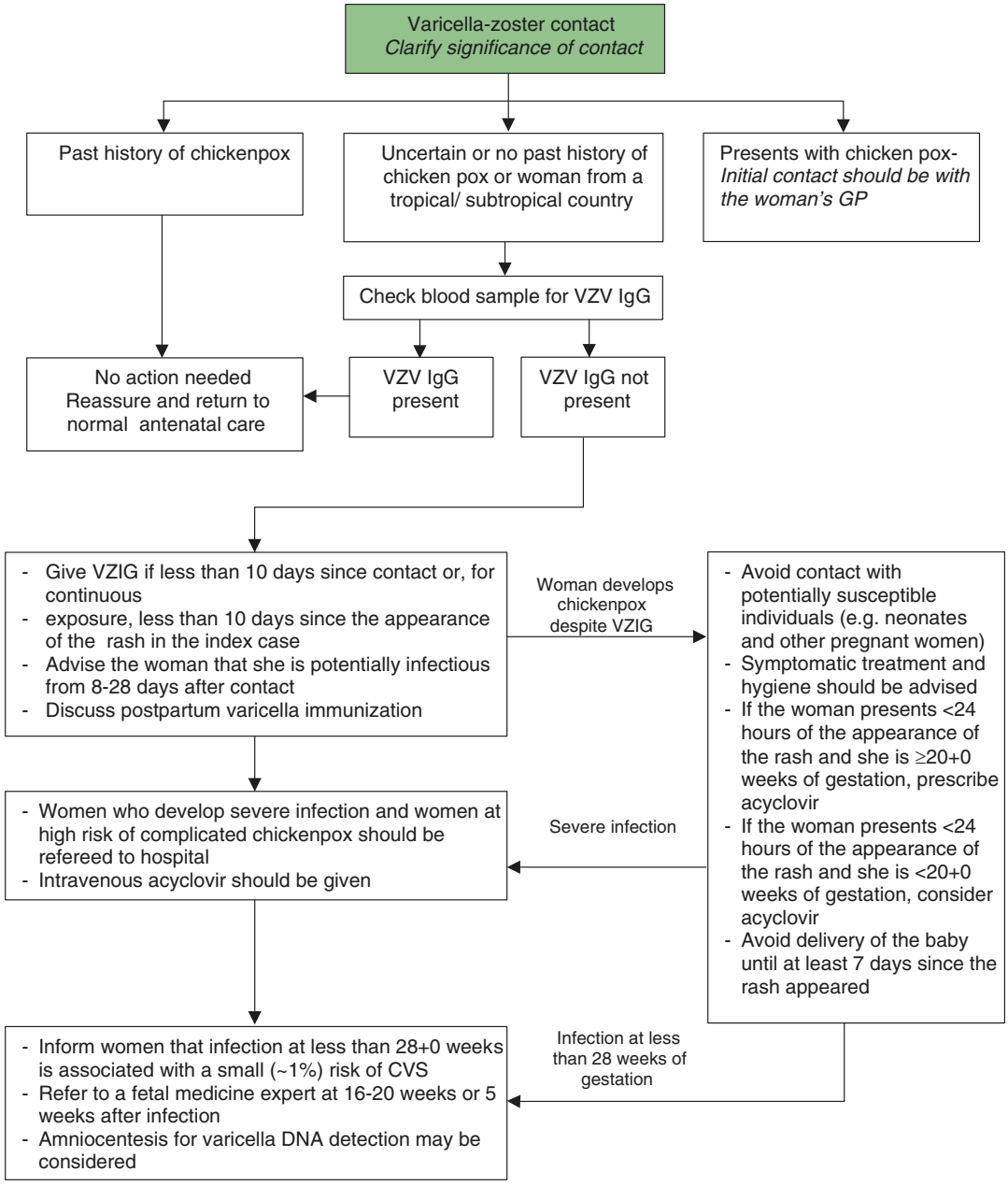
9.4 Conclusion

Varicella, rubella, and measles infections in pregnancy are the three important rash-associated viral infections which are associated with adverse maternal, fetal, and neonatal outcomes. Congenital varicella and rubella syndrome are associated with multiple congenital anomalies and much morbidity in the neonatal period while measles infection is not teratogenic but leads to increased incidence of spontaneous abortion or prematurity. There is no specific treatment for any of these viral infections and management is mainly supportive.

Key Points

1. Vaccination history must be reviewed as a part of women's preventive health care.
2. Varicella, although, has a self-limiting course in healthy children can potentially cause serious morbidity in adults and pregnant women.
3. The risk of congenital varicella syndrome amongst infected antenatal women is 0.4–2%. It is characterized by cutaneous scars, growth retardation, limb, ocular and neurological abnormalities.
4. Pneumonia is the most common complication of varicella during pregnancy which can lead to mortality if left untreated.
5. Oral acyclovir is the drug of choice for uncomplicated varicella while complicated presentation requires intravenous acyclovir at 10 mg/kg every eight hours.
6. Acquired rubella in pregnancy is generally a mild, self-limiting disease characterized by an erythematous maculopapular eruption followed by the development of polyarthritis and arthralgia.
7. Maternal-fetal transmission of rubella is the highest in first trimester as well as after 36 weeks gestation.
8. Fetal effects of rubella are usually witnessed with maternal infection in the first 16 weeks of pregnancy wherein it can result in spontaneous abortion, stillbirth, congenital defects, and intrauterine growth restriction.
9. Women infected with rubella prior to 16 weeks gestation should be offered pregnancy termination, due to the high risk for CRS.
10. Measles should be considered in pregnant women presenting with fever, rash and three C's of cough, coryza, and conjunctivitis.
11. The most common methods for confirming measles infection are detection of measles-specific IgM antibody and measles RNA by real-time polymerase chain reaction.
12. MMR vaccine is live attenuated and hence, is contraindicated during pregnancy. Also, women are advised to avoid conception for 1 month following the MMR vaccine. However, no cases of vaccine-associated CRS have been reported, hence termination of pregnancy is not an option if inadvertently vaccinated.

Appendix


Varicella-zoster contact
Clarify significance of contact
Past history of chickenpox
Uncertain or no past history of chicken pox or woman from a tropical/ subtropical country
Presents with chicken pox- Initial contact should be with the woman's GP
Check blood sample for VZV IgG
No action needed Reassure and return to normal antenatal care
VZV IgG present
VZV IgG not present
- Give VZIG if less than 10 days since contact or, for continuous
- exposure, less than 10 days since the appearance of the rash in the index case
- Advise the woman that she is potentially infectious from 8-28 days after contact
- Discuss postpartum varicella immunization
Woman develops chickenpox despite VZIG
- Avoid contact with potentially susceptible individuals (e.g. neonates and other pregnant women)
- Symptomatic treatment and hygiene should be advised
- If the woman presents <24 hours of the appearance of the rash and she is ≥20+0 weeks of gestation, prescribe acyclovir
- If the woman presents <24 hours of the appearance of the rash and she is <20+0 weeks of gestation, consider acyclovir
- Avoid delivery of the baby until at least 7 days since the rash appeared
- Women who develop severe infection and women at high risk of complicated chickenpox should be refereed to hospital
- Intravenous acyclovir should be given
Severe infection
- Inform women that infection at less than 28+0 weeks is associated with a small (~1%) risk of CVS
- Refer to a fetal medicine expert at 16-20 weeks or 5 weeks after infection
- Amniocentesis for varicella DNA detection may be considered
Infection at less than 28 weeks of gestation

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Parvovirus B19 Infection: Significance and Implications in Pregnancy

10

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10.1 Introduction

Parvovirus B19 infection also known as *erythema infectiosum, slapped cheek syndrome* or *fifth disease* is a common childhood illness caused by a single-stranded DNA virus. The B19 particle was first described by an Australian virologist Y. Cossart, in 1975 [1]. The accidental discovery was made during laboratory evaluation of serum from a blood donor for hepatitis B. Y. Cossart discovered an anomalous reaction in position 19 plate B. The term "Parvo" was derived from the Latin word parvum meaning small [2]. Initially, the virus particle was termed as "serum parvovirus-like particle" or human parvovirus. The International Committee on Taxonomy of Viruses in 1985, officially included this virus into the Parvoviridae family and designated the name B19 [3]. Parvovirus is among one of the simplest and smallest eukaroyotic viruses. Parvovirus B19 usually spreads through respiratory secretions but reports of transmission through blood and blood components is also noted. The disease results in mild febrile illness with the development of a bright red rash on the cheeks of the infected child appearing like a slapped cheek, and so the disease was popularly termed as the slapped cheek syndrome. This illness was given the name of "fifth disease" by Russian-French physician Leon Cheinisse in 1905, as it was listed fifth in order while proposing the six common exanthems. Cases are most infectious before symptoms develop. Infection in pregnant women during the first trimester can lead to fetal affection which may result in spontaneous abortion, fetal demise, congenital anemia, hydrops fetalis, and long-term neurological deficits.

10.2 Epidemiology

Parvovirus B19 is a highly contagious infection affecting all parts of the world. It can affect people of all age groups. The disease shows no racial or gender differentiation, but affection of female in the reproductive age group is associated with vertical transmission to the fetus and increased incidence of post-infection arthritis. The burden of the disease has not changed in the last few decades. Majority of the infection is acquired during childhood i.e. before 15 years of age. In the United States, 5–10% of children between 2 and 5 years acquire infection, but this increases to 50% by 15 years of age. There is a non-linear increase in the seropositivity to 60% by 30 years [4, 5]. A study from England and Wales reported

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21% seropositivity in children between 1 and 4 years which rose exponentially to 75% in adults under 45 years [6]. In Victoria, Australia, 28% of children between 0 and 9 years were documented to have protective antibodies. This percentage increased to 78% by 50 years of age [7]. A small number of adults acquire the infection annually from infected children which contributes to the highly immune adult population. The disease can occur throughout the year sporadically but is usually seen as an epidemic or outbreak in late winter or early spring in playschool children. The source of maternal infection during pregnancy is often the mother's older child. Despite the high prevalence worldwide, various studies in different parts of the world have reported that 20–50% of female in the reproductive age groups are not immune and are at potential risk of acquiring the infection. The seroconversion rate is between 0.5 and 1.5% [8]. The rate of fetal loss due to vertical transmission is 0.6–1.5% [9–12].

10.3 Morphology of the Virus

Parvovirus B19 belongs to the family *Parvoviridae*, sub-family *Parvovirinae* and genus *Erythrovirus*. The virion has a simple structure that is composed of a linear, single-strand DNA molecule and only proteins. It lacks an envelope and is arranged in icosahedral symmetry. It is the only virus of this family to have human affection. It is a small virus measuring 22–24 nm in diameter and has a molecular weight of 70–77 kDa [1, 13]. The virus encodes three proteins, the NS1—Non-structural protein, and two capsid proteins—VP1 and VP2 [14]. The NS1 protein plays an important role in the replication of the DNA and in apoptosis of the erythroid progenitor cells during the infection [15]. VP2 is the major capsid protein that acts as the cellular receptor of the virus. It binds to the P protein on the erythroid cells, resulting in internalization of the virus [16]. VP1 capsid protein has a unique region which is an addition of 227 amino acids to the amino acid sequence of VP2. This unique region serves as the main neutralizing epitope of B19. The virus is extremely resistant to lipid solvents and high temperatures due to the lack of a lipid envelope. It can survive at 56 °C for 60 min. Inactivation of the virus can be achieved by formalin, beta propiolactone, and gamma irradiation [17].

10.4 Pathogenesis and Transmission

The virus shows tropism towards human erythroid precursor cells (pronormoblasts, normoblasts) [18]. The glycolipid Globoside, commonly known as the blood group P protein is the hemagglutinin through which the virion binds to internalize into the host cell (erythroid precursor cells) and replicate [16]. The virus is cytotoxic to these cells, thus leading to suppression of erythropoiesis. In healthy children, the fall in hemoglobin levels is rarely more than 1 g/dl but in individuals with hemoglobinopathies or hemolytic anemia, the fall maybe 2–6 g/dl [19]. Individuals who genetically lack the P antigen (1 in 200,000) have natural immunity towards this infection [20].

P antigen is also present on the surface of endothelial cells, myocytes and megakaryocytes, but similar viral permission and replication has not been noted in these cells. This suggests that probably an unidentified second receptor is required for tropism. It has been postulated that expression of P antigen on these cell types may be responsible for the development of the rash, transplacental infection, and myocarditis by production of cytotoxic nonstructural NS1 protein of the virion even though internalization and replication is not possible [21].

The virus can be isolated both in the blood and respiratory secretions of the infected person 5–7 days before the rash appears. The blood picture at the time of infection shows the presence of large megakaryocytes also termed as the *lantern cells*. They are 25–32 μm in diameter with large nuclear inclusion bodies and cytoplasmic vacoulization. This may also be seen as dog ears on electro magnification [16, 22]. Individuals with human immunodeficiency virus (HIV) infection or chronic infections, lack these cells. Initially, during the viremia, the reticulocyte count falls to undetectable levels. They start recovering after

7–10 days. The suppression of erythropoiesis is seen clinically as anemia, thrombocytopenia and neutropenia 6–10 days after inoculation of the virus.

The incubation period is followed by the development of fever and the characteristic rash. This is immune-mediated and is therefore characterized by the detection of B-19 specific IgM antibodies. These antibodies are detectable for 2–3 months.

The disease has mainly three phases:

- *First phase*: It coincides with peak level of virus and RBC destruction. The patient at this time presents with fever, malaise, chills, myalgia, and the characteristic bright red "slap cheek" rash.
- *Second phase*: This is characterized by rash and arthralgia. There is no viremia and so the patient is no longer infectious. There is evidence of maculopapular rash on arms and trunks which fades into a lace-like reticular pattern. It is caused by immune complexes in the capillaries of the skin.
- *Third Phase*: It is characterized by frequent clearing and recurrences which may continue for weeks.

10.4.1 Virus Transmission

Both respiratory route and hand-to-mouth contact are the major modes of transmission for spread among children in schools and daycare centers. Parenteral transmission by blood or by infected blood products transfusion (clotting and immunoglobulin concentrates) has also been observed. Vertical transmission from the mother to the fetus has been noted in nearly 30% of cases [23].

10.5 Clinical Presentation

10.5.1 Maternal

Asymptomatic About 50% of non-pregnant females and 70% of pregnant women may be asymptomatic even after being infected by Parvovirus B-19 [24, 25].

Erythema Infectiosum The disease has an incubation period of 4–14 days, which may extend up to 21 days. During this time the patient develops nonspecific symptoms like fever, myalgia, malaise, headache, and rhinorrhea [4]. These symptoms affect 15–30% of the individuals and subside within 2–3 days followed by the appearance of a macular exanthem on the cheek 1 week later. The rash is bright red in color with circumoral pallor [8, 26]. After 1–4 days, the characteristic maculopapular rash develops which may extend to the distal extremities and become pruritic. This characteristic rash is more commonly seen in children.

Atypical presentation of the rash may be seen in adults. These features are manifestations of the immune response, by which time the viral replication is almost over. The development of the rash coincides with detection of IgM antibodies in the serum of the affected individual. Therefore, with the development of the rash, the patient becomes non-infectious. This is known as the *biphasic presentation* of the disease. The exanthema may also present as:

- Erythema multiforme
- Pruritus of the hand and soles
- Papular-purpuric "glove and socks" syndrome (PPGSS)—This is an uncommon manifestation, exclusive to Parvovirus B19 infection. There is an erythematous exanthem involving the hands and feet. This manifestation is common in young adults. The induration and erythema limit themselves at the ankle and wrist joint; rarely, involvement of the thigh, elbow, penis and vulva may be seen. During the course of evolution the skin changes may progress to petechiae, purpura, and even bullous eruptions. It usually resolves within 1–3 weeks with no residual scarring [8, 27, 28].

Transient Small Joint Arthropathy This is the main presentation in adults infected with Parvovirus B19 infection; it is the replacement of the characteristic rash of childhood. This is also immune-mediated, coinciding with increase in the levels of IgM antibodies. Arthropathy usually subsides within 1–3 weeks but in some it may last for months. It leads to polyarthralgia of hands,

wrists, ankle, and knee joints [24, 29]. The residual arthropathy of the knees is seen in only 10% of the individuals [8]. About 50% of pregnant women present with arthralgia [29].

Anemia and Transient Aplastic Crisis Tropism for erythroid precursor cells of the bone marrow results in anemia. In normal healthy adults and children the reduction in hemoglobulin levels is not more than 1 g/dl but in individuals with hemoglobinopathies, this may result in significant anemia and even apalstic crises. These conditions include sickle cell disease, thalassemia, autoimmune hemolytic anemia, hereditary spherocytosis and pyruvate kinase deficiency [25, 30–32]. In addition to the nonspecific prodromal symptoms, the patient has fatigue, shortness of breath and visible pallor. In some cases, fever and ecchymotic patches may develop due to varying degrees of neutropenia and thrombocytopenia. This may be due to cytopathic effects of megakaryocytes or immune mediated. In presence of hemolytic anemia, it may result in congestive heart failure also. The diagnosis of this condition is generally made by prodromal rise in reticulocyte count, followed by a fall to below detectable levels. The condition is usually self-limiting but in certain cases like patients with sickle cell anemia multiple blood transfusions may be required.

Other atypical presentations include vasculitis, myocarditis, glomerulonephritis, or encephalitis.

Parvovirus B19 infection has also been reported with idiopathic thrombocytopenic purpura, Henoch-Schönlein purpura, and pseudoappendicitis. It can at times, also precipitate hemophagocytic syndrome. Rare, fatal cases of parvovirus B-19 myocarditis are seen in transplant patients.

10.5.2 Fetal and Neonatal Manifestations

The overall risk of B19 infection in pregnancy is less (approximately 1–5%) [29, 33, 34]. Average risk of vertical transmission is approximately 30% [23, 35–37]. The overall risk of abnormal fetal outcome is 5–10%. The most significant affection to the fetus which is seen in the first half of pregnancy is spontaneous abortion. The incidence of fetal demise is 13% prior to 20 weeks and 0.5% beyond this period [17, 23, 25, 29, 37, 38]. Greater fetal affection at early gestation (9–16 weeks) has been postulated to be due to cytotoxic damage to rapidly expanding fetal hematopoietic system and myocardium prior to the development of anemia [17, 23, 29, 38, 39]. Maternal–fetal transmission usually occurs in pregnant women with high plasma viral loads. Parvovirus B19 replicates in the erythroid precursor cells which possess globoside, the cellular receptor necessary for parvovirus B19 infectivity. Many non-erythroid cells like megakaryocytes, cardiac myocytes, and placental trophoblastic cells also express this receptor. These different cell lines can thus be affected and result in fetal damage. The most common associated fetal affection with parvovirus B19 is non-immune fetal hydrops.

10.5.2.1 Hydrops Fetalis

Accumulation of fluid in at least two compartments of the body of the fetus i.e. subcutaneous, pericardial, pleural, and abdominal is defined as hydrops fetalis (Fig. 10.1). The presence of an edematous placenta may be a concomitant finding but is not essential for definition.

The term non-immune hydrops fetalis (NIHF) was introduced to differentiate cases in

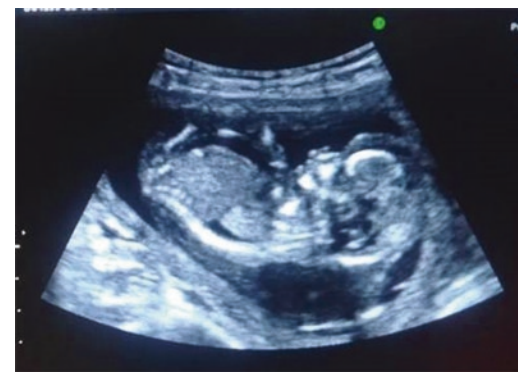

Fig. 10.1 Fetus showing scalp edema, pleural effusion, and ascites

a fetal hydrops caused by factors other than isoimmunization. Parvovirus B-19 is the most common infectious cause for NIHF. Fluid imbalance between the vascular and interstitial spaces along with a reduced lymphatic return is the main pathophysiology in development of non-immune hydrops fetalis [40]. NIHF accounts for approximately 90% of the cases of hydrops fetalis with a prevalence of 1 in 1700–3000 pregnancies [41, 42]. A median interval of approximately 3 weeks is postulated for development of hydrops fetus, if maternal parvovirus B19 infection happens before 20 weeks [43, 44]. Koch et al, reported NIHF was the main complication in 0.9–23% of pregnant women with proven parvovirus B19 infections [44]. Enders et al observed hydrops fetalis in 3.9% with the greatest risk to the pregnant women infected during gestational week 13–20 [45]. B19 infection is a major cause of fetal loss in the second half of pregnancy when other causes of spontaneous abortions are rare [46]. The possible mechanisms postulated for development of fetal hydrops in Parvovirus B19 infection are fetal anemia developing as a result of cytotoxic effect of the virus on fetal erythroid precursor cells, leading to hypoxia and high output cardiac failure. Tropism of the virus towards myocardial cells leads to myocarditis, resulting in cardiac failure which may also contribute to the development of hydrops. Other mechanisms responsible are direct damage to hepatocytes and indirect damage due to deposition of hemosiderin in hepatocytes following excessive breakdown of red blood cells [23, 24, 29, 38]. Intrauterine-packed red blood cell transfusions have been shown to improve anemia and may even resolve fetal heart failure and edema. Hydrops fetalis may rarely resolve spontaneously while in-utero [47].

10.5.2.2 Congenital Anemia

Theoretically, occurrence of congenital anemia is possible in fetuses affected by Parvovirus B19infection but follow-up studies of hydropic fetuses does not show such association [48–50]. Miller et al. in their research reported three infants with hydrops and congenital anemia following transplacental parvovirus B19 infection [38]. Viral DNA was confirmed in bone marrow of these infants. Heegaard ED et al. reported a series of 11 children with Diamond-Blackfan anemia, a type of congenital anemia; 3 of these children were found to harbor B19 DNA in the bone marrow [51]. These children showed spontaneous remission while others required steroid therapy. Another case of congenital anemia was reported by Rugolotto et al. [52]. Recently Heegaard E D et al. reported a case of congenital anemia consequent to B19 infection which required immunoglobulin therapy and multiple transfusions [53].

10.5.2.3 Thrombocytopenia

Idiopathic thrombocytopenic purpura (ITP) in children has been found to be proceeded by viral infection. A case series on ITP in children reported B19 parvovirus infection as the cause of ITP in 6 out of 47 children [54]. It has been postulated that parvovirus B19 causes thrombocytopenia by suppression of megakaryocte production in the bone marrow due to the cytotoxic effect of NS1 protein. It also is seen to cause immunologically mediated destruction of platelets by antiplatelet antibody formation.

10.5.2.4 Myocarditis

The presence of P antigen on the surface of myocytes has led to the evaluation of B19 parvovirus and its association with myocarditis. Cardiac tropism of B19 has been demonstrated by finding viral DNA in fetal myocytes on histopathological examination. Rare cases of myocarditis and heart failure due to B19 infection, are mentioned in literature [55, 56].

10.5.2.5 Neurological Deficits

Neonatal encephalopathy, neuropathy, complex regional pain syndrome, and neuralgic amyotrophy are some of the neurological complications reported subsequent to maternal parvovirus B19 infection. In the absence of hydrops or significant fetal anemia, the infection per se may not cause such complications. But evidence of viral DNA

in CSF has suggested that severe anemia and fetal hydrops may be an independent risk factor for long-term neurological sequelae [54–57]. Consideration could be made for cerebral imaging studies in neonates who had severe hydrops or anemia.

10.5.2.6 Congenital Anomalies

Currently, evidence that parvovirus B19 infection increases the risk of congenital anomalies in humans is lacking though there have been case reports of central nervous system, craniofacial, musculoskeletal, and eye anomalies [14, 31, 57–61] (Table 10.1).

10.6 Diagnostic Evaluation

Most cases of Parvovirus infection are self-limiting and therefore do not require diagnostic evaluation.

Culture In experimental models, B19 virus has been cultured from nasopharynx and bone marrow during viremia. Culture is technically difficult as no animal models exist for this disease.

Serology IgM antibodies have been identified in the sera of the patients 10–12 days after inoculation of the virus. This coincides with the development of the rash and is found in 90% of the cases. IgM lasts for 2–3 months in the body; IgG antibodies appear by 7 days and are detectable for life.

Parvovirus antibody testing in patients is performed using ELISA, Radioimmunoassay, or immuno-florescence techniques. In the presence of high viral loads, the virus and antibodies may form complexes that result in false-negative reports. In such conditions, viral DNA amplification by PCR is a better modality for diagnosis.

Viral DNA PCR PCR for Parvovirus B19 is a sensitive test to detect viral DNA in blood or other body fluids. Routinely serology is used for the diagnosis of infection. PCR DNA is a useful tool in diagnosis of chronic infection and for evaluating viral load in congenital infections to plan management.

Ultrasonography In the event of recent infection, fetal affection via transplacental transmission and development of hydrops fetalis is of concern. The women should be referred to fetal-medicine specialist. Serial ultrasounds should be performed 8–12 weeks after infection to detect development of hydrops fetalis [29, 38]. The ultrasound includes doppler measurement of MCA peak systolic velocity to assess for fetal anemia [57, 60, 62–65]. It has a sensitivity of 83–100% and a specificity of 93–100% to diagnose parvovirus-affected fetuses [59, 65]. The measurement is repeated every week. Increased placental thickness, echogenic bowel/ meconium peritonitis, first trimester increased nuchal thickness and amniotic fluid abnormalities are other radiological findings suggestive of parvovirus B19 infection. Other sonographic features of established hydrops fetalis include ascites, skin

Table 10.1 Reported congenital anomalies associated with parvovirus B19 infection during pregnancy

System involved	Anomalies
Neurological	Hydrocephalus, cerebellar hemorrhage, polymicrogyria
Cardiac	Myocarditis, Ebstein's anomaly, ventricular septal defect, cardiomyopathy, second-degree heart block
Ocular	Corneal opacification, aphakia, microphthalmia with multiple anomalies
Gastrointestinal	Hyperechogenic bowel, meconium peritonitis, fetal liver calcifications, portal tract fibrosis, hypoplasia of the abdominal muscles
Multiple anomalies and chromosomal aberrations	Cleft lip and palate, micrognathia and arthrogryposis Subcutaneous edema of the lower extremities, micropenis with perineoscrotal hypospadias, bifid scrotum, and secundum atrial septal defect Down's syndrome

Source: Ornoy, A. and Ergaz, Z. Parvovirus B19 infection during pregnancy and risks to the fetus. Birth Defects Research 2017;109: 311–323

edema, plural, and pericardial edema, and placental edema.

10.6.1 Prenatal Diagnostic Testing

Ultrasound Doppler evaluation acts as a guide to suspect congenital parvovirus B19 infection. Histopathology and immunohistochemistry have limited roles in diagnosis of infection.

Serological assays can be used only after 22 weeks when the fetus becomes capable of producing antibodies [66]. Fetal infection can be diagnosed using PCR (nested PCR or reverse transcriptase PCR) B19 viral DNA in amniotic fluid or cord blood. But invasive methods for diagnosis are not recommended for all suspected or confirmed maternal infections. The fetal-medicine specialist should ask for PCR for B19 parvovirus if amniocentesis is recommended for fetal indications. B19 DNA quantitative serum and tissue titers are useful in guiding clinicians in therapy. Bone marrow examination will show an absence of mature erythroid precursors following acute infection. In cases of placental or fetal infection, tissue immunohistochemistry demonstrates high specificity. As most pregnancies with infection result in favorable spontaneous remissions, prenatal diagnostic testing is used only when there is definite hydrops fetalis and evidence of fetal anemia.

10.7 Infection During Pregnancy

20–50% of the women in the reproductive age group are non-immune and at risk of aquiring infection during pregnancy [8]. At the outset of an outbreak, female employees, teachers, and mothers of pre-school and playschool children are at risk of developing infection [67, 68]. Studies have documented that the risk of transmission from household contacts is more than work place infection [24, 45, 69]. Hand washing at work and at home during such outbreaks has been shown to reduce the risk of infection. Studies have not documented that removal of female employees from such workplaces will reduce the indidence of infection [45, 67].

10.7.1 Exposure During Pregnancy

There is no recommendation for routine screening to detect parvovirus immunity in low-risk pregnancies [70]. In the event of exposure of women during pregnancy to parvovirus B-19 infection and/or development of signs or symptoms of the infection, it should be assessed whether she is immune by testing for both parvovirus B19-specific IgG and IgM antibodies [70, 71].

Parvovirus B19 IgM antibodies appear within 2–3 days of onset of the acute infection (10–12 days after inoculation). These antibodies persist up to 6 months. IgG antibodies appear a few days later and remain in the serum throughout life. Enzyme-linked immunosorbent IgM and IgG assays based on recombinant conformational epitopes of polyomavirus capsid proteins 1 and 2 or polyomavirus capsid protein 2 alone are recommended for diagnosis [45].

Presence of IgG antibodies in the absence of IgM suggests immunity following recent infection—The patient should be reassured regarding protection against fetal affection.

If only IgM antibodies are detected, it either reflects a very recent infection or a false-positive result;it is recommended to repeat the test after 1–2 weeks in such cases. If IgG is detected by this time then the test suggests recent infection. If both IgM and IgG are negative, it suggests the non-immune status of the patient and suceptiblity to infection. This may suggest that she is in the incubation period. Thus, if the woman has had exposure, she should be subjected to the tests again after 2–4 weeks to diagnose the infection. If both IgM and IgG are found positive in the sera, it suggests a recent infection. Repeat test after 2–4 weeks to document rise in IgG titers (Fig. 10.2).

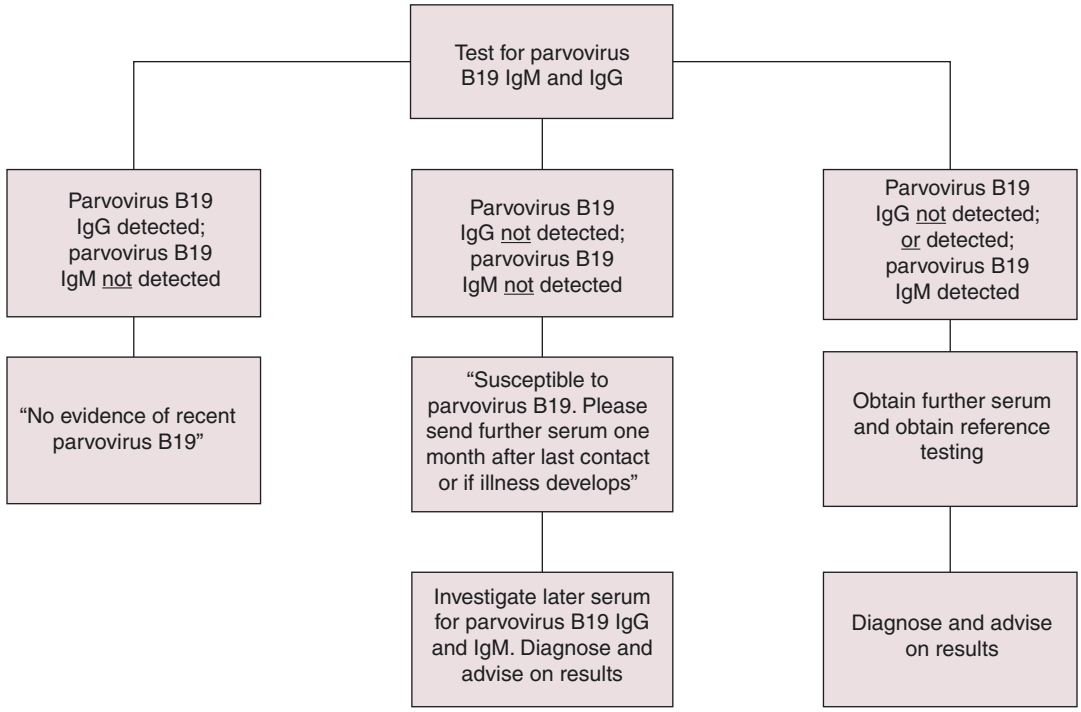

Fig. 10.2 Investigation for parvovirus B19 in pregnant women exposed to rash illness (adapted from the 2000 Public Health Laboratory Service Working Party on 'Rash Diagnosis in Pregnancy and Rubella Screening', subsequently reported)

10.8 Treatment

Most of the affections are mild and nonspecfiic, so do not require medications. Antipyretics and non-steroidal anti-inflammatory drugs can be given in case the patient is symptomatic. Patients with aplastic crises may require packed red cell transfusions.

10.8.1 Role of Immunoglobulins

Intravenous immunoglobulins are sterile purified IgG made from pooled human plasma containing more than 95% unmodified IgG and small amount of IgA and IgM. It is prepared from serum of at least 1000–15,000 donors per batch.

Parvovirus B19 acts through two different mechanisms to produce infection in the host. One is by active viral replication and the other is by producing innate immune response. The intravenous immunoglobulin (IVIG), is useful in acting against latent or persistent infection but its effectiveness in abolition of the lytic cycle of virus replication is not proven. IVIG is used as an infusion (0.4 g/kg of body weight/day) for 5 days or 1 g/kg/day for 2–3 days. It acts as a good neutralizing agent against the persistant infection, especially in immunocompromised individuals. It increases the reticulocyte levels and thereby causes increase in hemoglobin levels. It has been found to be effective in persistant parvovirus infection, parvovirus-associated chronic fatigue syndrome, and pure red cell aplasia in immunocompromised individuals.

In patients receiving immunosuppressive therapy, temporary reduction in the dose of therapy, confers sufficient immunity for the body to recover. One infection with parvovirus B19 confers lifelong immunity thereafter.

In HIV-infected individuals, symptomatic treatment along with highly active antiretroviral therapy is recommended.

10.8.2 Fetal Therapy

Delivery is the keystone in pregnancies more than 32–34 weeks gestation with fetus showing features of hydrops [59]. Nevertheless, before 32 weeks, delay in delivery with fetal therapy may still be more appropriate. During conservative management, weekly ultrasound & Doppler studies for measurement of peak systolic volume in middle cerebral artery(MCA-PSV) need to be done. If any feature of hydrops or fetal anemia appears, intrauterine transfusion has to be considered under expertise of fetal medicine consultant, considering that hydrops is a sign of cardiac decomposition that can lead to fetal death. Adverse effects to the fetus occur mostly, remote from term. Hydrops resolves spontaneously in about one-third of cases. Hydropic pregnancies managed expectantly stand a greater risk of fetal demise than those which were managed with active treatment. Research data suggests that intrauterine transfusion can bring about a significant reduction in mortality. de Jong et al suggested weekly monitoring of fetal anemia by MCA-PSV and to plan intrauterine transfusion if MCA-PCV is more than 1.5 MoM (multiples of median) [57]. Long-term studies on this protocol are still not available and need further research. Fetal hydrops usually resolves within 2 weeks after adequate intrauterine transfusions. In a study of intrauterine transfusions in the Netherlands, between 1997 and 2005, 25 transfusions were done in 24 hydropic fetuses. Thirty percent of the fetuses that underwent transfusion died. Among the survivors, about 30% had delayed psychomotor development at long-term follow-up [59].

Fetal complications due to parvovirus B19 generally resolve as the fetus generates its own immune response when compared with other causes of anemia and hydrops. Fetuses who are anemic but in the recovery phase can be managed conservatively if other signs of fetal well-being are present.

10.9 Prevention and Control

- Good hygienic practices which include frequent hand washing, bathing, using a handkerchief while sneezing/ coughing, not sharing drinks and utensils help to reduce contact with fomites and spread of B19 through respiratory secretions, fomites or aerosols.
- Standard infection control practices are recommended to reduce transmission of the B19 virus to healthcare workers from patients with aplastic crisis and patients having chronic B19 infection such as immunocompromised individuals.

10.10 Advances in Vaccine Development

At present, there is no vaccine against human parvovirus. Research in vaccine development against Parvovirus B19 has till now been directed towards development of a therapeutic approach to the disease. The main hurdle faced during development of such a vaccine is the unavailability of viral antigens. The viral replication is almost over by the time the clinical symptoms appear. The isolation of the virus through cell line models or animal model is not possible. Therefore, for expression of large amounts of recombinant genetic material, two different systems are under research, the Bacculovirus insect-based expression system and the Prokaryotic expression system.

Baculovirus Expression System In this system, the virus has been adapted to serve as an expression vector to generate recombinant proteins and multiprotein complexes including virus-like proteins (VLP) in insect cells. This system was utilized to produce two viral structural proteins VP1 and VP2 of the Parvovirus B19. These proteins have been found to produce

disease mimicking humoral response and also initiate neutralizing antibody production [67]. The MEDImmune vaccine MEDI-491 has been developed with VP1 and VP2 protein. Initially, aluminium hydroxide used as an adjunct in this vaccine was shown to produce a low antibody production. Thereafter, an emulsion-based adjunct MF 59 C was found to produce a moderately potent and well-tolerated immune response [68]. As these recombinant proteins are very similar to the mammalian proteins, therefore they have the disadvantage of generating adverse reactions similar to the disease process itself [72, 73].

Second Generation Vaccines Learning from the previous experience, vaccine candidate was produced by co-expression of VP2 and wild type or phospholipase negative VP1 structural protein in a fixed ratio from a single plasmid in the prokaryote *Saccharomysis cerevisiae* [74]. Sickle cell mice model with infection of the respiratory tract were used for this vaccine trial. Promising results have been demonstrated in sicle cell mice with VLP vaccine, encouraging further research in development of the vaccine [75].

10.11 Conclusion

Parvovirus B19 infection is an important differential diagnosis in a case of non-immune hydrops. Approximately 30–50% of pregnant women do not have immunity for parvovirus and vertical transmission is seen in about 30% of infected mothers. Even though the maternal symptoms are transient, the inflammation and red blood precursor cell destruction result in complications such as placentitis, fetal hepatitis, myocarditis, hypoalbuminemia, severe anemia, cardiac failure, hydrops, and death. Ultrasonography and Doppler are tools used for fetal surveillance to detect fetal anemia and cardiac failure. Timely intrauterine red blood cell transfusion can be life saving for the fetus. Studies have documented that children who survive intrauterine transfusion for B19 infection have a good neuro-developmental prognosis. Serology and PCR form the mainstay of diagnosis. A relationship between the severity of the disease and viral load has been postulated, which may contribute to the prediction of short and long-term fetal outcomes.

Key Points

- Parvovirus is a single-stranded DNA virus that is transmitted by respiratory secretions and hand-to-mouth contact. It is the commonest infectious cause for non-immune hydrops fetalis.
- Fetal infection is asymptomatic in 50% of cases and fetal loss occurs in fewer than 10% of primary maternal infections. Fetal death occurs mostly in the early second trimester, before the 20th week of gestation.
- Serology and PCR form the mainstay of diagnosis.
- Fetal surveillance is done to detect signs of fetal anemia and cardiac failure using ultrasound and Doppler.
- Treatment with intrauterine red blood cell transfusion can be life saving for the fetus.
- Development of vaccines may be a turning point in the reduction of fetal affection.

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Viral Hemorrhagic Fever

11

Edwina Goh and Ruchira Singh

11.1 Introduction

Viral hemorrhagic fever (VHF) describes a severe multisystem illness that can progress rapidly from acute febrile syndromes leading to profound hemorrhagic manifestations and causing increased mortality [1]. It comprises a group of diseases caused by four different families of RNA viruses:

- Arenaviridae: Lassa fever, Junin and Machupo
- Bunyaviridae: Crimean-Congo hemorrhagic fever, Rift Valley Fever, Hantaan hemorrhagic fevers
- Filoviridae: Ebola and Marburg
- Flaviviridae: yellow fever, dengue, Omsk hemorrhagic fever, Kyasanur forest disease

These viruses are termed as zoonotic, i.e., the main reservoirs for viruses causing hemorrhagic fever in humans are rodents and arthropods.

The four viral hemorrhagic fevers that would be discussed in this chapter are *Ebola Virus, Marburg, Lassa fever and Yellow Fever.*

These enveloped RNA viruses are limited geographically to the areas in which their hosts species reside. Hemorrhagic fever outbreaks have occurred sporadically worldwide, of which some have been declared as public health emergencies [2], and the main concern is that no specific treatment is available thus far, with a few exceptions.

Transmission of the virus to humans is through contact with rodent-infected fluids such as saliva, urine, and fecal matter. Arthropod vectors transmit the virus to humans via a bite. Some of these viruses can be transmitted through close human contact, or through contamination of their body fluids or contaminated objects [3].

11.2 Pathophysiology

Viral hemorrhagic fever present as severe febrile illnesses with vascular dysregulation and vascular damage [4]. This is manifested early in the course of the disease as mild hypotension, postural hypotension, flushing of the skin, and vasodilation of the conjunctivae. It gradually progresses to vascular damage with capillary leakage which is responsible for non-dependent edema and serous effusions in pleural and peritoneal compartments. Hemorrhages are prominent in Crimean-Congo hemorrhagic fever, but also observed as a presenting feature of Lassa fever and are associated with poor morbidity. Hemorrhages are associated with thrombocytopenia or severe platelet dysfunction and are seldom life-threatening. Shock is a characteristic of the terminal phase of viral hemorrhagic fever due

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to vascular dysregulation and vascular damage-causing capillary leakage.

Pregnant women are not immune from the effects of infection with viral hemorrhagic fevers, and in fact, they may face more severe consequences of disease, with increased morbidity, mortality, and associated increased risk of fetal loss or congenital harms to the developing baby [5].

Pregnant women represent an immunologically unique population as their immune system is influenced by signals originating from the placenta. The immune system is customized to prevent fetal/ paternal antigen rejection. The physiological changes help to sustain and protect the pregnancy [6]. The various infecting pathogens have varying transmission abilities and specific fetal affection during different stages of pregnancy: in utero infection or subsequent neonatal and infant development [7].

11.3 Etiological Agents

11.3.1 Filoviruses

Marburgvirus and Ebolavirus are filoviruses, belonging to the virus family called Filoviridae. Filoviruses can cause severe hemorrhagic fever in humans and non-human primates.

Filoviruses are zoonotic i.e. transmitting to humans from animals other than humans. The reservoir for Marburgvirus and Ebolavirus were first detected in fruits bats in Africa, though other reservoirs may exist. Marburgvirus has been isolated in several occasions from Rosettus bats in Uganda.

Marburg disease outbreaks occur once every 5 years since 1975 in the Democratic Republic of Congo, Angola, Uganda, Kenya, and South Africa. Some of these outbreaks involved gold and lead mines workers [8].

Outbreaks of Ebola Haemorrhagic Fever have been seen in the Democratic Republic of Congo, Sudan, Uganda, Gabon, and Ivory Coast. Six different species of Ebola virus have been identified: Zaire, Sudan, Taï Forest (formerly *Côte d'Ivoire ebolavirus*), Bundibugyo, Reston and Bombali. Of these, only four (Ebola, Sudan, Taï Forest, and Bundibugyo viruses) are known to cause disease in people.

The only natural host of Ebola virus is the Fruit bats of the Pteropodidae family. Transmission is through a close contract with the blood, secretions, organs, or other bodily fluids of infected animals such as fruit bats, chimpanzees, gorillas, forest antelope monkeys, or porcupines found ill or dead in the rainforest.

It is generally not possible to trace the pathway of transmission from natural reservoir to human host during an outbreak or isolated case among humans. But once humans are infected, the route of transmission is via personal contact between an infected individual or their body fluids, and another person. It was noted that during recorded outbreaks of hemorrhagic fever due to Filovirus infection, that caregivers and individuals who worked closely with infected individuals were at high risk of getting infected. Nosocomial (hospital-acquired) transmission by contact with infected body fluids—via reuse of unsterilized instruments, or other contaminated medical equipment—is an important factor for transmission of the disease. Filovirus infections in humans decline when close contact between uninfected and infected persons is minimized. Airborne spread among humans has not been clearly demonstrated, though there have been some displays in laboratory via small-particle aerosols.

11.3.2 Flaviviridae

The flaviviridae are positive, single-stranded, enveloped RNA viruses found in arthropods (primarily ticks and mosquitoes); they can occasionally infect humans. Yellow fever virus, Zika virus, dengue virus, Japanese Encephalitis, and West Nile virus belong to the family of Flaviviridae .

Transmission to humans in urban areas is via the bite of an infected Aedes aegypti mosquito [5]. Yellow fever has caused widespread morbidity and mortality throughout the world.

Yellow Fever was the original hemorrhagic fever described and Yellow fever virus was the first recognized etiologic agent of Viral hemorrhagic syndrome. The most notorious flavivirus that causes hemorrhagic fever currently is the dengue virus.

11.3.3 Arenaviridae

The arenaviridae viruses are generally associated with rodent-transmitted diseases in humans. Their genetic material is composed of only RNA. New viral particles called virions are created by budding from the surface of their hosts' cells. Lassa fever is part of the arenaviridae family.

Lassa virus causes lifelong infection in multimammate rats (rodents of Mastomys species) that are distributed over large parts of Africa. The virus causes no apparent disease in the natural host; however, viral replication in rodents leads to infection of various organs and subsequent shedding via urine and feces. The peak incidence happens between January and April, the later months of the rainy season. The disease affects individuals of all ages and both sexes. Table 11.1 summarizes the various diseases associated with the different viruses with their endemicity and incubation periods.

11.4 Ebola Virus Disease (EVD) and Marburg Virus Disease (MVD)

11.4.1 Epidemiology

The first filovirus was recognized in 1967 in Germany and Yugoslavia when a number of laboratory workers who were handling tissues from green monkeys imported from Uganda, developed a hemorrhagic fever. The virus was named after Marburg, Germany, the site of one of the outbreaks [10]. After this initial outbreak, the virus disappeared. Outbreaks and sporadic cases have been reported in Africa since.

The largest and most complex Ebola outbreak since its discovery happened in West Africa in 2014–2016 [11]. The World Health Organisation (WHO) made two health emergency declarations within a span of 5 years (in August 2014 and July 2019) from this Ebola outbreak. The 2014–2015 EVD epidemic in West Africa had a case fatality rate between 37 and 74%, and it was observed that majority of the affected patients were of reproductive age, 15–44 years [12]. Due to the paucity of data on attack rates in pregnancy, maternal and neonatal outcomes, it is difficult to comment on the burden of EVD in pregnancy [13].

The incubation period for EVD is typically between 3 and 21 days. Transmission is only rec-

Table 11.1 Summary of etiology of viral hemorrhagic fevers [8, 9]

Virus	Disease	Endemic regions	Vector	Incubation period	Associated mortality
Arenaviridae					
Lassa virus	Lassa hemorrhagic fever	West Africa	Rodents	5–16 days	±15%
Filoviridae					
Ebola virus	Ebola hemorrhagic fever	Africa	Fruit bats/African Green Monkey	2–16 days	25–90%
Marburg virus(Filovirus)	Marburg hemorrhagic fever	Africa	Fruit bats/African Green Monkey	2–16 days	25–90%
Flaviviridae					
Yellow fever virus	Yellow fever	Tropical Africa and South America	Mosquito	3–6 days	20%

Source: Paessler, S., & Walker, D. H. (2013). Pathogenesis of the Viral Haemorrhagic Fevers. Annual review of Pathology: Mechanisms of Disease, 8(1), 411–440

ognized from symptomatic patients. Humans are infectious once fever and other non-specific symptoms ensue. Severe gastrointestinal symptoms become apparent after the onset of generalized manifestations. Cytokine dysregulation causes progression to multiorgan failure and hemorrhagic shock commonly occurs.

11.4.2 Pathogenesis of Ebola and Marburg Virus Disease in Pregnancy

11.4.2.1 Transmission

Human-to-human transmission of Marburg virus disease (MVD) and EVD spreads via direct contact (broken skin or mucous membranes) with blood, secretions, or other bodily fluids of infected people, or contaminated surfaces and materials (e.g., bedding, clothing).

Nosocomial infection amongst healthcare workers happens while treating patients with suspected or confirmed Ebola or MVD. This happens when infection control precautions are not strictly practiced. Direct contact with the body of the deceased during burial ceremonies has also contributed to the transmission of these viral hemorrhagic fevers. Sexual transmission of the Marburg virus has been documented to be present in semen up to 7 weeks after clinical recovery. Sexual transmission may also occur with Ebola.

The interface between EVD and pregnancy was partially appreciated in recent outbreaks. Due to the cultural practices and caregiver roles, women were more likely to contract Ebola infection compared with men. Our understanding of EVD in pregnancy however remains limited, due to the lack of robust surveillance systems monitoring pregnancy statuses and outcomes for both mothers and their newborns [14].

Filovirus likely passes through the placenta and into fetal tissue via hematogenous spread as high viral titers of viruses causing hemorrhagic fever have been detected in placental tissues during acute EVD and recovery of the pregnant woman. Vertical transmission from maternal to fetus can occur during an acute infection leading to intrauterine fetal death, stillbirth, or neonatal death.

In the event of Ebola infection during pregnancy, the woman post recovery may continue to carry the virus in breastmilk, bodily fluids, or tissues; therefore poses the risk of transmission of the virus to the newborn via breast milk and others via body fluids. However, women who become pregnant after surviving Ebola disease are not at risk of carrying the virus [15].

11.4.3 Diagnosis

Pregnant women should ideally be tested rapidly to ensure appropriate treatment. Diagnosis is based on clinical presentation and travel or exposure history and confirmed with laboratory testing.

Diagnostic methods available:

- Antibody-capture enzyme-linked immunosorbent assay (ELISA)
- Antigen-capture detection tests
- Serum neutralization test
- Reverse transcriptase-polymerase chain reaction (RT-PCR) assay
- Electron microscopy
- Virus isolation by cell culture

Diagnostic methods recommended by WHO include:

- Automated or semi-automated nucleic acid amplification tests (NAAT): It is the gold standard for routine diagnostic evaluation. However, due to low sensitivity of NAAT during the first 72 h of symptoms, mandates that all negative tests during this period be repeated.
- Rapid antigen detection tests: recommended for screening purposes as part of surveillance activities. These tests are not available readily.

It is recommended that all reactive tests should be confirmed with NAAT.

Preferred specimens for diagnosis include:

- Whole blood collected in ethylenediaminetetraacetic acid (EDTA) from live patients with characteristic symptoms.
- When blood collection is not feasible or in postmortem cases, oral fluid specimens should be stored in universal transport medium.

Samples collected from patients are extreme biohazard risk; all biological specimens should be packaged using the triple packaging system for transportation nationally and internationally [15]. Appropriate precautions are to be followed when testing on non-inactivated samples in the laboratories with highest biological containment conditions.

11.4.4 Clinical Presentation and Disease Course

There is a significant overlap of clinical presentation and disease course for both EVD and MVD and both and can be managed similarly (Fig. 11.1). Both Marburg and Ebola are labeled as hemorrhagic fevers but need to be conceptualized as a gastrointestinal disease [16].

Filovirus infections for the gastrointestinal tract can cause life-threatening dehydration from severe diarrhea and vomiting. This can cause rapid intravascular volume depletion accompanied by electrolyte and acid-base disorders [16]. There is a high mortality rate when there is hypoperfusion, shock, and multiorgan failure. Elevated lactate signifies and this may present as a bacterial sepsis picture [16]. Symptoms improve in approximately 40% of patients by day 10 of ill-

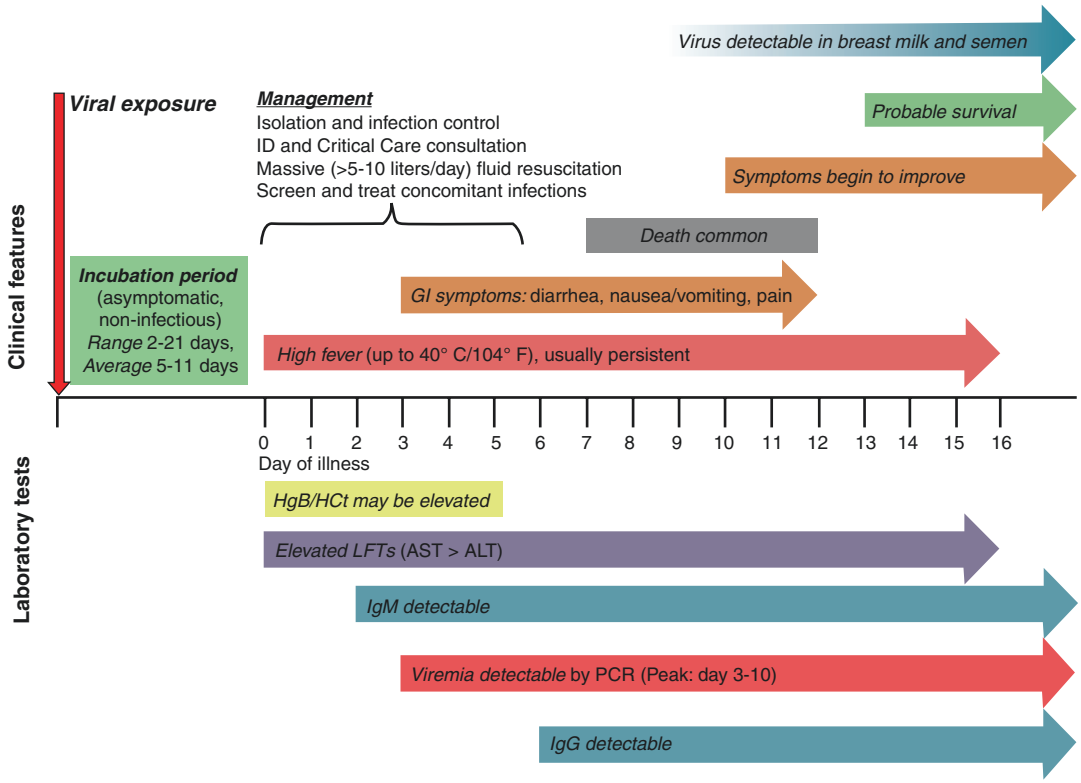

Fig. 11.1 Clinical presentation and disease course of Filovirus infection [17]. Adapted from: Bebell, L.M., & Riley, L. E. (2015) Ebola Virus Disease and Marburg Disease in Pregnancy: A review and Management Considerations for Filovirus Infection. Obstetrics & Gynaecology, 125(6), 1293–1298

ness and most patients alive at 2 weeks ultimately survive [18].

A person infected with Ebola is not contagious until they develop symptoms. Non-specific early symptoms mimic other common infections such as malaria, typhoid, or influenza, making clinical diagnosis difficult.

Illness caused by MVD begins with sudden onset high fever, severe headache, and severe malaise with muscle aches and pain being commonly present. Severe watery diarrhea with associated abdominal pain and cramping, nausea, and vomiting can begin on day 3 of contracting the virus and persist for a week. The classic description of patients at this phase has been described as showing "ghost-like" drawn features, deep-set eyes, expressionless faces, and extreme lethargy.

Severe hemorrhagic manifestations start between day 5 and 7. Fatal cases usually have some form of bleeding, often from multiple areas. Hematemesis, melaena, nose bleeds, gum bleed, or vaginal bleeding is reported. Spontaneous bleeding at venepuncture sites can be particularly troublesome. Vaginal and uterine bleeding is associated with a 93% mortality within 10 days of illness onset [19].

Patients with suspected EVD or MVD may present with multiple infections including other viral pathogens, malaria parasites, and bacteremia. During the severe phase of the disease, patients may have persistent high-grade fevers. In such cases, involvement of the central nervous system may result in confusion, irritability, and aggression. Death occurs most often between day 8 and 9 from the onset of symptoms in fatal cases. this is generally preceded by severe blood loss and shock.

The case definition during an Ebola or Marburg outbreak [19]:

- Sudden onset high fever and having had contact with
  - A suspected, probable, or confirmed Ebola or Marburg case
  - A dead or sick animal (for Ebola)
  - A mine (for Marburg) Or
- Sudden onset high fever and at least three of the following symptoms
  - Headaches
  - Anorexia/loss of appetite
  - Stomach pain
  - Vomiting
  - Diarrhea
  - Lethargy
  - Aching muscles or joints
  - Difficulty swallowing difficulty breathing
  - Hiccups; Or
- Any person with inexplicable bleeding; Or
- Any sudden, inexplicable death

11.4.5 Management

11.4.5.1 Supportive Care

The mainstay of Filovirus infection management is early, aggressive rehydration therapy. Initial management with massive fluid resuscitation is guided by maternal vital signs. Patients usually require 5–10 L or more of intravenous or oral fluid daily to maintain circulating blood volume in the setting of ongoing gastrointestinal loss [20]. Potassium levels, acid-base disturbances, and other electrolyte abnormalities need to be monitored and corrected early to prevent life-threatening arrhythmias and metabolic complications [20]. Causes of death remain poorly understood but are likely due (in combination or alone) to a process of septic shock and multi-organ failure [20].

Clear history taking of fetal movements, bleeding and rupture of membranes should be recorded. Pregnant women should be carefully counseled on the prognosis of ongoing pregnancy. The vast majority of fetuses die prior to delivery. In the rare event of a confirmed ongoing pregnancy, the woman should be sensitively told of the likely poor outcome for baby. The option of termination of pregnancy should be considered and discussed with the woman at an appropriate time [21].

Until recent advances in therapeutic care, nearly all cases of EVD in pregnant women resulted in miscarriage, stillbirth, or neonatal death [13]. New case reports suggest good outcomes for mother and babies; however, ongoing studies will be needed to determine neonatal sur-

vival rates and long-term sequalae as treatment options and supportive care improve for EVD in pregnancy [5].

11.4.5.2 Delivery

Care of the pregnant female should be carried out in designated Ebola Treatment Centre with facilities for delivery and management of pregnancy complications in women with ongoing or recovered EVD. The protocol is to reduce vaginal examinations to minimum and avoid artificial rupture of membranes [22]. Fetal monitoring is not mandatory and spontaneous vaginal delivery should be allowed. Current evidence does not provide a strong rationale for cesarean delivery because transmission to the fetus is definite and fetal or neonatal survival is unlikely [17].

The role of obstetric interventions such as fetal monitoring, induction of labor, cesarean delivery, or pregnancy termination is not clear when a woman is at greatest risk of vascular collapse due to the disease per se. Pregnant women with decompensated Ebola or Marburg disease may not survive surgical delivery [17]. Induction of labor is unlikely to benefit the baby and the effect on maternal morbidity is uncertain. At present, expectant management of labor seems the most appropriate strategy.

Placenta and any pregnancy-related tissue or fluids must be disposed of following Ebola-specific IPC protocol for potentially infectious material [22].

The newborn is assumed EVD-positive and care provided should be in accordance with full PPE and IPC protocols. Rapid RT-PCR Ebola testing of the newborn should be prioritized [22].

11.4.5.3 Breastfeeding

WHO has a clear guideline for the management of pregnancy and breastfeeding women in the context of Ebola virus disease [22]. In the event of suspected or confirmed acute EVD in a lactating woman or in a breastfeeding child, the recommendation is to stop breastfeeding. The child should be separated from the mother and provided breastmilk substitute as needed. The child should also be monitored for 21 days.

If both the lactating woman and her breastfeeding child are diagnosed with EVD, ideally breastfeeding should be discontinued and the two should be separated. However, if the child is under 6 months of age and does not have safe and appropriate breastmilk substitutes, or the child cannot be adequately cared for, then the option to not separate and continue breastfeeding can be considered.

A woman who has recovered from EVD, cleared viremia, and wants to continue breastfeeding should undergo two consecutive negative RT-PCR breastmilk tests for EBOV, 24 h apart before initiation of breastfeeding. Breastmilk substitutes should be given to the child in this duration.

11.4.6 Vaccine

Currently, no licensed vaccines are available against MVD though there have been trials in primates [23].

rVSV-ZEBOV Vaccine The most widely known and used vaccine to date. It is a live-attenuated vaccine using recombinant vesicular stomatitis virus to encode the glycoprotein of the Zaire strain. Limited data is available regarding the safety of the vaccine in pregnancy. This is because, pregnancy was an exclusion criteria in vaccine trials conducted during the West African outbreak from 2014 to 2016 and the Democratic Republic of Congo outbreak in 2018–2019 [24].

WHO Strategic Advisory Group of Experts (SAGE) in 2019, published an interim report on the rVSV-ZEBOV-GP vaccine advising that this vaccine has been evaluated and deemed compliant with WHO standards of quality, safety, and efficacy It further clarifies that the vaccine's use in research may include pregnant and lactating women within the framework of the clinical trials limited to the EVD outbreaks in affected areas.

11.4.7 Prevention

An important aspect of EVD treatment is the following up of any potential contacts of an infected person. For preventive strategies to be formulated, rigorous contact tracing and case finding has to be done to prevent increase the spread of the disease.

11.5 Yellow Fever

11.5.1 Epidemiology

Two yellow fever outbreaks in the Dominican Republic of Congo (DRC) in 2016, which spread across countries triggered a response by WHO and alongside a few organizations and numerous countries, developed the Eliminate Yellow Fever Epidemics (EYE) Strategy which aims to control the spread of yellow fever [25].

Many countries in Africa and Central and South America are either endemic for or have regions that are endemic for yellow fever. A modeling study based on African data sources estimated the burden of yellow fever during 2013 was 84,000–170,000 severe cases and 29,000–60,000 deaths [25]. A severe and prolonged rainy season is associated with an abundance of vectors, which may be linked to enhanced yellow fever virus circulation [26].

11.5.2 Transmission

Yellow Fever (YF) is transmitted by the bite of Aedes aegypti mosquitoes in tropical Africa and South America. Zoonotic cycles involving sylvatic mosquitoes (vectors) and non-human primates (hosts) occur in tropical forests and on the edge of the African savanna. Humans exposed to these mosquitoes can become infected and be carriers. Yellow fever virus-infected carriers can bring the virus into an urban area, where abundant Aedes aegypti mosquitoes then transmit the virus from person to person, which leads to an epidemic. Yellow fever virus is also maintained vertically in mosquito populations by transovarian transmission.

Occasionally travelers who visit yellow fever endemic countries bring the disease to countries free from yellow fever.

There is no report of sexual transmission of yellow fever virus.

11.5.3 Pathogenesis

Apoptosis and necrosis of hepatocytes and Kupffer cells happen in the liver of humans with fatal yellow fever. This affects mainly the midzone of the lobule, sparing the cells adjacent to the portal triad and the terminal hepatic vein. Passler et al in their study have shown mitosis in the hepatic biopsy specimens of patients who die on day 8 of illness suggesting that regeneration and resolution occur in survivors [8].

Yellow fever infection leads to renal swelling and microvesicular steatosis of tubular epithelial cells and minimal inflammatory responses. Decreased renal perfusion associated with hypotensive shock and virus-induced injury to infected tubular epithelial cells can lead to anuria. Nearly all patients who develop anuria die [8].

The pathogenesis of the hemorrhagic manifestations is better understood in yellow fever than in other VHFs. The principal cause of bleeding is decreased hepatic synthesis of clotting factors.

There are limited publications or reviews regarding YF infection impact in pregnancy and associated maternal, fetal, or neonatal outcomes. However, similar to other flaviviruses such as the Zika virus and dengue virus, case reports suggest that the YF virus can be transmitted vertically from an infected pregnant woman to her fetus [27].

11.5.4 Clinical Presentation and Disease Course

Approximately one-third of people who are infected with yellow fever virus become ill [8]. The incubation period is 3–6 days and the onset

of fever and headache is abrupt. Of these patients, approximately 80% recover without suffering classic yellow fever. The remaining 20% pass through three clinical stages [8]:

- Infection
- Remission
- Intoxication

Infection During the 3–4 day period of infection, viremia is detected, peaks, and then falls rapidly. Signs and symptoms include pyrexia ≥39 °C, myalgia, nausea, vomiting, bradycardia that is relative to the level of fever and conjunctival congestion. Marked albuminuria may be present in severe cases.

Remission A period of remission is characterized by improvement of the symptoms for up to 2 days.

Intoxication The period of intoxication starts 3–6 days after the onset of illness. The period of viremia phases out, and the production of IgM-neutralizing antibodies predominate. This phase is characterized by re-appearance of fever, nausea, and vomiting and the patient develops hemorrhages, jaundice and progresses to renal failure. The serum bilirubin level rises and peaks at around day 6 of the onset of illness. A rapid fall is observed after day 7. Hemorrhagic manifestations include haematemesis, haematuria, epistaxis; bleeding gums; menometrorrhagia; and petechiae and ecchymoses of skin, mucous membranes, and serosal surfaces. In severe cases, involvement of the kidneys is seen with rise in albuminuria on days 3 and 4, approaching nephrotic syndrome levels. Development of severe oliguria or anuria, elevated serum urea, and creatinine concentrations are signs suggestive of terminal illness. These patients progress to develop agitation, delirium, seizures, stupor, and coma. The terminal stage is characterized by hypotensive shock, hemorrhages, and metabolic acidosis. The case-fatality rate for classic yellow fever is 20%. Death usually occurs between days 6 and 8 of illness [8].

11.5.5 Diagnosis

The diagnosis of a yellow fever infection is made by use of highly sensitive and specific tests: RT-PCR and detection of the NS1 antigen. RT-PCR can also be performed on serum, urine, and saliva samples. IgM ELISA test can be performed for the detection of antibodies to yellow fever virus [26]. Serology assays have limitations due to the possibility of cross-reactivity with other flaviviruses.

11.5.6 Treatment

Early and pro-active supportive treatment in hospitals improves survival rates. There is currently no specific anti-viral drug for yellow fever but supportive care to treat dehydration, liver and kidney failure, and fever improves outcomes. Associated bacterial infections should be treated with antibiotics.

11.5.7 Prevention

11.5.7.1 Vaccine

It is a live attenuated vaccine. YF virus vaccine is to be used in pregnancy with precautions as the virus is known to cross the placenta barrier. The vaccine is recommended for use only in pregnant and lactating women only in case of an epidemic or if the pregnant woman is traveling to a high-risk area such as an outbreak zone [28]. WHO also recommends the same considering that YF exposure and infection outweigh the risks of vaccination.

WHO approved Yellow fever vaccines provide protection against infection starting 10 days following the administration of the vaccine. The certificate of vaccination against yellow fever is valid for life for the person vaccinated, beginning 10 days after the date of vaccination [29].

11.5.7.2 Vector Control

The infection can be prevented by eliminating potential mosquito breeding sites, including the

application of larvicides to water storage containers and other places where standing water collects.

11.5.7.3 Epidemic Preparedness and Response

Prompt detection of yellow fever and rapid response through emergency vaccination campaigns are essential for controlling outbreaks. However, underreporting is a concern—the true number of cases is estimated to be 10–250 times what is now being reported.

The Eliminate Yellow Fever Epidemics (EYE) Strategy was developed to respond to the increased threat of yellow fever urban outbreaks with international spread. The objective of EYE is to ensure that more than one billion people are protected against YF through vaccination by 2026 [25].

11.6 Lassa Fever

11.6.1 Epidemiology

Lassa fever (LF) is endemic to West Africa. Despite the advances in technology, pregnant women reportedly have a poorer prognosis with maternal case fatality rates ranging from 7% in early pregnancy to 30% in late pregnancy. The risk of mortality due to Lassa fever is significantly higher in pregnant women as compared to non-pregnant women and in the third trimester more than the first two trimesters [5]. Evacuation of the uterus can significantly improve the mother's chance of survival [30]. Neonatal and fetal losses are reportedly high at 75 and 92%, respectively, with most fetal losses occurring in early pregnancy [30].

There are not many studies of pregnant women with LF. The infection presents with non-specific early signs and symptoms of the disease, sometimes overlapping with other common infectious diseases in the region, such as malaria, influenza, and bacterial sepsis, resulting in large variability of capturing its prevalence [31].

11.6.2 Transmission

Lassa virus is transmitted to humans via ingestion or inhalation. *Mastomys* rodents shed the virus in urine and droppings. Any direct contact with these materials, either through touching soiled objects, or eating contaminated food, or exposure to open cuts or sores can lead to infection. *Mastomys* rodents live in and around human habitations. They survive on leftover human food items or improperly stored food. Direct contact transmission of rodents with human is common due to such close existence. *Mastomys* rodents are sometimes consumed as a food source and infection may occur when rodents are caught and prepared. Aerosol or airborne transmission may also occur during cleaning activities, such as sweeping. Tiny particles in the air contaminated with infected rodent excretions when inhaled by humans can also result in infection.

Person-to-person transmission may also occur after exposure to virus in the blood, tissue, secretions, or excretions of a Lassa virus-infected individual. Casual contact (skin-to-skin contact without exchange of body fluids) however does not spread the Lassa virus. Nosocomial transmission happens where appropriate PPE is not available or not used or through contaminated medical equipment, such as reused needles.

The virus is excreted in semen for 3 months after infection; however, it is not known how frequently it may be transmitted through sexual intercourse.

11.6.3 Diagnosis

Clinical diagnosis can be difficult as the symptoms of Lassa fever can be non-specific and mimic those of other endemic infections, especially early in the illness. So, laboratory testing is needed to confirm the diagnosis.

Lassa fever is most often diagnosed by using:

- Enzyme-linked immunosorbent serologic assays (ELISA), which detect IgM and IgG antibodies as well as Lassa antigen

- Reverse transcription-polymerase chain reaction (RT-PCR) can be used in the early stage of disease. The virus can be cultured in 7–10 days, but this procedure should only be done in a high containment laboratory with good laboratory practices.
- Antigen detection tests
- Virus isolation by cell culture
- Immunohistochemistry, performed on formalin-fixed tissue specimens, can be used to make a post-mortem diagnosis.

Laboratory Findings

- Early lymphopenia
- Late neutrophilia
- Moderately depressed platelet count
- Abnormal platelet function

AST >150 and high viremia have a poor prognosis for the patient. Severe disease may be accompanied by albuminuria and haemoconcentration.

11.6.4 Clinical Presentation and Course of the Disease

The incubation period is 6–21 days. Signs and symptoms of Lassa fever typically develop within 1–3 weeks after the patient comes into contact with the virus. The classic sign of Lassa fever are swollen face and neck; however, this only occurs in about 10% of cases.

The clinical features of maternal Lassa are generally non-specific. The most common symptoms reported was that of nausea/ vomiting, headache, and fever [32]. Approximately 80% of patients present with mild symptoms which go undiagnosed. The mild symptoms include slight fever, weakness, general malaise,, and headache. In 20% of infected individuals, however, disease may progress to more serious symptoms including hemorrhages (in gums, eyes, or nose), respiratory distress, repeated vomiting, facial swelling, pain in the chest, back, and abdomen, and shock. Hearing loss, tremors, and encephalitis have also been reported. Death may occur within 2 weeks after symptom onset due to multi-organ failure.

Table 11.2 Classical clinical course of Lassa fever [33]

Stage	Symptoms
1 (days 1–3)	General weakness and malaise High fever >39 °C, constant with peaks of 40–41 °C
2 (days 4–7)	Sore throat (with white exudative patches) very common Headache; back, chest, side or abdominal pain Conjunctivitis Nausea and vomiting Diarrhea Productive cough Proteinuria Low blood pressure (systolic <100 mmHg) Anemia
3 (after 7 days)	Edema of the face and neck Convulsions Mucosal bleeding (mouth, nose, eyes) Internal bleeding Encephalopathy with confusion or disorientation
4 (after 14 days)	Coma Death

Source: Licking Lassa fever: a strategic review. London: Merlin, 2002

The clinical course of Lassa fever is discussed in Table 11.2.

Hemorrhage develops in approximately 20% of Lassa fever patients as compared to 50–60% of patients with Ebola. Patients with LF presents feeling fatigued and "feverish" for a few days, whereas significant illness in Ebola/Marburg begins more abruptly and evolves more rapidly [34]. The chief feature of this fatal illness is impaired or delayed cellular immunity leading to fulminant viremia [34, 35]. As the symptoms of Lassa fever are so varied and non-specific, clinical diagnosis is often difficult. Lassa fever is also associated with occasional epidemics, during which the case-fatality rate can reach 50% in hospitalized patients.

Approximately 15–20% of patients hospitalized for Lassa fever die from the illness. However, only 1% of all Lassa virus infections result in death. Case fatality rates are higher in pregnant women than non-pregnant individuals, especially later in gestation, with high rates of fetal or perinatal loss associated with

infection. Spontaneous abortion is a serious complication of infection with an estimated 95% mortality in fetuses of infected pregnant mothers. The condition of mothers improves rapidly after the evacuation of the uterus whether by spontaneous abortion or normal delivery.

The death rates for women in the third trimester of pregnancy are particularly high (80%) either dying themselves or losing their child.

Groups at higher risk of death from Lassa fever include [36]:

- Female gender
- Pregnancy, especially in the third trimester (threefold increase in risk of death)
- Elderly
- Children <18 years

The most common sequelae of Lassa fever is deafness, and this has no relationship to the severity of viral illness. Various degrees of deafness occur in approximately one-third of infections, and in many cases, hearing loss is permanent [37] During convalescence, transient alopecia and ataxia may occur.

11.6.5 Treatment

Ribavirin, the antiviral has been used in seven studies: two case reports, one case series and four cohort series. 73.94% of pregnant women survived while on ribavirin. There were however no data available to compare the survival rates among those who received ribavirin with those who did not receive ribavirin. Therefore, there is no conclusive evidence for the use of ribavirin for the management of Lassa fever in pregnancy [32].

Laboratory animals trials have rendered ribavirin technically contraindicated in pregnancy due to findings of teratogenicity and fetal loss; however, its use is still considered a life-saving measure given the extremely high maternal and fetal mortality.

The results of a retrospective cohort study reports, that for women with a live fetus at initial evaluation, the positive outcomes observed show contrasts with previous reports, which supports a conservative approach to obstetric management of Lassa fever in pregnancy [38].

11.6.6 Vaccine

At present, no licensed vaccine is available for use in humans against Lassa virus. However, a target product profile developed under the WHO blueprint that provides a set of preferred and minimal or critical characteristics for a Lassa virus vaccine that can be used preventatively in non-emergency contexts as well as in reactive, emergency settings which also include administration in pregnancy [9, 39].

11.7 Conclusion

VHFs vary from mild to severe infections, with case-fatality rates greater than 60% (e.g., filoviruses), to mostly asymptomatic infections, wherein a minority of infected persons develop a hemorrhagic fever (e.g., Yellow Fever virus). Table 11.3 gives an overview of all the important VHF. The pathophysiology of viral hemorrhagic fever in pregnancy is still very limited, leaving significant gaps in our understanding of how these diseases may specifically or differentially affect pregnant women and a developing fetus or neonate [5]. It is imperative that resources be dedicated to gaining a greater understanding of the pathogenesis of these diseases in pregnant women [13].

Table 11.3 Viral hemorrhagic fevers

	Ebola	Marburg	Lassa fever	Yellow fever
Virus Family	Filoviridae	Filoviridae	Arenaviridae	Flaviviridae
Reservoir (host)	Fruit bat	Fruit bat	Rodents	Humans/Monkeys
Transmission (vector)	Fruit bat	Fruit bat (Roesettusaegypticus)	None	Aedes aegypti mosquitoes
Incubation period (days)	3–21	3–21	5–16	3–6
Diagnosis	Acute phase: RT-PCR, virus isolation in cell culture, antigen detection or IgM by ELISA Convalescence phase: IgM and IgG antibodies by ELISA			
Treatment	Supportive treatment Associated bacterial or parasitic infections can be treated with antibiotics or anti-parasite drugs			
Vaccine	Limited evidence in pregnancy for rVSV-ZEBOV-GP vaccine	No license vaccine to date	No licensed vaccine to date	To be used with precaution in pregnancy

Key Points

1. Viral hemorrhagic fever (VHF) describes a severe multisystem illness that can progress rapidly from acute febrile syndromes leading to profound hemorrhagic manifestations and causing increased mortality.
2. Despite the name VHF, some do not develop hemorrhage. In some VHFs, the percentage of patients with bleeding is <50%, and in many patients with bleeding, the hemorrhage is not clinically significant.
3. Filovirus infection presents more like a gastrointestinal disease with diarrhea and vomiting symptoms.
4. Yellow Fever is transmitted by mosquitoes and bleeding is caused by decreased hepatic synthesis of clotting factors
5. Lassa Fever is transmitted by rats. Eighty percent of people who have Lassa Fever have no symptoms.
6. A high index of suspicion is warranted when travelers from West Africa present with a pyrexia of unknown origin, especially if symptoms appear up to 21 days after leaving the endemic area.
7. There are currently no specific antivirals for any of these VHFs. Antibiotics are used for the treatment of associated bacterial infections.
8. We are still a long way from having a vaccine that is safe for use in the prevention of pregnant women from acquiring these VHFs.

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12 Maternal Hepatitis: Important Considerations

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12.1 Introduction

Pregnancy is considered to be an immunosuppressed state. There occurs flare-up of many infections in pregnancy with viral hepatitis being one of the most common. Viral hepatitis is also considered to be one of the most common causes of jaundice in pregnancy among varied causes with hepatitis E being most common among all and most severe as well (Table 12.1). Hepatitis virus infects and replicate in human hepatocytes and cause a similar type of symptoms in the acute stage of infection. Infected hepatocytes are damaged by the host immune response itself leading to symptoms.

Jaundice in pregnancy is considered to be one of the major indirect causes of maternal mortality. The likely causes of maternal death are hepatic encephalopathy, acute hepatorenal failure, disseminated intravascular coagulation, post-partum hemorrhage, and gastric hemorrhage.

This chapter will be highlighting the causes of viral hepatitis, i.e., A, B, C, D, E, G, their transmission, obstetrical complications, preferable mode of delivery, immunization of baby to pre-

Table 12.1 Differential diagnosis of jaundice in pregnancy

Trimester of pregnancy	Liver disease induced by pregnancy	Pre-existing liver diseases that worsen during pregnancy	Liver diseases incidental to pregnancy
First	Hyperemesis gravidarum	Cholelithiasis Primary biliary cirrhosis Dubin–Johnson syndrome	Acute viral hepatitis Drug-induced hepatitis
Second and third	Intrahepatic cholestasis of pregnancy Pre-eclampsia and Eclampsia HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome Acute fatty liver of pregnancy Hepatic rupture	Wilson's disease Cirrhosis Budd–Chiari syndrome Autoimmune hepatitis Hepatic adenoma Hepatocellular carcinoma	Acute viral hepatitis Drug-induced hepatitis

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vent infections and breastfeeding, and the long-term maternal and fetal complications. Other rare causes of hepatitis are due to infections with herpes simplex virus, Epstein Barr virus, cytomegalovirus and influenza, auto-immune and drug induced.

12.2 Hepatitis A

12.2.1 Virology

Hepatitis A virus belongs to the family of Picornaviridae. It is a single-stranded, non-enveloped RNA virus with one known serotype and seven known genotypes worldwide.

12.2.2 Epidemiology

1.4 million new cases occur globally each year [1]. Its prevalence is directly related to the sanitary conditions of the region. Infection occurs more commonly in children and they become immune by adulthood in high endemic regions. Infection is seen among adults in low-endemic areas and more severe, so efforts should be made to prevent infection in these areas.

12.2.3 Pathogenesis and Transmission

Its route of transmission is fecal-oral route [2]. So, it is more commonly seen in developing countries with poor hygiene and sanitation facilities. Rarely, sexual, bloodborne and vertical transmission can also be seen. Vertical transmission is rare due to the formation of anti-HAV IgG antibodies that cross the placenta and protect the baby after delivery. The average incubation period is 30 days. Virus enters the bloodstream from the gut and subsequently enters the liver, infecting hepatocytes. Viral particles are then shed into the biliary system and in stools increasing further transmission. Viremia can be seen during this phase and can lead to small risk of perinatal transmission. HAV is not cytopathic to the liver directly.

12.2.4 Clinical Presentation and Detection

There occurs low-grade fever, nausea, vomiting, anorexia, jaundice, dark urine, pale stools, and tender hepatomegaly. These symptoms may last for 4–6 weeks.

Diagnosis is by detection of anti-HAV IgM antibodies.

12.2.5 Hepatitis A and Pregnancy

Pregnancy does not alter the course of the disease. Effect of HAV on pregnancy depends on the period of gestation. In the first trimester, although it has no teratogenic effect, can cause fetal liver injury [3]. There is an increased risk of placental abruption, premature rupture of membranes and preterm labor pains, but data is lacking [4]. Acute liver failure with hepatitis A is rarely seen [5].

12.2.6 Management

Management is supportive. Vaginal delivery is preferred and cesarean section is done as per the obstetric indications. Breastfeeding is not contraindicated.

Vaccine is safe in pregnancy and can be given and also immunoglobulins in case of contact with infected person. Immunoglobulin is known to be effective in preventing HAV in 80–90% of cases. The Centre for Disease Control and prevention (CDC) supports the use of vaccine in pregnancy if indicated [6]. Babies born to women with hepatitis A should be given immunoglobulin within 48 h, if mother has contracted infection within 2 weeks prior to or 1 week after delivery.

12.3 Hepatitis B

12.3.1 Virology

Hepatitis B virus belongs to the family of Hepadnavirus. It is an enveloped virus, partially double stranded with a circular DNA genome [7]. It has ten genotypes (A to J).

Hepatitis B antigen and antibody are grouped into three categories:

1. Surface antigen (HBsAg), its lipid envelope and antibody.
2. Core antigen (HBcAg), its inner nucleocapsid essential for virus packaging and antibody.
3. Precore antigen (HBeAg), related to infertility and antibody.

HBsAg can be detected in the serum from several weeks before the onset of symptoms after contracting the infection to months in cases of chronic infection. HBcAg cannot be detected in bloodstream, but its antibody can be detected. HBeAg if present is suggestive of acute infection and also dictates the severity of the same.

12.3.2 Epidemiology

It is known to affect 2 billion people worldwide with 360 million carriers who are at risk of developing chronic liver disease [8]. In developed countries, HBV infection is more common among those with multiple sexual partners and intravenous drug abusers. In developing countries, which are areas of a high prevalence of HBV infection, the main source of infection is MTCT. So, the prevention of perinatal transmission remains an important way to decrease the worldwide impact of HBV infection and its consequences.

12.3.3 Pathogenesis and Transmission

Its route of transmission is sexual, bloodborne, and vertical. MTCT accounts for almost 90% of global prevalence of the disease [9]. Among those infected in-utero or in early life, 90% will develop chronic infection [10]. Virus enters and propagates in hepatocytes and then viral particles are released back into the bloodstream, causing viremia. Immune system in majority of patients is able to clear the infection.

12.3.4 Clinical Presentation and Detection

Natural history of hepatitis B infection is variable. Only one-third of adults experience symptoms suggestive of acute hepatitis. The symptoms are malaise, anorexia, nausea, vomiting, fatigue, upper abdominal pain, and patients may have a tender enlarged liver. Minority, 0.1–0.2% will develop fulminant hepatic failure and is due to immune-mediated cell lysis of hepatocytes.

Chronic hepatitis B infection is defined as persistence of Hepatitis B surface antigen for more than 6 months after initial exposure to the virus and accounts for nearly 5% of all infected adults. Nearly, 15–40% of people with chronic HBV infection may develop cirrhosis, liver failure, and hepatocellular carcinoma.

The diagnosis is usually made by detection of HBsAg, HBeAg, and HBV DNA levels in maternal blood.

12.3.5 Hepatitis B and Pregnancy

In every pregnant woman, HBsAg screening is recommended in their first trimester or first visit. All HBsAg positive women should undergo contact tracing and screening should be done for partners and children. Also screening for HIV and HCV should be done in these cases. It is preventable by vaccination which is safe during pregnancy and is recommended in cases of exposure to HBV.

Acute HBV infection in pregnancy is associated with increased risk of hepatic flare. Immunological changes in pregnancy and postpartum period can lead to flare-up of liver disease and also decompensation. Increase in ALT of at

least 3–5 times above the reference range is seen [11]. Hepatic flare is more commonly associated with HBeAg positive status. There can also be an increased risk of transmission to fetus that increases with gestational age. In cases of acute infection, mother-to-child transmission risk is 10% in early and up to 60% in late gestation. It has no teratogenic effect but is associated with prematurity [12]. There occurs increased risk of preterm delivery and gestational diabetes mellitus [13, 14]. Acute liver failure has also been reported [15].

Patients should be monitored with liver function test and coagulation profile especially prothrombin time.

Chronic infection in absence of cirrhosis does not have any effect on pregnancy outcome. Chronic infection with liver cirrhosis can complicate in second trimester of pregnancy. There can be variceal bleed, liver failure, and even death. Obstetrical complications associated are abortion, placental abruption, preterm labor, fetal growth restriction, and stillbirth.

The most important factor responsible for causing perinatal transmission is maternal viral load [15]. Viral load of more than 10^9 IU/ml has been correlated with an increased risk of intrauterine transmission [16]. Those with high viral load of more than 200,000 IU/ml should be considered for antiviral therapy to decrease the risk of perinatal transmission from 28 to 30 weeks of gestation Fig. 12.1 [17]. Tenofovir is the preferred drug (300 mg/day) and can be continued for first 6 weeks postpartum. It is known to be associated with less incidence of drug resistance as compared to other antiviral drugs [18]. In pregnant women with no indications for continuing antiviral therapy and whose babies have received immunoprophylaxis, it can be stopped at birth. Other approved antiviral drugs are Lamuvidine (100 mg/day; FDA category C drug) and telbivudine(600 mg/day; FDA category B drug). Antiviral therapy can also be started in cases with acute liver failure and protracted severe hepatitis.

Second factor responsible for increased risk of MTCT is the status of HBeAg. HBeAg reactive HBV infection is associated with high-level HBV replication and such mothers have a 70–90% risk of transmitting hepatitis to the baby as compared to the risk of 10–40% in HBeAg negative mothers [17].

Invasive procedures should be avoided, including amniocentesis and internal fetal monitoring during labor in order to decrease the possibilities of MTCT. In patients with HBV viral load less than 7 log 10 copies/ml, invasive testing, i.e., amniocentesis can be recommended after discussing the risk of perinatal transmission with parents [19].

HIV co-infection does not increase the risk of MTCT in HBV infection due to use of antiretroviral therapy which also reduces HBV DNA levels [20].

12.3.6 Management

Treatment of acute hepatitis B infection during pregnancy is primarily supportive. Women already on treatment with tenofovir should continue the same during pregnancy. Patients who are HBeAg positive with high viral load as described above will benefit from use of antiviral therapy by decreasing the risk of perinatal transmission.

Mode of delivery is vaginal and operative delivery is as per obstetrical indications.

Infants born to HBsAg positive mothers should be given 100 IU of hepatitis B immunoglobulin (HBIG) within 12 h of birth and vaccine within 24 h. The schedule of vaccination is followed as per national guidelines given to all babies regardless of HBsAg status of the mother. This approach helps in decreasing the risk of infection in neonates from 90 to 5–10% [21]. In women positive for HBeAg, MTCT was found to be as low as 2%, when HBIG and vaccine birth doses were administered within a median time of 1.3 and 1.2 h, respectively [22]. So, immunoprophylaxis and use of antiviral therapy in third trimester of pregnancy can significantly reduce the rate of MTCT. Anti-HBs antibody and HBsAg levels should be measured in infants born to mothers with chronic hepatitis B, 3–12 months (usually at the age of 9 months) after completing the primary vac-

cine course [18]. This is due to transplacental transfer of maternal HBV markers, HBeAg, anti-HBe, and anti-HBc, which may remain in baby circulation for up to 9 months. WHO suggests annual testing of HBeAg, ALT levels, and HBV DNA levels in infants infected via perinatal route [23]. Breastfeeding is not contraindicated, unless in the presence of cracked or bleeding nipples.

All HBsAg positive mothers should be followed up post-partum for hepatitis flare, chronic liver disease, and hepatocellular carcinoma. They should be advised to follow up with gastroenterologist as well. In a retrospective study, it was found that nearly 47% of patients diagnosed with chronic HBV during pregnancy received HBV specialty care in the post-partum period and the aim should be to further increase the percentage [24].

12.4 Hepatitis C

12.4.1 Virology

Hepatitis C virus is an enveloped single-stranded RNA virus of the Flaviviridae family with 7 genotypes and 84 different subtypes [25]. Envelope proteins express hypervariable regions that are responsible for causing high rates of mutation. This is one of the reasons that account for high propensity of HCV to cause chronic infection.

12.4.2 Epidemiology

It affects more than 170 million people worldwide and around 8% pregnant women [26].

12.4.3 Pathogenesis and Transmission

The major mode of transmission is bloodborne, sexual, or vertical. Mother-to-child transmission is 4–7% per pregnancy among those with detectable viremia. High HCV viral loads >100,000 copies/ml or co-infection with HIV is associated with an increased risk of MTCT [27]. Anti-HCV should be done in pregnant women at high risk of infection. In areas with a prevalence of HCV infection more than 0.03%, routine screening is recommended as in the USA [28, 29]. Universal screening is better than risk factor-based screening strategies, but the Society for Maternal-Fetal Medicine (SMFM) and the ACOG have not advocated for universal screening for pregnant women, as no effective intervention during pregnancy is identified that can modify the mother to child transmission of HCV.

12.4.4 Clinical Presentation and Detection

Acute HCV occurs during the first 6 months of exposure and if not cleared, progresses to chronic hepatitis. The signs and symptoms are similar to acute hepatitis A and B. Rate of spontaneous clearance of HCV infection is around 20–25%.

Chronic hepatitis C forms the major cause of cirrhosis and hepatocellular carcinoma worldwide. Antiviral therapy can reduce chronicity and its complications, but are not recommended during pregnancy.

Definitive diagnosis is based on the presence of HCV-RNA. Presence of antibody is not a reliable way to confirm the diagnosis. Liver function test should be done along with platelet count and prothrombin time. HCV-positive women should also be tested for HIV, HBS, syphilis, gonorrhea, and chlamydia.

12.4.5 Hepatitis C and Pregnancy

Acute HCV have unknown effects on pregnancy outcome. Patients with chronic hepatitis C may undergo premature ovarian failure. Those who conceive are susceptible to abortions, gestational diabetes mellitus, pre-eclampsia, fetal growth restriction, preterm labor pains, and stillbirths [30]. There is a 20-fold increased risk of developing intrahepatic cholestasis of pregnancy [31]. Also,

cephalhematoma, intraventricular hemorrhage, and seizures are seen in a neonate born to HCV-infected mother. Infants born to HCV-infected women should be screened with anti-HCV at 12–18 months of age. Usually, babies do well with the rare occurrence of severe hepatitis in them.

HCV RNA levels are seen to increase all throughout the pregnancy followed by drop in the post-partum period. These effects are likely due to the immunosuppressive effects of pregnancy on HCV. There can be a possibility of clearance of HCV infection post-partum and thus HCV-RNA levels should be repeated post-partum.

12.4.6 Management

Treatment of acute HCV infection is supportive. Direct-acting antivirals (DAA) have substantial role in the treatment of HCV infection outside pregnancy. Antiviral treatment i.e. ribavirin is contraindicated during pregnancy due to its teratogenic effect. Use of drugs i.e. ledipasvir and sofosbuvir are under trial for use during pregnancy, the results of which are pending. Mode of delivery is vaginal and operative delivery is as per routine obstetrical indications. Breastfeeding is not contraindicated in the presence of mono-infection and avoided in presence of co-infection with HIV or cracked or bleeding nipples.

There is no vaccine or immunoglobulin available for hepatitis C.

12.5 Hepatitis D

12.5.1 Virology

Hepatitis Delta virus is a single-stranded circular RNA. It is also known as defective virus as it requires the assistance of HBsAg for its proliferation. It has eight genotypes [32]. Around 5% of chronic carriers of HBV are co-infected with HDV.

12.5.2 Epidemiology

It affects around 15–20 million people worldwide [33].

12.5.3 Pathogenesis and Transmission

The major mode of transmission is parenteral and vertical transmission is rare. It is due to perinatal prophylaxis given for hepatitis B positive antenatal women.

12.5.4 Clinical Presentation in Pregnancy and Detection

HDV infection increases the risk of progressive liver disease and cirrhosis. There are limitations of studies on the positive or negative effects of pregnancy on HDV infection. No studies are available on possible effects of HDV infection on fetal and neonatal outcomes, but maybe similar to HBV monoinfection.

Detection of anti-HDAg IgM is suggestive of presence of acute infection. Pegylated interferon is the antiviral available for the treatment of HDV infection but is not recommended in pregnancy.

12.6 Hepatitis E

12.6.1 Virology

Hepatitis E belongs to the family of hepeviridae and genus orthohepevirus. It is an icosahedral, non-enveloped, single-stranded positive RNA virus. There are seven known genotypes of the virus and 1–4 affects humans.

12.6.2 Epidemiology

Hepatitis E is the most common sporadic as well as an endemic cause of hepatitis among adults in Asia and parts of Africa. Peak incidence occurs between 15 and 40 years of age. Nearly, 20 million people are infected annually with 70,000 deaths due to hepatitis E worldwide [34]. This accounts for nearly 3.3% of total mortality due to viral hepatitis [35]. Genotype 1 and 2 are prevalent in developing countries, genotype 3 in developed countries and genotype 4 in Asia and Europe [36].

12.6.3 Pathogenesis and Transmission

The mode of transmission is feco-oral route. Incubation period ranges from 2 to 9 weeks and period of infectivity is for 14 days after the onset of jaundice. Vertical transmission is seen ranging from 33 to 100% [37]. Transplacental transmission can lead to neonatal hepatic necrosis and even death in some cases. HEV genotypes 1 and 2 are transmitted via above-mentioned modes and types 3 and 4 are of zoonotic origin ingested via infected pork. Perinatal transmission is associated with genotype 1.

Once ingested, hepatitis E virus appears first in the liver, followed by viremia and is shed in stools thereafter. Liver injury coincides with elevation in ALT levels and anti-HEV IgM.

12.6.4 Clinical Presentation and Detection

Incubation period of hepatitis E virus ranges between 2 and 10 weeks. The infection has usually mild-moderate severity in the non-pregnant population with mortality of 0.4–4% [38]. The infection can range from asymptomatic, common among children to anicteric, icteric to fulminant hepatitis in adults. HEV infection does not cause chronic hepatitis, cirrhosis, or hepatocellular carcinoma.

Diagnosis is made by the detection of IgM antibodies to HEV.

12.6.5 Hepatitis E and Pregnancy

The attenuated cellular immunity in pregnancy is causative behind progression to fulminant hepatic failure and mortality rate of 5–25% [39]. Maternal case fatality rate of 3.2–70% was found in a meta-analysis involving 23 studies [40]. Median case fatality rate in fetus and neonates was found to be 33% and 8% respectively in a systematic review [40].

Obstetrical complications seen with hepatitis E infection are antepartum hemorrhage, premature rupture of membranes, preterm labor pains, postpartum hemorrhage, disseminated intravascular coagulation, and intrauterine death. There can be mild anicteric hepatitis in neonates born to HEV-positive mothers and they may also suffer from acute hepatic failure. There can be associated complications of preterm delivery.

12.6.6 Management

Management is supportive. Early delivery may be required in severe cases. Liver transplantation may be considered in cases with fulminant hepatic failure. There is no vaccine or immunoglobulin for the prevention or for post-exposure prophylaxis. Vaginal delivery and breastfeeding are not contraindicated.

Prevention of HEV infection is important to prevent the severe effects of the infection in pregnancy. Water hygiene and sanitation facilities should be taken care of to prevent the spread of infection.

12.7 Hepatitis G

12.7.1 Virology

Hepatitis G virus is a single-stranded RNA chain with positive polarity. It has a structure similar to hepatitis C virus. It has two envelope proteins E1 and E2 and antibodies are formed against these with E2 being more prevalent. It has five different genotypes. It has an average detection rate of 1.7% [41].

12.7.2 Pathogenesis and Transmission

The mode of transmission is through contaminated blood and its products. Rarely, it can be transmitted via sexual contact in those with multiple sexual partners. Vertical transmission is determined by the maternal viral load and co-infection with HCV and HIV. The rate of transmission is up to 75–80% [42]. Screening for the detection of HGV is not recommended in pregnancy.

12.7.3 Clinical Presentation in Pregnancy

Jaundice is the most common clinical presentation and definitive diagnosis is by detection of either HGV-RNA levels or antibody to HGV-E2. Management is supportive. Infants born to HGV-positive women do not develop clinical or biochemical signs suggestive of liver disease even after the presence of persistent infection for 1 year.

12.8 Approach to Pregnant Woman with Viral Hepatitis

The approach to a pregnant patient with viral hepatitis presenting with jaundice in pregnancy is described below (Fig. 12.1).

12.8.1 History

Pregnant women can get infected with hepatitis virus in all three trimesters. Presentation can range from being asymptomatic to mild symptoms to fulminant hepatic failure. The various symptoms are yellowing of sclera or urine, fever from low to high grade, nausea, vomiting, anorexia, diarrhea, abdominal pain, fatigue, malaise, and myalgia. High-grade fever in cases of acute viral hepatitis (AVH) can be a sign of progression to fulminant hepatic failure (FHF). Loss of consciousness can be a sign of fulminant hepatic failure. There can be history of altered sleep pattern and generalized slowing suggesting progression of patients to encephalopathy.

Patients with chronic infection with hepatitis B or C may progress to a state of decompensated

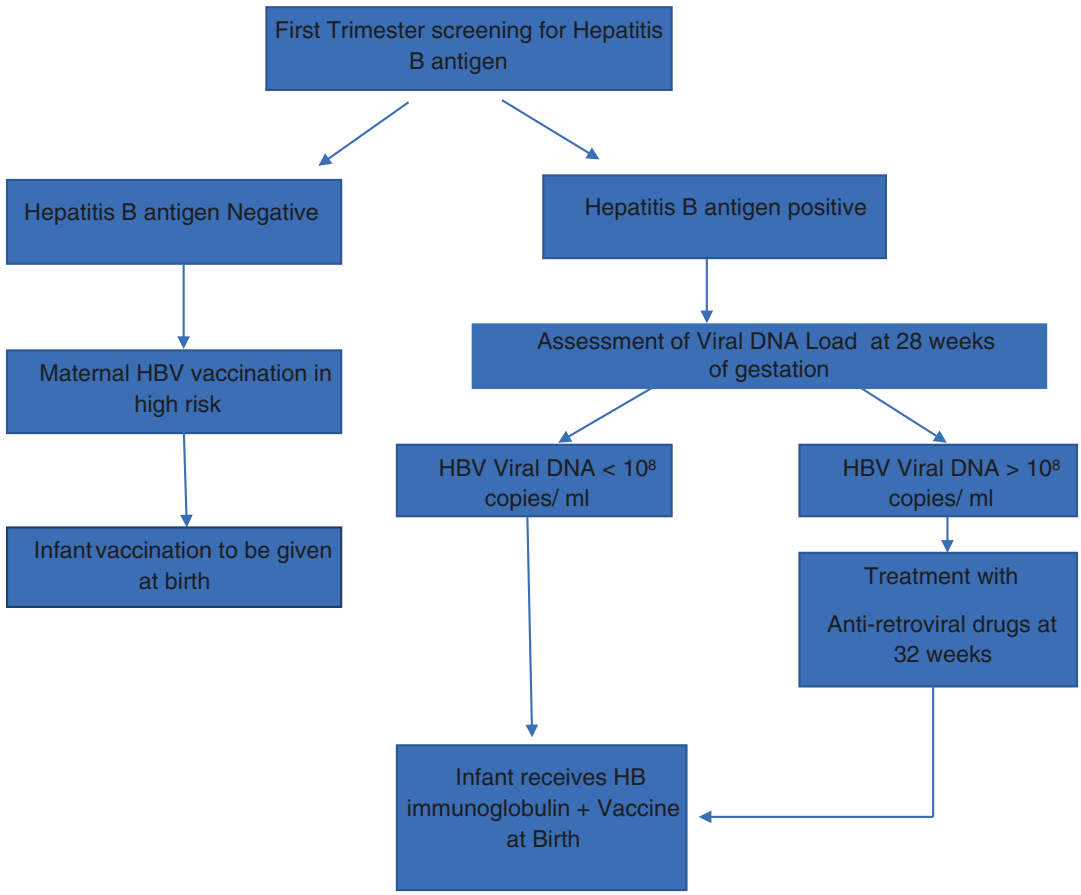

Fig. 12.1 Evaluation of pregnant women for hepatitis B

cirrhosis leading to ascites, hepatic encephalopathy, bleeding of esophageal varices, or coagulopathy with associated renal failure in some.

History of contact with persons infected with hepatitis, travel to areas endemic to hepatitis or intake of contaminated water and food, may point toward the possibility of hepatitis A and E.

History of multiple sexual partners or sexual contact with person infected with hepatitis B, C or D can point towards the diagnosis. History of intravenous drug abuse or use of contaminated blood should also be enquired.

Occupational hazards as in health care professional and paramedics should also be asked as it makes this group vulnerable to getting infected with blood-borne infections including hepatitis B, C, and D.

The differential diagnosis of jaundice in pregnancy has been highlighted in Table 12.1. It is difficult to distinguish between different types of viral hepatitis and thus definitive diagnosis is based on identifying viral serology on laboratory testing.

12.8.2 Examination

On examination, a patient with AVH may appear ill and dehydrated. Icterus is appreciated and distribution of it is assessed. Pallor, edema, and vitals are seen. There can be associated anemia, pedal edema, and raised blood pressure. Level of consciousness or grades of hepatic encephalopathy as detailed in Table 12.2 should also be assessed and documented. Presence of severe jaundice with altered sensorium may be a sign of fulminant hepatic failure.

Per abdominal examination is done to assess hepato-splenomegaly. Hepatomegaly may be a sign of acute or chronic liver disease. It can also be tender in AVH. Reduced liver dullness may be seen in cases of FHF.

Obstetrical examination is then proceeded in the usual manner to assess for fetal well-being.

Table 12.2 Grades of hepatic encephalopathy (West-Haven Index)

Grade	Clinical features
Minimal	No clinical abnormalities
I	Patient sleepy and irritable
II	Patient drowsy with intermittent disorientation
III	Patient disoriented and confused
IV a	Patient comatose, respond to painful stimuli
IV b	Patient comatose, not responding to painful stimuli

12.8.3 Laboratory Testing

Complete blood count, liver and renal function tests and coagulation profile are done. Leukocytosis up to 20,000–25,000/mm^3 may be seen in cases of AVH. There can be associated thrombocytopenia and deranged coagulation profile suggestive of FHF with DIC. Alanine transaminase is more specific of liver disease and may be raised up to 2000–3000 IU/l. Serum ammonia levels are measured in cases of fulminant hepatic failure with signs of encephalopathy. Urine bilirubin and urobilinogen can also be measured. Viral serology is the main test to determine the type of viral hepatitis (Table 12.3). In cases, where acute hepatitis is associated with viral serology, then search for additional viruses and causes have to be done.

12.8.4 Management of Acute Hepatitis in Pregnancy

Management of acute hepatitis in pregnancy is always supportive as described under various headings of viruses. The termination of pregnancy is not required in cases of acute hepatitis.

The rates of MTCT of hepatitis during antepartum and peripartum period as well as the high-risk factors for transmission have been detailed in Fig. 12.2.

12.9 Management of Fulminant Hepatic Failure in Pregnancy

Pregnant patients with viral hepatitis can present with severe jaundice in altered sensorium with or without deranged coagulation profile in liver failure. Management of such a patient requires a multidisciplinary approach involving coordinated efforts by the senior obstetrician, anesthetist, intensivist, hepatologist, neonatologist, and liver transplant team if need arises.

The priority is stabilization of the patient. The aim should be to obtain optimum hemodynamics, adequate volume replacement to ensure optimum renal perfusion, start vasopressors if need arises, treat cerebral edema, correct coagulopathy, evaluate for infection and start antibiotics, correct metabolic abnormalities including hypoglycemia, dyselectrolytemia and give adequate nutrient supplementation. Elective ventilation should be done for patients with grade three and four hepatic encephalopathy. Antibiotics for gut prophylaxis include Rifaximin 550 mg twice

Table 12.3 Recommended tests for acute viral hepatitis

Type of virus	Recommended test
HAV	Anti-HAV IgM
HBV	Anti-HBc IgM, HBsAg, HBeAg, HBV DNA
HCV	Anti-HCV IgM
HDV	Anti-HDV IgM
HEV	Anti-HEV IgM
HGV	Anti-HGVE2 IgM

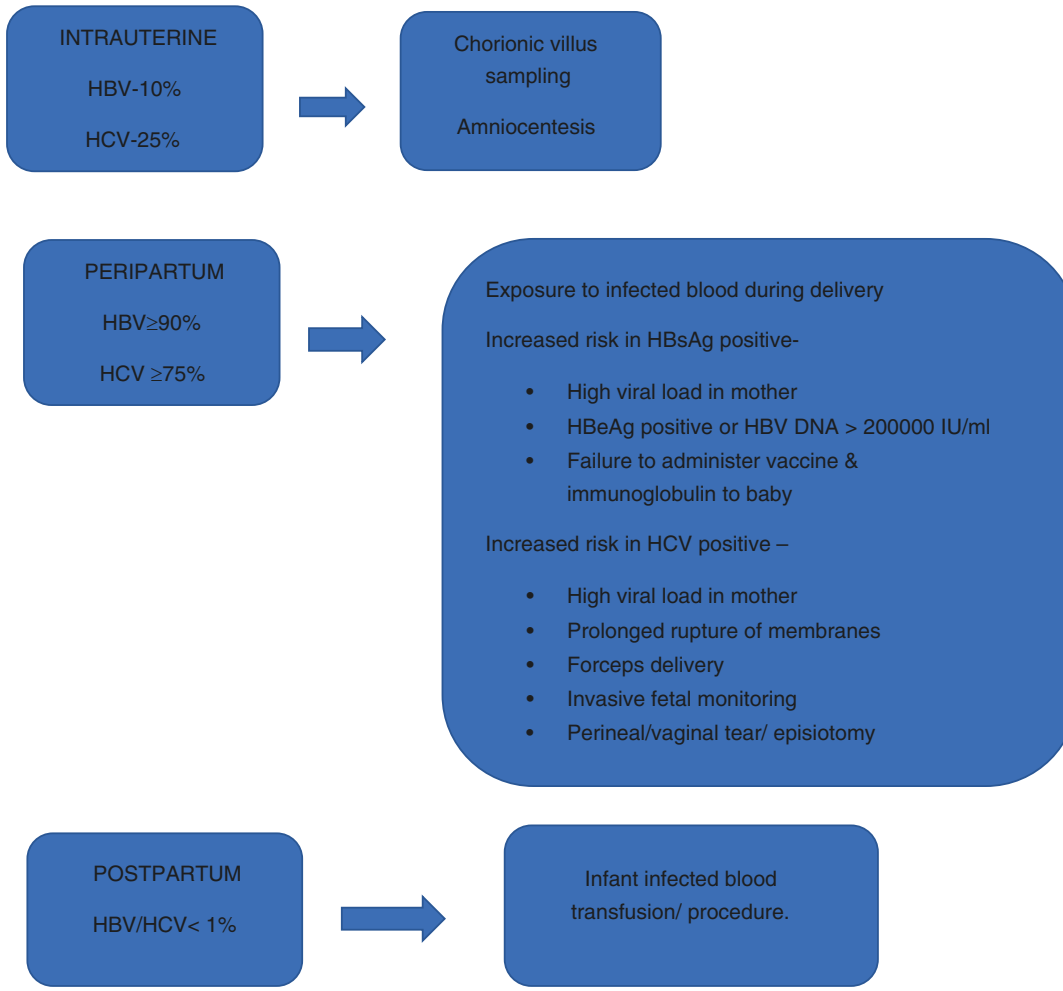

Fig. 12.2 Mother to child transmission in women with chronic viral hepatitis

daily via oral or nasogastric route, Metronidazole 400 mg twice daily via oral or nasogastric route, Flumazenil 1–3 mg I/V Or L-ornithine L-aspartate 20–30 g I/V over 4 h for 3–7 days. Figures 12.3 and 12.4 provide a broad algorithm of medical and obstetrical management for such a patient.

Patients in fulminant hepatic failure even if not in labor at initial presentation generally go into spontaneous labor. Around 80–90% of patients go into spontaneous labor within 24–48 h of presentation. There is no role of termination of pregnancy except in cases whose condition is stabilized for 24–48 h, or those with intrauterine demise, preterm premature rupture of membranes, or postdatism. Induction of labor is also required in cases where a clinical condition has deteriorated and liver transplantation is required.

In patients presenting in labor, the delivery should be conducted by senior obstetrician. The preferable mode of delivery is vaginal. As most of the patients have deranged coagulation, peripartum fresh frozen plasma(FFP) should be transfused to keep PT INR < 2. FFP is transfused in a dose of 15 ml/kg body weight stat followed by 2 units every 8 h till at least 24 h after delivery. During delivery, caution must be taken to prevent traumatic and atonic postpartum hemorrhage.

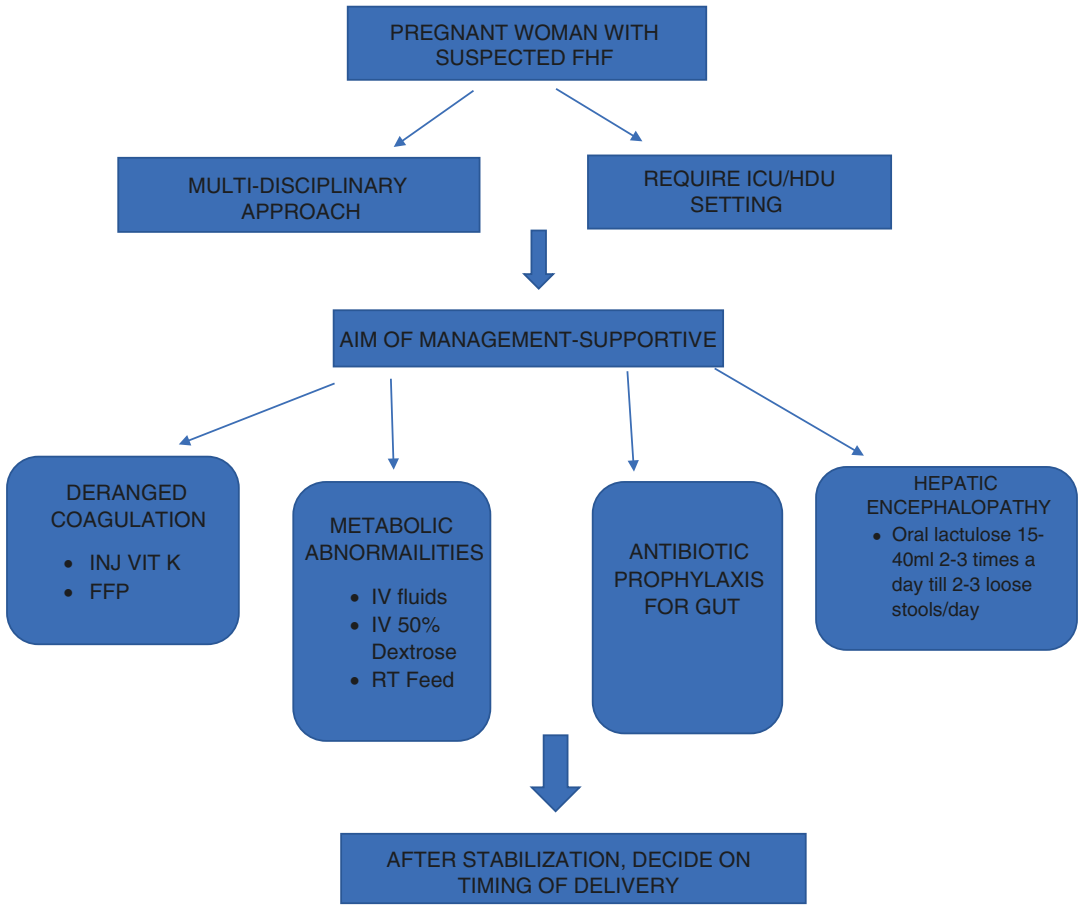

Fig. 12.3 Medical management of pregnant women with fulminant hepatic failure (FHF)

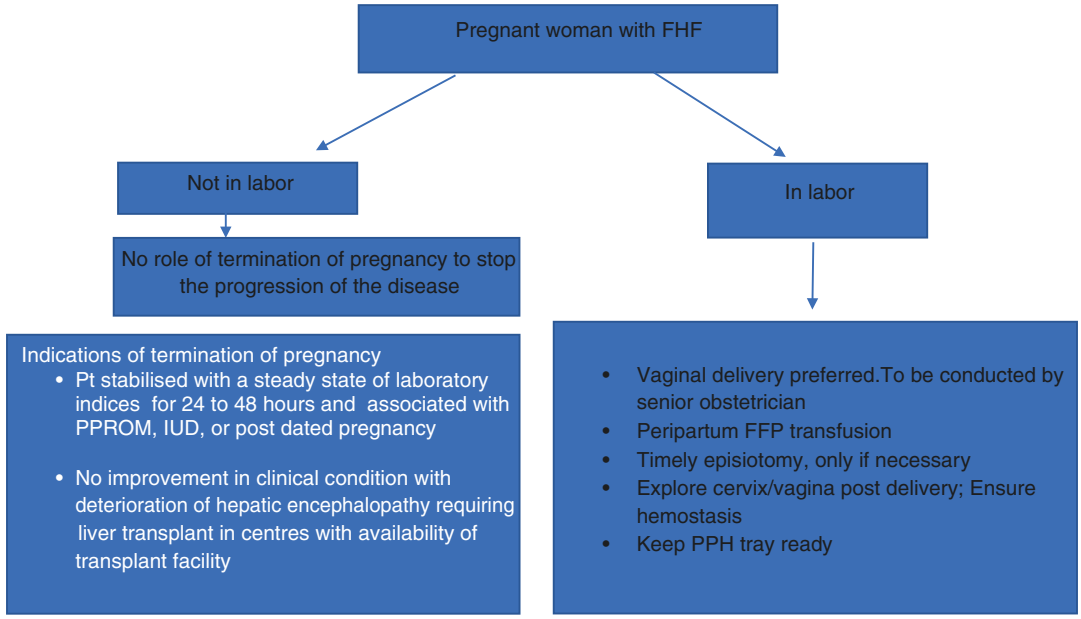

Fig. 12.4 Obstetrical management of pregnant women with FHF

12.10 Conclusion

Multipronged approach involving obstetrician, pediatrician, nurses, midwives, gastroenterologists, intensivist is essential for effective management of pregnant patients with viral hepatitis for optimal outcome. Timely interventions help in preventing or decreasing the negative outcome of hepatitis on mother and fetus.

Key Points

- HAV infection during pregnancy can lead to MTCT and also fetal injury in some cases.
- Patients with chronic HBV infection have an increased risk of gestational diabetes mellitus and prematurity. Risk of MTCT is increased in cases with high viral load and HBeAg positivity. It can be decreased with the use of antiviral therapy during the third trimester and with immunoprophylaxis to newborns of HBsAg-positive mothers.
- HCV infection may have an increased rate of adverse pregnancy outcomes including IHCP. Mother-to-child transmission is 4–7% per pregnancy among those with detectable viremia.
- HDV infection increases the risk of progressive liver disease and cirrhosis. MTCT of HDV is rare and its management is same as HBV infection.
- HEV infection is associated with increased risk of maternal and fetal morbidity and mortality. Early delivery may be required in cases with fulminant hepatic failure.
- Vertical transmission is determined by the maternal viral load and co-infection with HCV & HIV in cases with HGV. The rate of transmission is up to 75–80%.

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Maternal Enterovirus Infection

13

Nitin Srivastava

13.1 Introduction

Enteroviruses are one of the most common viral infections of newborns and children. The infection has a predilection for summer months and is commonly known as the "summer flu". They are a group of viruses belonging to the picornaviridae family and are called "entero" because of their ability to multiply in the gastrointestinal tract but they are not a prominent cause of gastroenteritis. They associated with varying clinical syndromes ranging from minor febrile illness, to potentially fatal conditions (aseptic meningitis, encephalitis, paralysis, myocarditis, and neonatal sepsis) or development of chronic diseases like Type 1 Diabetes mellitus and dilated cardiomyopathy. Enteroviruses are exclusively responsible for specific syndromes such as epidemic pleurodynia, hand foot and mouth disease, herpangina and poliomyelitis. Most of these affections are self-limiting and require only symptomatic treatment. Most adults have already acquired infection during childhood and develop immunity for the infections. Data on enterovirus infections during pregnancy appear to be very rare. Several authors have documented fetal and neonatal complications implicated to enterovirus but no known conclusive evidence is available. But any pregnant female with unexplained febrile illness should be investigated for enteroviruses and they remain an underestimated cause for obstetrical and neonatal complications.

13.2 Enterovirus: Morphology

Enteroviruses are members of the family Picornaviridae. They are single-stranded RNA virus affecting humans and other mammalian species. The RNA genome is surrounded by an icosahedral capsid comprising four viral proteins which is 27 nm in diameter. They have no lipid envelop. Each capsid is comprised of 60 subunits, made from four structural proteins (V1–V4). These serotypes affecting humans were initially divided into five species (poliovirus and four non-poliovirus human enteroviruses) based on differences in the pathogenic potential and the host affected [1]. A new classification scheme has now been introduced in 2012 and published as an update to the 9th issue of virus taxonomy from the International Committee on Taxonomy of Viruses and further corrections to this have been issued. The genus Enterovirus of the family Picornaviridae has nine enterovirus species (namely, Enterovirus A, B, C, D, E, F, G, H, and J) and three rhinovirus species (Rhinovirus A, B, and C) [2]. In 2015, a new enterovirus was discovered in cam-

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els, which is apparently the first representative of a new species, Enterovirus I (Table 13.1).

At present 90 known serotypes of enterovirus exist [3, 4]. These are called enterovirus because of their ability to multiply in the gastrointestinal tract but these viruses are not prominent cause of gastroenteritis [5]. They are stable at a pH from 3 to 10, differentiating them from other picornaviruses (including rhinoviruses), which are unstable below pH 6. Absence of the lipid membrane makes this virus stable in acidic environments, even in stomach. They can be inactivated by chlorine-containing cleansers but they are resistant to standard disinfectants and can stay active for days at room temperature. Temperatures above 50 °C can inactivate them.

Table 13.1 Classification of enteroviruses

EV species	Serotypes
A	Coxsackie virus A 2−8, 10, 12, 14, 16, Enterovirus 71, 76, 89−92, 114, 119−121, Simian enterovirus-19,43,46, A13or Ba13(baboon)
B	Coxsackie virus A 9, Coxsackie virus B 1−6, Echovirus 1−9, 11−21, 24−27, 29−33, Enterovirus 69, 73−75, 77−88, 93, 97, 98, 100, 101,106, 107, Enterovirus B69 (EVB69), 73–75, 77–88, 93, 97, 98, 100, 101, 106, 107, 110–112 (from chimpanzee), EVB113 (from mandrill), and simian enterovirus SA5
C	Poliovirus 1−3, Coxsackie virus A 1, 11, 13, 17, 19−22, 24, Enterovirus 95, 96, 99, 102, 104, 105, 109, 116−118 Poliovirus 1−3, Coxsackie virus A 1, 11, 13, 17, 19−22, 24, Enterovirus 95, 96, 99, 102, 104, 105, 109, 116−118
D	Enterovirus 68, 70, 94, 111 (from human and chimpanzee), and EV-120 (from gorilla)
E	Bovine enterovirus group A 1–4
F	Bovine enterovirus group B 1–6
G	Enterovirus G 1–16
H	Enterovirus H1 (EVH1) contains 3 monkey viruses (SV4, 28, A-2) and plaque virus
Rhinovirus A, B and C	Rhinovirus (RV) A1, 2, 7, 13, 15, 16, 18, 19, 25, 28, 36, 38, 41, 43, 45 A47, 49, 51, 53, 68, 71, 73, 78, 80, 82, 85, 88, 90, 94, 96 and 100–109 Rhinovirus (RV) B3, 6, 14, 17, 26, 27, 35, 37, 42, 48, 52, 69, 70, 72, 79, 83, 84, 86, 91, 93, 97, 99 and 106 Rhinovirus C 1–55
Other unclassified Enteroviruses	

Source: Nikonov OS, Chernykh ES, Garber MB, Nikonova EY. Enteroviruses: Classification, Diseases They Cause, and Approaches to Development of Antiviral Drugs. Biochemistry 2017 Dec;82(13):1615–1631

13.3 Epidemiology

Enteroviruses (EV) are responsible for about one billion infections each year worldwide, of which majority are asymptomatic (90%) [6]. The enteroviruses have a ubiquitous distribution. The spread of EV can be sporadic, endemic, epidemic, and even pandemic. Of epidemiological importance are the outbreaks of viruses, the changing patterns of infections, and the emergence of new strains. Several serotypes can cocirculate during the same period and within the same population. Most enterovirus infections except AHC are notifiable.

Poliomyelitis (polio) is a highly infectious enteroviral infection affecting children under 5 years of age. It targets the nervous system and is an important cause of flaccid paralysis. The worldwide prevalence of poliomyelitis has decreased significantly because of improved economic conditions and the availability of vaccines. In 1994, the World Health Organization declared polio eradicated from the Western Hemisphere. In 2003, six developing countries were considered endemic for the disease: Afghanistan, Egypt, Nigeria, Niger, India, and Pakistan [7]. In 2014, WHO announced the South-East Asia Region poliomyelitis eradicated. Only one strain of the known three strains of poliovirus—Wild Type 1 still exists in the World as in 2020, in Pakistan and Afghanistan [8].

Non-polio enteroviruses account for 10–20 million symptomatic infections per year. The infections are seen to be more prevalent in children of lower socioeconomic status, probably due to overcrowding, poor hygienic conditions, and more chances of fecal contamination.

Two enteroviruses are the main etiological agents responsible for large-scale outbreaks of acute hemorrhagic conjunctivitis (AHC), the enterovirus D70 (EV-D70), and an antigenic variant of coxsackie virus A24 (CV-A24v). AHC has been seen to occur as 2–3 yearly epidemics in tropical countries during the hot and rainy seasons. Countries like Singapore, Thailand, Brazil, China, and India have experienced several outbreaks during the last decades [9]. AHC was first recognized in the United States in 1981 during an epidemic in Florida. The prevalence is higher in southern areas than in northern areas of the United States.

Hand-foot-and-mouth disease (HFMD) is a common, typically mild and self-limiting illness affecting young children under 5 years of age. The most common etiological agents are enterovirus A71 (EV-A71) and coxsackie virus A16 (CV-A16). During the last 10–20 years, major outbreaks of HFMD have occurred in the Asia-Pacific, becoming an important public health problem [10].

Enterovirus D68 (EV-D68) is similar to rhinoviruses. It results in respiratory diseases in children aged 0–4 years. In the last decade, EV-D68 has resulted in small epidemics in Asia, Europe, and USA. In 2014, the largest outbreak of severe respiratory illness occurred in the USA due to EV-D68 [11].

13.4 Transmission

The main route of transmission for most enteroviruses is the fecal-oral route. A few exceptions to this is the coxsackie virus A21, which spreads via respiratory secretions [3], and enterovirus 70, which is secreted in the tears and can spread through fomites and fingers [4]. The virus is shed in the feces and in the secretions of the upper respiratory tract for days prior to symptom onset. The incubation period of the disease ranges from 3 to 10 days. During this time the virus replicates in the regional lymph nodes and involves the reticuloendothelial tissue [5]. In-utero transmission in late gestation has been seen in pregnancy. Intrapartum exposure to maternal blood, genital secretions, and stool have also been documented as routes of transmission. Post-natal exposure to oropharyngeal secretions from mother and other sources can also be responsible for neonatal infection. Serotype-specific humoral immunity is important for control and eradication of the disease. IgM antibodies develop within 1–3 days of the infection and last for 2–3 months while IgG antibodies develop within 7–10 days and last life long after natural infection.

13.5 Clinical Features

The peak incidence is seen in spring/summer months in non-tropical regions. More than 90% of adults are asymptomatic or experience a non-specific febrile illness. Any pregnant woman with unexplained febrile illness must be investigated for enterovirus.

13.5.1 Polio Enterovirus

Most infections of poliovirus are asymptomatic. After an incubation period of 3–6 days 5% of patients present with minor illness known as abortive poliomyelitis manifested by fever, malaise, sore throat, anorexia, myalgia, and headache. This infection usually resolves within 3 days. Very few patients can present with aseptic meningitis.

After aseptic meningitis, it can be followed by severe back, neck, muscle pain and by rapid or gradual development of motor weakness. It can have a biphasic presentation with aseptic meningitis followed first by apparent recovery but 1–2 days later by the return of fever and development of paralysis. Weakness is generally asymmetric, proximal, commonly involves legs but may involve arms, abdominal, thoracic, and bulbar muscles. Paralysis develops during febrile phase

of illness. Urinary retention may also occur. Examination reveals weakness, fasciculations, decreased muscle tone and diminished or absent reflexes. Bulbar involvement may present with dysphasia, dysphonia, difficulty in handing secretions, paralysis of phrenic or intercostal nerves, and involvement of respiratory center in medulla. It recovers with some function weeks to months after infection. Some patients have residual neurological sequelae. Paralytic polio is more common among older individuals, pregnant women and persons who do strenuous exercise. Tonsillectomy predisposes to bulbar poliomyelitis and intramuscular injections increase the risk of paralysis in the involved limbs.

There have been reports on transplacental effects of poliomyelitis in pregnancy before the era of widespread immunization. Perinatal transmission of the virus was observed when maternal infection occurred late in pregnancy. These infections were associated with an increased rate of spontaneous abortions and stillbirths. Paralysis of newborn infants (congenital polio) has also been documented.

13.5.2 Non-polio Enterovirus

90% of the non-polio enterovirus infections are asymptomatic or result only in a nonspecific febrile illness. The other manifestations of the disease include:

Nonspecific Febrile Illness It is the most common clinical presentation and is mainly seen in summer season. It has an incubation period of 3–6 days. About 90% of patients present with acute onset of fever, malaise, and headache. The fever persists for a week and shows a biphasic pattern. They may be accompanied by sore throat, nausea, and vomiting; the symptoms may resolve in a week.

Pleurodynia It is caused by group B coxsackievirus. It manifests as sudden onset of fever which is accompanied by spasmodic muscular pain in the chest and abdomen. The spasms last for 15–30 min and are worsened by coughing or on deep inspiration. The patients may have associated nausea, vomiting, and headache. Coxsackie viruses B3 and B5 are generally responsible for epidemics, affecting more than one family member at one time [12].

Aseptic Meningitis and Encephalitis Group B coxsackievirus and echovirus are the causative organisms in 90% of cases of aseptic meningitis in patients younger than 1 year and 50% of cases in older children and adults [13]. Patients with aseptic meningitis present with acute onset of fever , chills, headache, photophobia, and pain on eye movement, nausea and vomiting is also common. Examination reveals meningismus without localizing neurological signs; drowsiness or irritability may be present. Examination of CSF reveals pleocytosis, predominantly lymphocytes are seen and cell count does not exceed more than 1000/μL. CSF glucose level is normal and proteins are normal or slightly raised. It is more common in summer compared to other viral meningitis which is more common in winter. It is more severe in adults compared to children. Neurological sequelae are rare and patients have excellent prognoses. Encephalitis is less common and is mild with a good prognosis. It can be diagnosed by increasing lethargy, disorientation, and sometimes seizures.

Myocarditis and Pericarditis Enterovirus are the most common viral causes of acute myopericarditis. Coxsackievirus B and its RNA have been detected in pericardial fluid and myocardial tissue in some cases of acute myocarditis and pericarditis. Most cases of myocarditis occur in newborns and more than two-thirds in males. Newborns have severe disease and some cases can lead to dilated cardiomyopathy and chronic constrictive pericarditis as a sequel. Adolescents and adults present with an upper respiratory tract infection that is followed by fever, chest pain, dyspnea, arrhythmias, and heart failure.

Acute Hemorrhagic Conjunctivitis (AHC) The most common etiology is Enterovirus70 which is responsible for large-scale epidemics, though Coxsackievirus A24 also results in similar dis-

ease. The disease is highly contagious. Unhygienic conditions, sharing of towels, and reusage of bathing water have been suggested as contributory factors for the spread of the disease [14]. AHC presents as acute onset of ocular pain, swelling of the eyelids, foreign body sensation, watery discharge, and photophobia. The infection begins in one eye and involves the other within a few hours. The patients may experience fever, headache, and malaise. The symptoms improve in 2–3 days and subside by 7–10 days.

Exanthems This is the leading cause of exanthems in children in summer and fall. Exanthems are associated with enterovirus 9 and 16. Rashes may be discrete or confluent beginning on the face spreading to the trunk and extremities. Enterovirus rash is not associated with lymphadenopathy. Other rashes associated with enteroviruses are erythema multiforme, vesicular, urticarial, petechial, bullous, or purpuric lesions.

Hand Foot and Mouth Disease (HMFD) It is a disease of children younger than 10 years. The most common etiological agents isolated is Coxsackievirus and enterovirus 71. It has an incubation period of 3–6 days. The disease generally presents as epidemics that recur every 3 years. Children present with fever, anorexia, malaise, sore throat and vesicles on the buccal mucosa, tongue, and dorsum of hand. Vesicles may form bullae and quickly ulcerate. Lesions can also be present in the oral cavity, tonsillar pillar, buttocks, and feet. They can have severe complications like meningitis, myocarditis, and pulmonary hemorrhage.

13.6 Diagnosis

The diagnosis of enteroviral infection is usually made based on clinical findings but laboratory confirmation can be done using serological tests, viral isolation by cell culture, and polymerase chain reaction (PCR).

Serology Antibody detection by microneutralization is not a very popular test for diagnosis as it is serotype-specific, not very sensitive, and poorly standardized. It usually measures a fourfold decline in the antibody titers between the active and convalescent phases of the disease [14].

Viral Culture Isolation of enterovirus in cell culture is the traditional diagnostic procedure. The sensitivity of viral culture ranges from 60 to 75% [15]. Cultures are more likely to be positive in the earlier stage of the disease than in late stages. The virus can be isolated from nasopharyngeal secretions, blood, feces, or CSF depending on the site affected. Multiple site sampling increases the yield of the culture. Poliovirus can be easily cultured from nasopharyngeal secretions and stool but CSF isolation is more difficult. Enteroviruses vary significantly in their ability to grow in different mammalian cell lines. Laboratories usually inoculate the specimen into a minimum of three cell lines or may use and five or six cell lines to increase the yield. Coxsackievirus A requires inoculation into special cell culture lines or into sucking mice. The cytopathic effect produced by the enterovirus is detected by indirect immunofluorescence using a broadly specific monoclonal antibody.

WHO recommends that all specimens suspected of containing polioviruses be inoculated into the following two cell lines: L20B cells, a genetically engineered mouse cell line expressing the human poliovirus receptor; and RD cells, derived from a human rhabdomyosarcoma. The use of these two cell lines for the laboratory diagnosis of poliomyelitis permits the standardization of techniques and provides high sensitivity for poliovirus detection [16].

Polymerase Chain Reaction This is a highly sensitive and specific and rapid test. It has a sensitivity of 100% and specificity of 97% for detecting enteroviral RNA in CSF specimens [17]. PCR of CSF is less likely to be positive after 3 days of the infection. In that case, PCR from the throat and rectal swabs should be considered. However rectal and throat swabs are less specific than CSF.PCR of serum is also highly sensitive and specific in the diagnosis of disseminated disease.

In 2008, a multiplex real-time PCR (RT-PCR) assay was developed for simultaneous detection, identification, and quantification of enterovirus 70 and a coxsackievirus A24 variant. The technique has been used as a rapid diagnostic method to evaluate for enterovirus-related AHC [18].

Histology No specific histopathological finding is seen in affected target organs. Most enterovirus infections usually produce nonspecific inflammatory changes, consisting of lymphocytic infiltrates and cellular destruction.

13.6.1 Enterovirus Infection and Pregnancy

Non-poliovirus infections are very common, especially during the summer season. Most adults generally have immunity from previous childhood exposures. There is limited information available about infections during pregnancy in literature. At present, no data is available regarding the maternal-fetal transmission rate and no recommendations for the diagnosis, screening, or management of these infections during pregnancy. Poliovirus is now on the verge of eradication, but literature has cases of polioviruses reported in all trimesters of pregnancy.

13.6.1.1 Management of Pregnant Women with Unexplained Febrile Illness

In a pregnant female with febrile illness when all other common bacterial or viral causes have been excluded, investigation for enteroviruses using RT-PCR is recommended. Preferably the mother's plasma or otherwise the anorectal stool swab/stool sample is taken for RT-PCR. The RT-PCR is positive in blood during the acute febrile phase. Even after the fever subsides, the virus is shed in the stool for about 3 weeks. Thus positivity in the blood is highly specific for acute infection but positivity in stools is not. CSF and amniotic fluid RT-PCR is highly sensitive and specific.

If enteroviral infection is confirmed, the fetus is at high risk of miscarriage in early gestation, IUFD in second half of pregnancy or congenital infection. The fetus is subjected to close monitoring. Fetal ultrasonography is recommended monthly to look for cerebral ventriculomegaly, cardiomyopathy with ventricular dysfunction [19] and polyhydramnios associated with ascites, pericardial and pleural effusions which can be lethal due to multi-organ failure [20]. In case an abnormal finding is picked up on ultrasonography, the frequency of ultrasound can be increased according to the finding and requirement. The amniotic fluid RT-PCR is tested for fetal EV.

13.6.1.2 Maternal Implications

The infection is more common in multipara, as they can contract infection from their young children who are the primary hosts. The symptoms in pregnant women do not differ from those of adults in general. HFMD is common in pregnancy especially during epidemics and may be associated with onychomadesis, i.e., nail shedding from the proximal nail matrix. This benign complication is common in children but has been reported in pregnancy also. But in spite of this at present, there is insufficient evidence that HFMD increases the risk of serious pregnancy complications.

13.6.1.3 Fetal/Neonatal Effects

There is no clear evidence that non-polio enterovirus infection during pregnancy increases the risk of severe complications like miscarriage, stillbirth, or congenital defects. The enterovirus has been postulated to cross the placenta and cause fetal death. Placental infection localized to Hofbauer cells, syncytiotrophoblast, and cytotrophoblast cells of the terminal villi has been documented. Researchers have reported cases documenting strong causal relationships but further prospective studies are required.

Miscarriage Several authors have reported isolation of enterovirus from patients with unexplained miscarriage. The probable mechanism suggested is inflammation of the uterus, placental injury, and insufficiency resulting in implantation defects. Researchers have also documented high IgM levels in pregnant women who experienced miscarriage before the 13th week of gestation,

suggesting acute infection [21–23]. Poliovirus has also been implicated in causing miscarriage with first trimester infections.

Intrapartum Complications Herpangina has been associated with low birth weight, preterm labor, and SGA infants [24].

Intrauterine Fetal Death Many researchers have reported fetal loss associated with enterovirus infection. The probable mechanisms reported are placental damage and interference in organogenesis. Coxsackie and Echovirus have been isolated from amniotic fluid and placental tissues of patients with suspicion of infection, adverse sonographic findings, or on autopsy of fetuses [25–29]. These authors also highlight that unless and until the virus is being searched for with the use of advanced molecular technology, the infectious cause of the stillbirths can be missed.

Congenital Malformations It has been found that coxsackievirus is associated with orofacial clefts.

Neonatal Infection Infection contracted during pregnancy shortly prior to delivery can result in the transmission of the virus to the baby. These babies usually have only mild illness, but in rare cases, they may have a severe infection. All neonates born to mothers with confirmed enterovirus infection must be subjected to cord blood RT-PCR. In the absence of infection in the neonate, further monitoring can be stopped. If the cord blood sample is positive for enterovirus, then the neonate should be evaluated with platelet count and liver function test. Reported data suggests infected neonates present with jaundice and altered sensorium. They are found to have hepatitis and liver failure [30, 31]. Echovirus and coxsackievirus were isolated from blood, stool, and oropharynx of these neonates. The infection in most cases was found to be fatal. National Reference Center for Enterovirus in Lyon France in 2012 reported data of neonates infected with enterovirus, of which 34 cases (28%) were diagnosed within the first 8 days of life. Most neonates presented with symptoms related to respiratory and liver disease. On evaluation 23% had hepatitis, 12% had myocarditis and 15% developed encephalitis. Bonin et al suggested that neonates presenting with arrhythmias and signs of cardiac failure should be evaluated for fetal myocarditis and investigated for enterovirus infection [32].

An increase in the incidence of neonatal poliomyelitis was observed with paralytic maternal infection shortly before delivery [32].

Coxsackievirus infection in pregnancy has been associated with an increased risk of insulin-dependent diabetes mellitus in the newborn. It was found that newborns with intrauterine exposure of serologically verified infections of coxsackievirus and other enterovirus were two times more prone to have insulin-dependent diabetes mellitus.

13.7 Treatment

The best treatment for an enterovirus infection is prevention. Vaccine is available for poliovirus. But for non-polio enteroviruses, supportive treatment to reduce the symptoms is given. Most of the infections are mild and self-limiting. Currently, there are no antiviral medications approved for the treatment of enterovirus infections. If there is cardiac, hepatic, or CNS involvement then intraventricular or intrathecal immunoglobulins are required. Intravenous immunoglobulins with high titers of antibodies are used in neonates with life-threatening infections. Glucocorticoids are contraindicated. Pleconaril, an antiviral drug is under research for the treatment of neonatal enterovirus sepsis.

Pleconaril, is a 3C protease inhibitor drug, which has been awaiting FDA approval as an intranasal spray to treat rhinoviral infections. In the past, doctors have used the drug for compassionate treatment only in life-threatening enteroviral infections. Pocapavir and vapendavir are two other antiviral drugs also being tested for the treatment of enterovirus infection.

13.8 Prevention

- Vaccination—Children should be vaccinated against poliovirus till the disease is completely eliminated from the world.
- HMFD vaccine development—Clinical trials for five types of vaccines against EV-A71 are underway in China, Taiwan, and Singapore. Three of these vaccines have entered phase III randomized, double-blind, placebo-controlled trials in China [33]. The safety profile and protective efficacy of these ranges between 90.0 and 97.4%. The disadvantage is that they do not provide protection against the other causative serotype CV-A16 or any other serotypes. The vaccine development is a positive step toward curbing the disease.
- The habit of washing of hands should be inculcated among children and adults
  - After using the toilet
  - Before eating
  - Before touching their eyes, mouth, or nose
  - When caring for someone who is sick.
- Use a hand sanitizer if you do not have soap and water handy
- Try to have less contact with people who are sick
- Clean surfaces at home regularly with disinfectant

13.9 Conclusion

Non-polio enteroviruses can damage the embryo and fetus causing fetal loss, stillbirth, cardiac and orofacial abnormalities. Polio virus is also teratogenic and embryotoxic but due to mass immunization against polio virus, the incidence has reduced drastically even in developing countries. It is important that pregnant women who have nonspecific febrile illnesses should be investigated for enterovirus. At present, no data is available regarding the maternal-fetal transmission rate and no recommendations for the diagnosis, screening, or management of these infections during pregnancy. The best treatment for an enterovirus infection is prevention and handwashing and avoiding crowded areas during pregnancy is important to reduce transmission and acquiring the disease.

Key Points

- Enteroviruses (EV) account for about one billion infections each year; the majority remain asymptomatic. They are called enterovirus because of their ability to multiply in the gastrointestinal tract but these viruses are not prominent cause of gastroenteritis
- The main route of transmission for most enteroviruses is the fecal-oral route and it primarily affects children.
- They are associated with varying clinical syndromes ranging from minor febrile illness, to potentially fatal conditions (aseptic meningitis, encephalitis, paralysis, myocarditis, neonatal sepsis) or the development of chronic diseases like Type 1 diabetes mellitus and dilated cardiomyopathy.
- Data of enterovirus infections during pregnancy appear to be rare but enteroviruses are important cause for early fetal loss, stillbirth, neonatal sepsis, and cardiac abnormalities in neonates. The severity of disease in pregnancy is directly proportional to the complications seen in pregnancy.
- At present, no data is available regarding the maternal-fetal transmission rate and no recommendations for the diagnosis, screening, or management of these infections during pregnancy.

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Part IV

Parasitic Infections

Toxoplasmosis in Pregnancy

14

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14.1 Introduction

Toxoplasma gondii, an organism causing toxoplasmosis, is an intracellular protozoan commonly infecting mammals and other homoeothermic animals. It belongs to the class *coccidian* and consists of only one species. It causes fatal food-borne disease in the USA and is the third most common cause for it [1]. It is the disease of immune-compromised, involving patients affected with HIV AIDS, infants, patients suffering from chronic illnesses, cancers, or patients on immunosuppressant but rarely causes symptomatic infection in healthy individuals. One-third of healthy people infected with Toxoplasma remain asymptomatic while others may suffer from flu-like symptoms like headache, myalgia and rarely become carriers resulting in the spread of the disease without getting the illness for their entire life [2].

It is one of the most common infections in humans. Worldwide, the seroprevalence for Toxoplasmosis varies from 1 to 100% depending upon the environmental and the socio-economic conditions, food products, harvesting practices, hygiene, and human practices [3]. The incidence is higher in warm and humid areas due to higher transmission rates [4]. An American study demonstrated that 11% of women belonging to reproductive age (15–44 years) had IgG antibodies to *T. gondii* in their serum if born in America but in women born outside the US, the prevalence increased to 28.1% [5].

Toxoplasmosis in pregnant women presents clinically in a similar way as others but because of its high prevalence and possible affection on the fetus, it needs exclusive consideration. Congenital toxoplasmosis, one of the 'T'ORCH infections, is a morbid condition with an incidence of about 400–4000 per year [6]. The seroprevalence of toxoplasmosis in India varies from 4.7 to 51.8%. The acquisition of toxoplasmosis in the antenatal period, as indicated by maternal seroconversion rates varies from 0.2 to 1% [7].

14.2 *Toxoplasma gondii*: Life Cycle and Clinical Manifestations

Toxoplasma is an obligate intracellular protozoan existing in three forms.

Tachyzoite is the proliferative stage of the organism, present in a non-immune host in the bloodstream and lymphatics during which they travel to different tissues and nucleated cells. After invading the tissue and cells, the tachyzoite multiplies rapidly, causing lysis of the cells and

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thus releasing further tachyzoites in the neighboring cells, leading to necrosis of the tissue. This causes the manifestations of signs and symptoms of acute toxoplasmosis.

Bradyzoites are the cyst form (Tissue cysts) of the protozoa which are formed after the acute infection is over. These are the slowly multiplying forms present in the host cells particularly in the brain, eye, skeletal muscle, and cardiac muscle. These cysts may remain dormant for years or throughout life before getting reactivated in states of any immunosuppression. The cysts may contain thousands of bradyzoites.

Oocysts are resistant forms. They are found in the feces of infected cats. They are the main reservoir of this organism in nature and are the cause for the spread of infection in environment [8, 9].

14.2.1 Life Cycle

Life cycle of the parasite includes a definitive host in which the sexual multiplication occurs and one intermediate host consisting of the asexual cycle. Felines represent the only definitive host and rest all animals are the intermediate host. Human beings represent the dead-end hosts, i.e., they are incapable of transmitting the infection to other animals or humans.

The cats become infected by ingesting the tissue cysts or oocysts excreted from birds or mice. These ingested cysts are released into the environment, multiply with sexual reproduction, and the unsporulated cysts are released in feces in millions. The resistant oocysts sporulate in the soil and can remain there for more than a year. Vectors like earthworms transport the oocyst from the deposit site to raw eatables.

The risk factors of acquiring the infection include accidental ingestion of these oocysts from undercooked raw meat, pork, lamb, and beef containing tissue cysts [8], or unwashed fruits and vegetables containing these cysts on their surface. Children might get infected while playing with cats or playing with dirt containing oocysts via hands [10]. Blood transfusion, organ transplantation, or inhalation of sporulated cysts are some of the rare modes of transmission. Latest evidence also suggests water as the source of transmission [11]. The proliferative forms invade the bloodstream via intestine and spread throughout body via blood vessels and lymph fluid in different organs.

14.2.2 Clinical Manifestations

Most infections are asymptomatic. After an incubation period of about 10–23 days, flu-like symptoms may appear including headache, malaise, myalgia with fever and chills. Posterior cervical lymph node enlargement may be evident including other lymph nodes. Some features mimic infectious mononucleosis-like presence of atypical lymphocytosis on peripheral blood pictures. In severe cases, usually, in immunocompromised states, acute disseminated toxoplasmosis may occur causing encephalitis, myocarditis, hepatitis, pneumonitis, and ocular toxoplasmosis. Ocular toxoplasmosis usually involves the posterior pole of the eye manifesting with cystoid macular edema, band keratopathy, chronic iridocyclitis, cataract formation, secondary glaucoma, and retinal detachment [12]. These clinical manifestations can also occur after reactivation of the latent phase of the infection acquired earlier in life in immunocompromised conditions like AIDS.

14.3 Toxoplasmosis in Pregnancy and Congenital Toxoplasmosis

Infection during pregnancy is not more severe than in non-pregnant women and similarly, only a few cases are symptomatic [8]. Congenital toxoplasmosis is essentially the only fear of maternal toxoplasmosis which spreads by the trans-placental route [13]. There is no evidence that toxoplasmosis can transmit through breastfeeding [14]. The vertical transmission occurs in about 40% of pregnancies if the mother is infected for the first time during the pregnancy out of which 90% are asymptomatic mothers; this is by the crossing of placenta by tachyzoites via

blood [15, 16]. Mothers who have been infected before conception rarely transmit the infection to the fetus, by reactivation of the disease in the states of immunosuppression [5, 17]. There have been rare instances where an immunocompetent mother who acquired infection before conception has been found to cause congenital toxoplasmosis [18].

The prevalence of congenital toxoplasmosis varies from 0.1 to 0.3 per 1000 live births. The overall risk of transmission is 30%. Children affected with congenital toxoplasmosis are mostly normal developmentally [19]. As gestational age advances, the risk increases, i.e., at 13 weeks less than 15%, at 26 weeks 44% risks, and at 36 weeks almost 71% [20] (Fig. 14.1).

The congenitally infected newborns, although being asymptomatic, develop adverse sequelae by second or third decade of their life in almost all the cases [22]. But only 4% of infants experience permanent neurological damage, bilateral visual impairment, or die [23]. Congenital toxoplasmosis presents most commonly with neurological and ocular changes. Multifocal and diffuse parenchymal necrosis occurs which later transforms into calcifications and microglial nodules. Obstruction in the Foramen of Monro and aqueduct of Sylvius via the sloughed off necrotic tissues may lead to hydrocephalus. Later on, atrophy of brain tissues and thereon microcephaly occurs [20]. Ocular manifestations of congenital toxoplasmosis are due to choroidoretinitis, the most frequent ocular pathology, due to inflammation and necrosis of choroid and retinal tissues. This occurs due to the rupture of the cyst in the ocular tissues. One risk factor for choroidoretinitis is the presence of cerebral calcifications [21].

Although the transmission of infection is more with the increase in the period of gestation, the severity of affection to the fetus is less with the advancement in gestational age. Infections that take place in third trimester usually are subclinical in the early neonatal period [21]. Early gestational infections within 8 weeks lead to termination of pregnancy rather than fetal affection, but later on usually results in severe disseminated fetal infection, which can also lead to fetal demise in utero.

A study done in Europe found that the brain lesions were 20% after maternal infection at 10 weeks of gestation but 15% at 15 weeks of gestation and even lesser when infection was expected to be transmitted in third trimester [21]. Eye lesions were still high at more than 15% in late third trimester (Fig. 14.2).

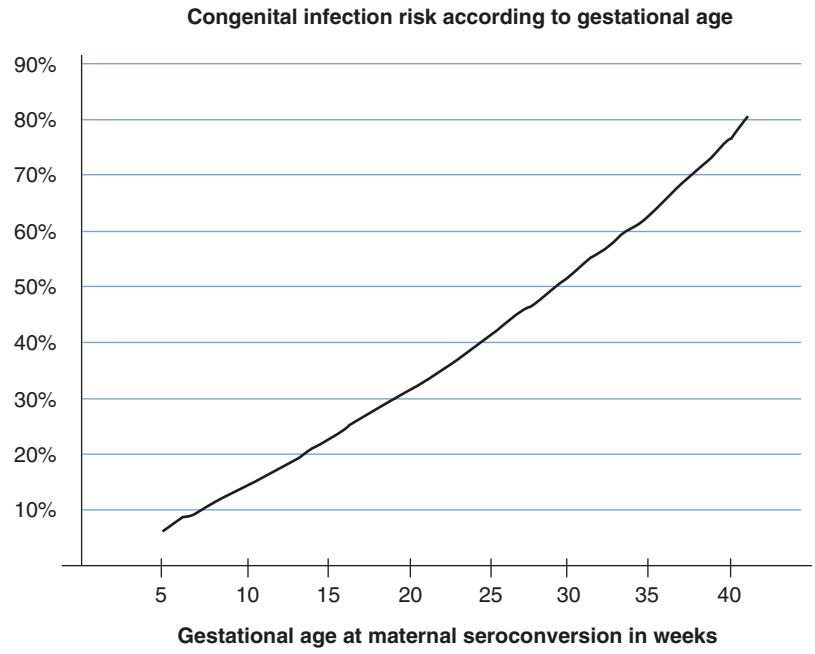

Fig. 14.1 Risk of congenital infection with an increase in gestation. Adapted from SYROCOT [21]

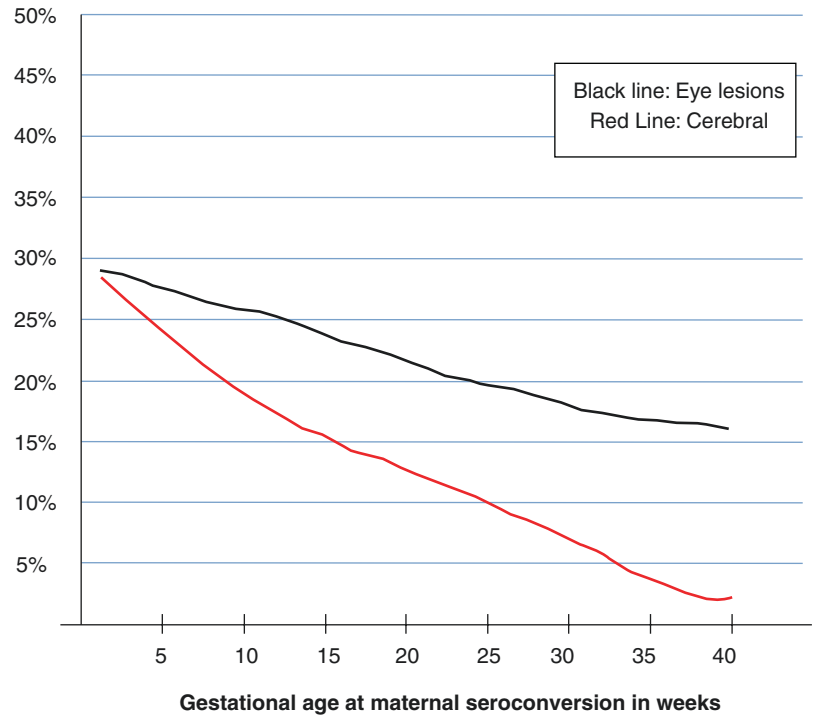

Fig. 14.2 Risk of cerebral and eye lesions with gestational age. Adapted from SYROCOT [21]

Most common features of congenital toxoplasmosis (CT) are hydrocephalus, chorioretinitis, and intracranial calcifications. Other features of CT include encephalomyelitis, convulsions, mental retardation, hepatomegaly, rash, anemia, erythroblastosis, strabismus, hearing and visual impairments, nystagmus and, growth and developmental delays [5]. Microphthalmia, psychomotor retardation, hypotonia, microcephaly, prematurity, and dysmaturity can also be the presenting features. About 80% of children asymptomatic at birth may develop neurological manifestations if not treated [24]. Therefore, every infection acquired in pregnancy must have a prompt diagnosis and treatment.

Antenatally, two-thirds of the scans show absolutely normal features. The common features of intrauterine infection on ultrasound include the presence of intracranial calcification, microcephaly, hydrocephalus, symmetrical cerebral ventricular dilatation while ascites, hepatosplenomegaly, pericardial effusions, echogenic focus in bowel, or severe intrauterine growth restriction may also be seen sometimes.

14.4 Diagnosis and Management of Toxoplasmosis

As toxoplasma infection is asymptomatic, few countries (e.g., Austria and France) with high prevalence rates adopt for universal and repeat screening tests by serological assays for diagnosis of acute toxoplasma infection. Universal screening is also opted in women suffering from immunocompromised states like HIV AIDS, transplant patients on chronic immunosuppression, etc. The earlier the diagnosis, the earlier the treatment can be provided and lesser is the time available with the parasite to cause the tissue destruction thus improving the overall neonatal outcome. Screening tests are otherwise administered if toxoplasma infection is suspected, for example in cases of antenatal ultrasound features suggestive of the disease or previous pregnancy affected with toxoplasmosis (ACOG Practice Bulletin 2003), or mother showing signs and symptoms of an acute toxoplasma infection. The screening algorithm is shown in Fig. 14.3. Sometimes, the diagnosis is made postnatally when the newborn

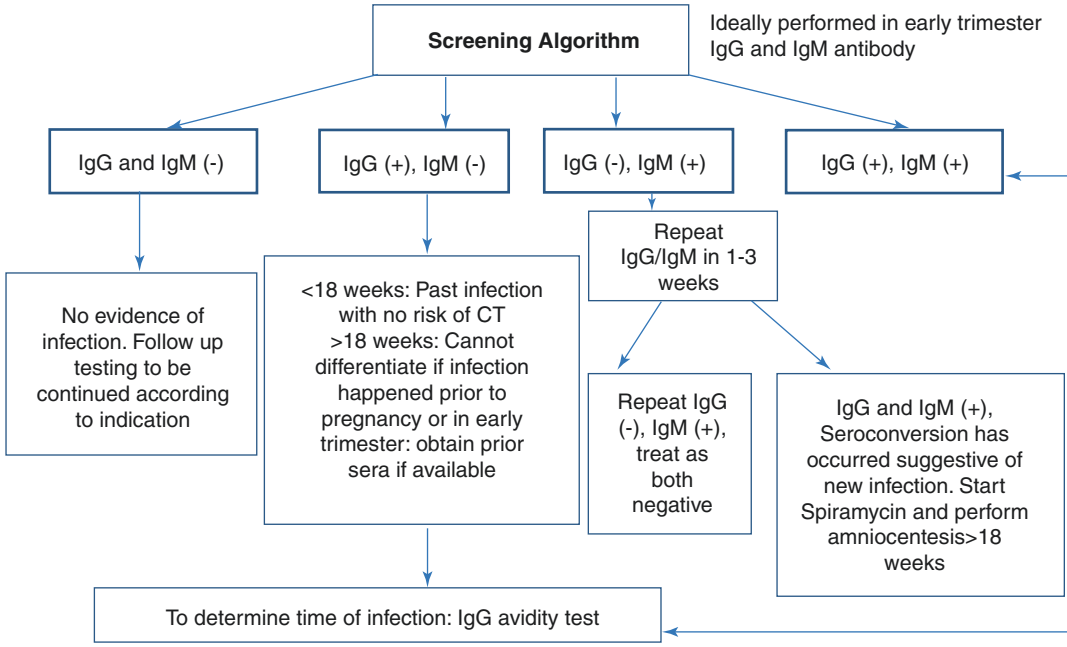

Fig. 14.3 Screening algorithm for toxoplasmosis infection in pregnancy

shows signs of congenital toxoplasmosis [9]. The testing is done in order to provide early prenatal treatment, thus preventing the infection to the fetus or reduce the severity of the infection.

Diagnosis of Maternal toxoplasmosis is based on the following methods:

- Tissue cultures from placenta, blood, or body fluids of mother– isolating *T. gondii*, but this method is rarely used as it requires a long time and high-grade laboratories.
- Tissue sections or body fluid smears- direct visualization of tachyzoites.
- Serological tests: Sabin Fieldman Dye test, Immunofluorescence antibody test, ELISA, Agglutination tests, IgG Avidity test [22].
- Polymerase chain Reaction in amniotic fluid sample (100% specific).

14.4.1 Diagnosis of Congenital Infection in Pregnant Woman

The serological test in mothers is done to diagnose that the infection exists, and to differentiate a recent infection from the old one. Congenital toxoplasmosis is caused by acute infection in mothers and hence differentiating acute from chronic is important.

Two antibodies, IgG and IgM specific for *T. gondii* are used in diagnosing infection. IgM antibody forms early after an acute infection from the 5th day and reaches a maximum level at around 1.5–2 months, after that it falls rapidly [8]. Whereas, IgG antibodies are formed after a week or 2, attain the highest level from 3 to 6 months, and are present thereafter. Although IgM antibodies fall after acute infection subsides, they may sometimes persist for years (15–18 months average) and both IgG and IgM may show false-positive results [25].

Interpretation of these antibodies is crucial in making a correct diagnosis and treatment of the infection. If both IgG and IgM antibodies are absent before or early in pregnancy, it is indicative of absence of previous infection [26]. If IgG antibodies are present with negative IgM antibodies, it suggests a chronic infection. If both IgG and IgM are positive, it can be suggestive of an acute infection, but the possibility of low titers of IgM antibodies from the previous infection cannot be ruled out. For a suspected recent infection,

perform a repeat test within 2–3 weeks, if similar results are there; perform further tests [8].

To help in the diagnosis of acute infection, new tests like IgG avidity test have come up [27]. It measures the strength of IgG antibody binding to *T. gondii*. If the infection is recent, the avidity of binding of IgG antibodies is low, and it takes about 5–6 months for the avidity to become high. Thus, patients with recent/acute infection will have a low avidity whereas patients who had acquired infection previously will show a high IgG avidity index. The sensitivity of IgG avidity can be up to 100% [28] (Table 14.1). Further management based on avidity testing is discussed in Fig. 14.4.

If IgG avidity test is suggestive of acute infection, further steps for prenatal diagnosis of congenital toxoplasmosis in the fetus include detection of *T. gondii* DNA by real-time polymerase chain reaction analysis of the amniotic fluid. It is done as low IgG avidity can persist for months [29]. The common target is the 35-multicopy B1 gene [14]. It is recommended to be performed after 18 weeks of gestation and after 4 weeks of an acute infection [20]. It is advantageous as it is associated with a low risk of fetal demise compared with previous tests like cordocentesis. Amniocentesis is performed only if there are ambiguous serological test results or ultrasound findings are suggestive of congenital toxoplasmosis [30]. *T. gondii* DNA PCR tests have also been tried on umbilical cord samples (cordocentesis) but it has a higher risk of intrauterine deaths and is less sensitive [31]. We can also extrapolate the severity of infection by the parasite load in amniotic fluid. A higher parasite load reflects high possibility of fetal severity and affection. A Japanese study compared the accuracy of the IgG avidity test and found that about 56% of women who had low IgG avidity had a positive PCR testing from an amniotic fluid sample [31]. Sensitivity of amniotic fluid PCR is highest if done at 17–21 weeks period of gestation. Negative results on PCR may still not rule out congenital infection. Ultrasound should be done monthly for women diagnosed with toxoplasmosis to look for fetal affection.

14.4.2 Diagnosis of Congenital Infection in the Neonate

Detection of IgM antibodies has the greatest importance for the diagnosis of congenital toxoplasmosis in neonate. IgM antibodies are large molecules and hence they do not cross the placenta and IgM antibodies are produced by the fetus. Hence, the presence of IgM antibodies

Table 14.1 Interpretation of serological testing for *Toxoplasma gondii* infection

IgG	IgM	Interpretation
Negative	Negative	No serological evidence whether acute or chronic infection but the pregnant woman is at risk of infection
Negative	Equivocal	Repeat testing after 2–3 weeks as IgM may have false-positive results, If repeat is same, treat as negative
Negative	Positive	Acute infection likely, confirm the infection as high false-positive rates and persistence of IgM antibodies
Equivocal	Equivocal/negative	Indeterminate, Obtain another sample
Equivocal	Positive	Repeat test after 2–3 weeks, if similar result, perform confirmatory test
Positive	Negative	Previous infection >6 months back, no intervention
Positive	Positive	Infection within 12–18 months, perform confirmatory test at higher laboratory

Confirmatory test : IgG avidity and amniocentesis
Adapted from Montoya and Liesenfeld [14]

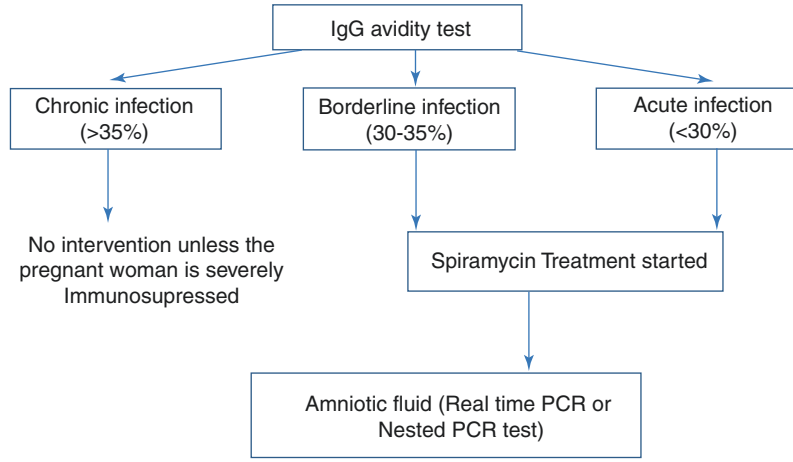

Fig. 14.4 Management of toxoplasmosis infection based on avidity testing

suggests infection in-utero. Similar serological methods are applied for the diagnosis as mother's IgA and IgG are also applied simultaneously. The presence of antibodies indicates infection but has no correlation with the severity [32]. Rarely, samples are taken from placenta or fetal tissues to visualize *T. gondii* cysts and ascertain the occurrence of vertical transmission via giemsa stain or immunoperoxidase staining [33].

14.5 Management of Toxoplasmosis

14.5.1 Treatment of Acute Infection Diagnosed in Mothers with No Fetal Affection

Maternal toxoplasmosis is rarely harmful to immunocompetent mothers, who may not require treatment at all, but the purpose of treating the infection is to prevent congenital toxoplasmosis. Spiramycin is a macrolide antibiotic used in the treatment when there is absence of fetal affection confirmed by a negative amniotic fluid PCR. It is given at a dose of 1 g every 8 h/day (1 g contains 3 million units) as soon as the maternal infection is confirmed and until delivery [14, 34, 35]. Earlier the treatment given, lesser are the chances of vertical transmission, and later the in-utero infection occurs, less severe are the clinical manifestations in the newborn. It is not used for the treatment once fetal infection is confirmed as it does not cross placenta. The incidence of infected infants is 50% less in each trimester if spiramycin treatment is used compared to the preceding years when there was no treatment [36]. Maternal ocular toxoplasmosis, if developed, requires an expert opinion whether antibiotics are needed or not as the course is unpredictable and may the condition may recover without any treatment as well. Most clinicians would still provide treatment for ocular toxoplasmosis, using a combination of Pyrimethamine, Sulfadoxine and systemic or intravitreal corticosteroids in varying regimens [12]. Alternative treatments are cotrimoxazole combination with corticosteroids, rarely usage of intravitreal clindamycin for severe cases [37]. Some cases may even require surgery if complications of ocular toxoplasmosis occurs.

Management of immunocompromised seropositive pregnant women is important as there are risks of disseminated toxoplasmosis, and reactivation of latent infection, both of which can have a dreadful effect on the mother and the baby (transmission of infection in early gestation). CD4 cell count is a useful method to start a prophylactic treatment for the mother. A woman having CD4 cell count of less than 200 cells/ml should receive cotrimoxazole (having a combination of 80 mg trimethoprim and 400 mg sulfamethoxazole in a single-strength tablet) once a day. In women having immunosuppression because of causes other than HIV or if CD4 cell count is more than or equal to 1200 cells/ml, spiramycin treatment is suggested for the duration of the pregnancy.

Although these strategies are not backed by many studies they are still applied by clinicians [14].

14.5.2 Antenatal Management If Fetal Affection Has Been Confirmed

Antenatally, treatment via antibiotics is given to limit fetal damage after transmission. The aim is to limit the damage as *T. gondii* cannot be eradicated. Pyrimethamine and sulfadiazine are used as a "gold standard" combination which is eight times more effective than either pyrimethamine or sulfadiazine used alone [38]. Other combinations of drugs have been studied in animal models that have shown anti-toxoplasma activity including Trimethoprim/Sulfamethoxazole and Clindamycin/ Sulfamethoxazole but are not clinically used [35].

If congenital infection in the fetus is confirmed by PCR testing after 18 weeks of period of gestation, treatment is done with Pyrimethamine: 50 mg twice a day for 2 days followed by 50 mg daily; sulfadiazine: 75 mg/kg initial dose, followed by 50 mg/kg twice a day (maximum, 4 g/day) along with folinic acid (leucovorin): 10–20 mg daily (throughout the treatment and 1 week after completion of pyrimethamine) [14]. Sulfadoxine has been recently used for its longer half-life and better compliance [39]. Pyrimethamine is not recommended in the first trimester due to increased risks of teratogenicity and bone marrow toxicity both to mother and the fetus and thus, spiramycin is given until a confirmatory amniocentesis report is available which is, later on, switched to Pyrimethamine [14]. Treatment is usually given for 4–6 weeks. No RCTs are there which can opine on the effectiveness of the treatment [40] (Fig. 14.5). But studies have shown that when treated with pyrimethamine and sulfadiazine, placental cultures had *T. gondii* only 50% of times whereas those who had not received any treatment in prior decades had 95% of times *T. gondii* in them [41]. There is evidence of decrease in the severity of disease such as meningitis and mortality in infants treated antenatally [42].

If the infection acquired is very early, use of Pyrimethamine is precluded. If the antenatal affection is severe with features like hydrocephalus or severe ventricular dilatation, then termination of pregnancy can also be offered after expert opinion and discussing with the pregnant woman; a confirmed diagnosis is mandatory from either amniotic fluid PCR or fetal blood sampling before the decision for termination is taken [43]. Mothers having toxoplasma chorioretinitis must also be treated as it is taken as a marker of acute infection [14].

14.5.3 Management of Congenital Toxoplasmosis

Diagnosis of congenital toxoplasmosis in neonates is also based on serological evidence, tissue culture, PCR and presence of signs and symptoms of disease at birth with history of maternal infection. If the maternal infection was proven to be acquired during pregnancy then the treatment is started whether or not the child shows any signs of infection. If the maternal infection was acquired but amniotic fluid PCR was negative or unavailable, then serological tests are done after 10 days of life. If diagnostic criteria are met, the treatment is started (Fig. 14.6).

There is a diagnostic dilemma if the child shows clinical signs of toxoplasmosis at birth but no testing was done during the antenatal period. In this case, simultaneous testing of mother and newborn should be done with IgG and IgM. If maternal serology is positive and acute infection is diagnosed, treatment for congenital toxoplasmosis is started. Along with this, neonatal IgM, IgG, and IgA antibody testing is done after 10 days of birth. If diagnostic criteria are met, treatment is started. If serology in neonate is negative, then repeat testing after 1 month and 2 monthly thereafter is repeated till 12 months of age (Fig. 14.7).

In congenitally affected newborns, daily oral pyrimethamine (1 mg/kg) for 2 months followed by 0.5 mg/kg for 10 months and sulfadiazine (100 mg/kg) with folinic acid (and not folic acid) 10 mg three times weekly is given for 12 months [40].

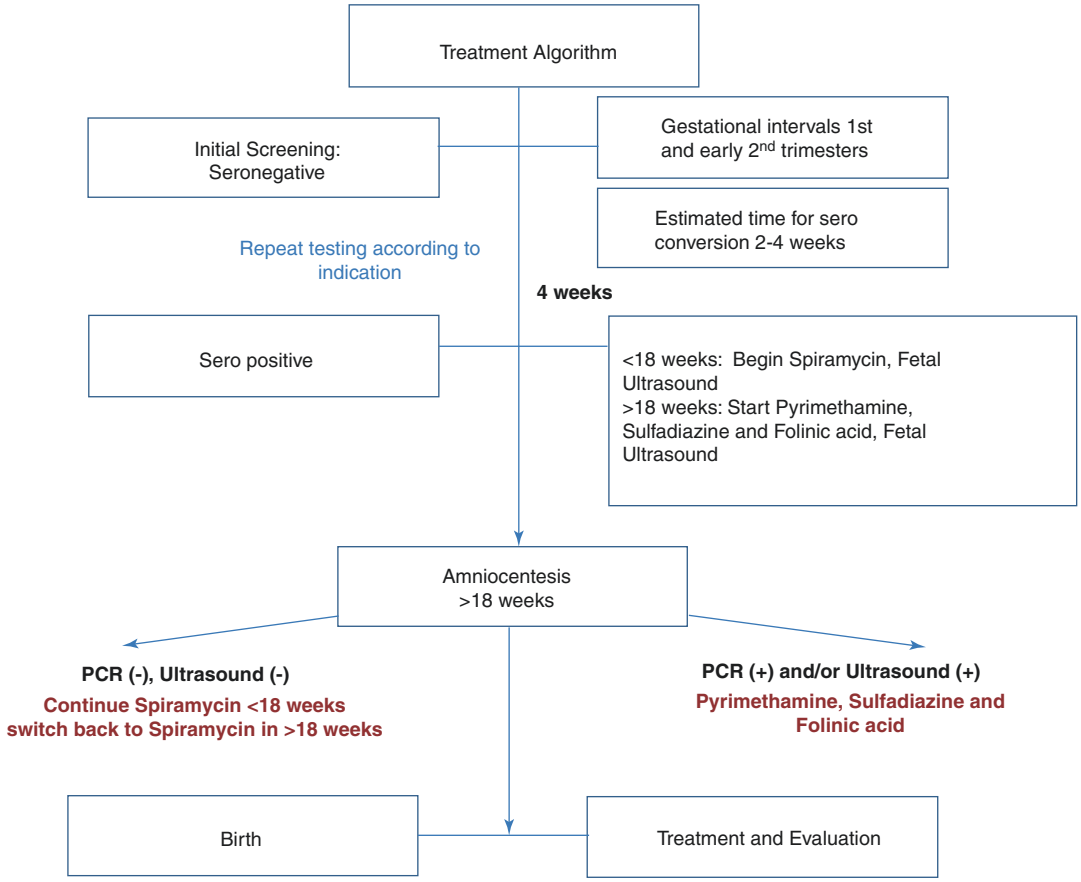

Fig. 14.5 Treatment algorithm. Adapted from Boyer et al. [43]

Monitoring of IgG levels is done to see the response of the treatment but the treatment should not be discontinued if IgG levels are not detectable before 12 months as they tend to fall. After completion of treatment, a follow-up examination is done 3 monthly for 1 year and 6 monthly during the 3rd year and yearly thereafter for life long. It should be combined with regular eye examinations. If eye signs of active infection are present after the completion of the therapy then a repeat treatment for 3 months can be given [20].

The management must consist of multidisciplinary involvement including otorhinolaryngologists, ophthalmologists, and neurologists. The need for long-term follow-up is essential. As hearing disabilities may not be evident at birth therefore all children born to mothers suspected of having toxoplasmosis must be screened for hearing loss. Corticosteroids are added if active cerebral involvement or chorioretinitis is present. Overall, studies suggest a good prognosis of children born live [45]. Even after immediate treatment, 10% of neonates may still develop severe disease.

14.6 Prevention from Toxoplasmosis

As toxoplasmosis is an asymptomatic infection and routine screening is not cost-effective in areas of low prevalence, all the women of reproductive age group and pregnant women must be made aware of methods of prevention from contracting toxoplasmosis. Following are the methods to decrease the risk of getting infected:

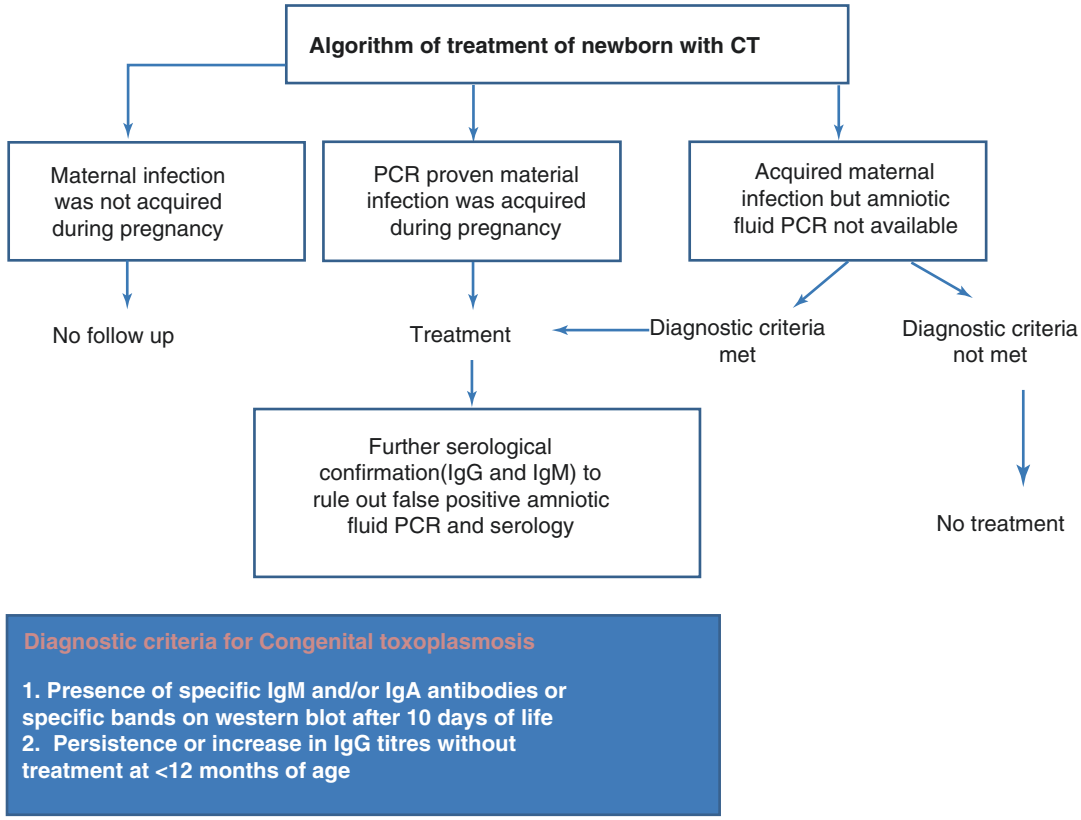

Fig. 14.6 Management of newborn with CT. Adapted from Pomares and Montoya [44]

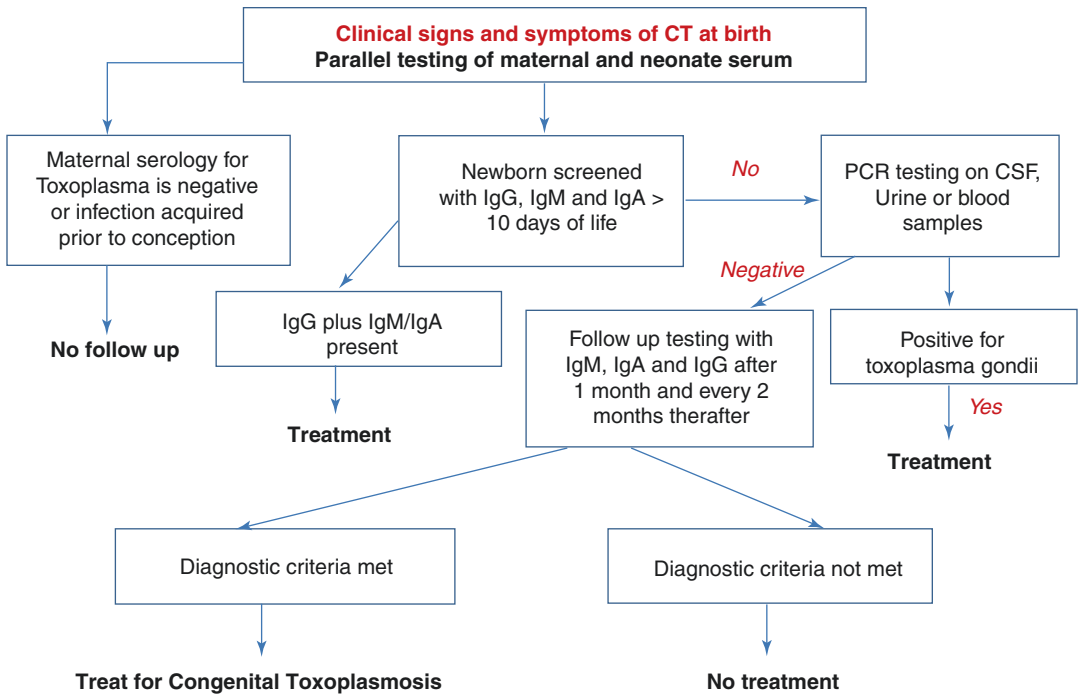

Fig. 14.7 Detection of congenital toxoplasmosis in the newborn. Adapted from Pomares and Montoya [44]

Primary prevention
1. Consumption of well-cooked meat heated to temperatures of 165–170 °F [16]. Freezing to at least 20 °C for 24 h and thawing also kills *T. gondii* cysts [13]
2. Always wash fruits and vegetables before consumption
3. Avoid contact with items that are potentially contaminated with cat faeces, prevent children from playing near sand dust and cats, avoid playing with stray cats
4. Wash hands thoroughly after handling raw meat or vegetables soiled by earth, after gardening, changing cat litter (wearing gloves, hand washing with soap and water)
5. Thoroughly wash all utensils that are in contact with undercooked meat
6. Health education to be provided to all the pregnant women to prevent toxoplasma infection [43]

Secondary prevention
1. Universal screening programme for early detection of antibodies specific to *T. gondii* in pregnant women, starting early treatment and preventing fetal affection
2. Universal screening on pregnant mothers can only be applied in states of high prevalence keeping in mind the cost-effectiveness ratios
3. Neonatal universal screening programme (detection of toxoplasma-specific IgM antibodies): identification of 70 and 80% of cases of congenital toxoplasmosis [46]
4. All tests require confirmation before starting treatments as false-positive rates are high

14.7 Conclusion

Toxoplasma infection in a pregnant woman may results in congenital toxoplasmosis (CT) of the neonate; worldwide, 400–4000 children are born with congenital toxoplasmosis every year. 90% of the infected woman are asymptomatic but the rate of vertical transmission is 40% which increases with advancing gestational age. Most infected newborns develop adverse neurological and ocular sequelae by second or third decade of their life. Most common features of congenital toxoplasmosis include hydrocephalus, chorioretinitis, and intracranial calcifications. Spiramycin, a macrolide antibiotic is used in the absence of fetal affection to prevent vertical transmission, while combination of Pyrimethamine and sulfadiazine is the "gold standard" used in the presence of fetal affection. Prevention of maternal toxoplasma by health education and routine screening of women living in areas with high prevalence is of paramount importance.

Key Points

- The risk of congenital sequelae and complications in fetus infected in early pregnancy is 85%.
- Diagnosis in mother is by serological tests for specific antibodies.
- If maternal infection occurs, a detailed ultrasound examination to identify markers, with consideration to parasitological culture of amniotic fluid and molecular studies PCR on amniotic fluid should be done.
- Prevention by health education is of paramount importance. If a woman has acquired an infection, it is recommended to conceive after 6 months of interval [23].
- Prenatal education regarding methods of prevention of the disease in areas of high prevalence must be offered and mothers must be educated about the consequences of congenital toxoplasmosis.
- Antiparasitic therapy to prevent congenital transmission or limit fetal damage after transmission should be encouraged.
- Termination of pregnancy may be an option if early affection has been confirmed.
- As toxoplasmosis is an asymptomatic infection and routine screening is not cost-effective in areas of low prevalence, all the women of reproductive age group and pregnant women must be made aware of methods of prevention from contracting toxoplasmosis.

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Cysticercosis, Schistosomiasis, and Leishmaniasis

15

Vandana, Kanak Dubey, and Ritu Khatuja

15.1 Introduction

Infections due to parasites are common occurrence worldwide. Recent increase in cysticercosis, toxoplasmosis, schistosomiasis, leishmaniasis may be attributed to an increase in the rate of international travel as well as more number of immigrants coming from areas infested with these parasites.

Many parasitic infections which are encountered in tropical areas have a really devastating effect on the health system of less developed or developing countries. In cases of infections associated with pregnancy, it is the type and the number of parasites harbored by the patient along with the immunity level of such patient which decides the effect on maternal and fetal health.

It has become very important for the clinicians to update themselves with the knowledge regarding development and clinical presentations of these parasites. The decision to treat these infections, especially during pregnancy, presents as a challenge as one has to weigh the favorable outcomes against the unwanted effects of antiparasitic drugs. The greatest hindrance is unavailability of substantial data regarding the safety profile of these drugs during pregnancy. Therefore, such drugs are advised only in fatal situations or when the benefits associated clearly outscore the risks. Clear information should be given to pregnant females regarding the risks of such treatment. It is advisable to hold back treatment if the infection is of no immediate danger to the mother or fetus.

15.2 Cysticercosis

Cysticercosis is caused by the larval stage of *Taenia solium* (pork tape worm). Pigs are the intermediate or secondary hosts and humans the definitive hosts. Contaminated food or drinking water is the usual cause of cysticercosis with improperly cooked food being the main source of infection. Eggs are excreted by a person suffering from taeniasis (infection with adult worm). Pigs get infected by eating human excreta infected with eggs of *Taenia solium*. Human hosts usually acquire the cysts from a carrier of tapeworm in their family [1].

T. solium infection is prevalent in low-socioeconomic countries like Latin American, Asia, and sub-Saharan Africa, including China and India [2, 3].

Non-specific gastro-intestinal symptoms are mostly observed in Taeniasis. Also, weight loss, abdominal pain, nausea, diarrhea, and even constipation may be observed in *T. solium* infection.

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Table 15.1 Presenting features associated with various locations of cysticerci

Location of cysticerci	Presenting features
Skin (Cysticercosis cutis)	Cysts are located subcutaneously, especially on the extremities and trunk [4]. They may sometimes be painful.
Muscles	Inflamed muscles initially accompanied with fever, eosinophilia, and increased size. This may be followed by atrophy and scarring. In most cases, cysticerci die and become calcified [5].
Eye (Ophthalmic cysticercosis)	Visual difficulties that fluctuate with position of eye, retinal edema, hemorrhage, a decreased vision, or even a visual loss [5].
CNS (Neurocysticercosis)	Epilepsy, hydrocephalus, meningitis, and encephalitis. Seizure and hydrocephalus are associated with parenchymal and ventricular lesions, respectively, while hydrocephalus along with stroke may be associated with subarachnoid lesions.

The larvae (cysticerci) of *T. solium* may develop in skin, muscles, eyes, or central nervous system. Presenting features depend upon the location of cysticerci (Table 15.1).

15.2.1 Cysticercosis in Pregnancy

Pregnancy is often considered to make a female more susceptible to infection. Hormonal upheavals and decreased responsiveness of immune system contribute to the increase in susceptibility.

Treating cysticercosis in pregnancy can be very challenging. Also, the limited knowledge among the practitioners regarding cysticercosis in pregnancy makes the diagnosis and hence the treatment difficult.

Medical practitioners, in areas populated with large immigrants, may come across patients infected with neurocysticercosis (NCC) [6, 7]. In women with neurocysticercosis severe morbidity and death have been observed. In developing countries, NCC has become an important cause of acquired epilepsy. About one-third of cases related to seizures in areas infested with *T. solium* and 50 million people worldwide are estimated to suffer with NCC [8].

15.2.2 Clinical Features Observed in Pregnant Ladies

Clinical manifestations of NCC in pregnancy range from being asymptomatic to a fatal increase in intracranial pressure. Pregnant females with NCC commonly present with complaints of headaches and focal or generalized seizures. Many studies have also reported features like altered mental conditions, coma and even death among such ladies [9, 10].

Stage of infection, cyst location, and response of host to injury are factors mainly responsible for the symptoms due to NCC. Despite being fully viable, the cystic lesions may be subclinical or even asymptomatic while dead and decaying forms cause granulomas and calcifications which ultimately present with perilesional inflammation and seizures [11].

15.2.3 Confounding Factors in Diagnosis

Pre-eclampsia or eclampsia appears to be the biggest confounding factor while diagnosing NCC in pregnancy. Whether it is seizure or visual disturbances and altered mentation, all are more often linked with pre-eclampsia and eclampsia rather than NCC. Diagnosis becomes all the more confusing if the seizures due to NCC appear in second half of pregnancy [7, 12, 13]. Even headache, which is the most common complaint of young females may be considered "normal" during pregnancy [14].

15.2.4 Diagnosis

NCC should be considered a principal as well as one of the most common causes of first-time sei-

zure in pregnant ladies [15]. Diagnosis poses lots of problems in case of human cysticercosis. A series of investigations comprising histological and serological analysis, imaging with scans to follow-up along with epidemiology and above all, clinical features, are suggested to be important for diagnosis [16].

15.2.4.1 Patient History

Several studies have actually pointed at the importance of detailed personal, social, and family history.

Paying due attention to some of the key points like occupational history (e.g., association with pig farms), food habits (regular consumption of pork meat), and history of migration from endemic areas or of contact with immigrants from endemic areas, can further help in arriving to a valid conclusion.

15.2.4.2 Imaging Studies

Imaging methods like X-ray, CT scan, and MRI can be used for detection of the disease. X-rays are helpful in identifying the calcified larvae lodged in subcutaneous and muscles while CT and MRI help in locating the lesions in the brain [17, 18] (Fig. 15.1).

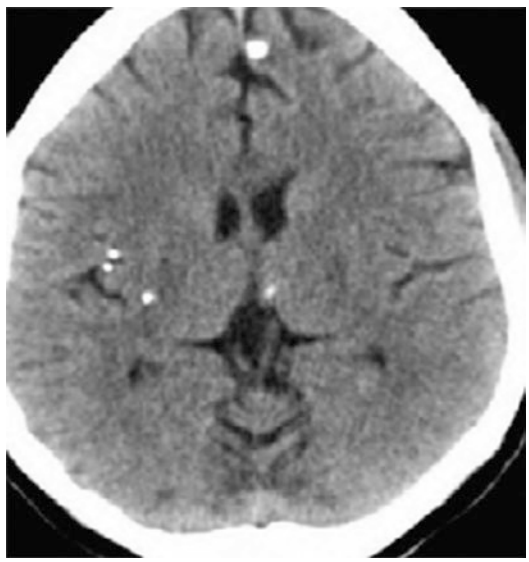

Fig. 15.1 Showing calcified larvae in CT scan of brain

Viable parasites appear as cystic lesions. MRI helps in visualizing scolex. Lesions can also appear as "contrast enhancing lesions surrounded by edema." "Hypointensity of the vesicular fluid on T2-weighted images when compared with CSF" is a very initial sign of death of a cyst. Dead parasites are often visualized as parenchymal calcifications in the brain [19].

Small and non-calcified cysts, enhancement around calcifications or edema, and subarachnoid or intraventricular lesions can be easily identified by MRI. Though CT scan is considered superior to MRI for observation and evaluation of calcified lesions, its sensitivity is relatively lower for lesions which are subarachnoid or intraventricular.

In pregnant women with suspected NCC, early imaging studies need to be done. Non-gadolinium MRI is not considered to be teratogenic. Hence, it should be the test of choice during pregnancy.

In case of CT scan, "narrow collimation, wide pitch, and shielding" is needed [20].

15.2.4.3 Serology

Serum antibodies can be detected by enzyme-linked immuno electrotransfer blot (EITB) assay. Its sensitivity, in case of more than one parenchymal cyst or subarachnoid disease, is around 98%. This, however, decreases to 50–60% in case of only one cyst and is also poor in case of calcified cysts.

ELISA test—In case of unavailability of EITB, ELISA can be used to test cerebrospinal fluid in order to detect anticysticercal antibodies [21].

15.2.5 Management

15.2.5.1 Treatment of Taeniasis in Pregnancy

Niclosamide or praziquantel can be used to treat taeniasis in pregnancy after the first trimester [22, 23]. Both of them belong to category B drugs. Since niclosamide is not absorbed well, hence, it may be a safer option to use during pregnancy. A mild cathartic, taken shortly after the anthelmin-

thic, prevents the continued release of infective eggs and proglottids from decaying adult worms left behind in the intestinal tract [23]. Hence, a combination of single dose niclosamide and a mild laxative is considered an effective prescription for pregnant as well as postpartum women. Praziquantel, though not as effective as albendazole, is preferred because of latter's greater teratogenic potential [24].

15.2.5.2 Treatment of Pregnant Symptomatic Neurocysticercosis Patients

In this case, treatment should be aimed at controlling the seizures and other symptoms of infection [6]. Anti-epileptics can be successfully used albeit cautiously to treat seizures as a result of NCC.

Altered pharmacokinetics and potential teratogenicity should be kept in mind. Greater teratogenic potential of valproic acid and phenobarbital is a known fact [25]. Monotherapy is generally preferred; adequate control of seizures, with only one agent, has been observed in quite a few cases [26].

2

The decision of using antihelminthics to treat neurocysticercosis in pregnancy is a complex one and requires expert opinion. An increase in inflammation and cerebral edema may be observed while treating with antihelminthics. Therefore, if the clinical condition of the patient is not severe enough to warrant their use, it is advisable to defer them until the control of seizure or until after delivery [27, 28].

Co-administration of corticosteroids is also recommended in order to control the edema which may occur because of immune response to the dying parasites [29]. Symptoms may worsen once the corticosteroids are tapered. Hence, it is better to avoid them in cases of calcified lesions [30].

Calcified *T. solium* cysts are the most common radiological finding in NCC [31]. Perilesional edema, which results due to these cysts, is a foci of repeated seizures. Anti-inflammatory or immunosuppressive drugs, if used with anti-epileptics, prove to be beneficial for such patients.

Patients suffering with acute hydrocephalus should undergo immediate surgical management in order to either divert the drainage of cerebrospinal fluid or to remove the parasite from ventricles [32].

15.2.6 Prevention

Taeniasis and cysticercosis are preventable diseases. Treatment of this disease can be done by interventions at different stages in the life cycle of the parasite.

- Widespread chemotherapy of infected individuals and imparting proper knowledge to people regarding cleanliness of self and surroundings are the most important ways of discontinuing the transmission of eggs from human fecal matter to other humans and/or pigs.
- Pig meat (pork) should be properly inspected and cooked completely before consumption.
- Pigs should be adequately treated or vaccinated as well as housed in enclosed areas in order to separate them from human feces. This is a very effective way of curbing infection.

15.3 Schistosomiasis in Pregnancy

Despite immense modernization in the health care system, schistosomiasis still remains a threat in developing countries due to deficiency of proper health infrastructure, contaminated water, and poor sanitation facilities. More than 200 million people worldwide are infected by *Schistosoma mansoni*, *Schistosoma japonicum*, and *Schistosoma haematobium*. The prevalence of Schistosoma infections in women living in endemic areas ranges from 5 to 67%. Women are more susceptible to this infection as they carry out their daily domestic chores in infested water and can subsequently develop female genital schistosomiasis [33, 34].

15.3.1 Infection and Transmission

Humans and snails are the definitive and intermediate hosts, respectively, for this parasite. The adult organism lives in venous system of intestine and urinary bladder of definitive host. Eggs of the parasite are passed out via stool (*S. mansoni* and *S. japonicum*) and urine (*S. haematobium*), hatch in water, infect the snails, and develop into their infective form (cercariae). These cercariae infect humans by penetrating the skin when they come in contact with infested water. These finally reach and reside in the portal venous system and urinary bladder venous plexus. The eggs released by female adult worms are either excreted through fecal matter or urine in order to continue the life cycle of parasite or remain trapped in tissues which causes immune reactions and progressive damage to organs [35].

15.3.2 Clinical Manifestations in Pregnancy

Symptoms of schistosomiasis vary according to reaction of body to parasite eggs.

Intestinal schistosomiasis may present with pain abdomen, diarrhea, and blood in stool. Advanced infection is very often associated with hepatomegaly, splenomegaly, ascites, and hypertension of the abdominal blood vessels.

Urogenital schistosomiasis (mainly caused by *S. haematobium*) classically causes hematuria (blood in urine). This may be associated with fibrosis of ureter and bladder, kidney damage and even bladder cancer in late stages. Pelvic discomfort, sandy patches in mucosa, contact bleeding, and vaginal discharge are the presenting symptoms, especially in women [36].

Besides pregnancy associated morbidities, pregnant women in schistosoma infested areas suffer from urogenital schistosomiasis [36]. Hormonal and immunological alterations which occur in pregnancy significantly modify the immune status of a pregnant female.

Like other infections, the burden of infection due to Schistosoma is more grave in primi mothers [37]. There has been observed a reduction in infection with increased gestational age. This most probably is the effect of increased frequency of micturition associated with as the pregnancy advances [38].

Increased proneness towards infection owing to the reproductive hormones, especially progesterone, is overshadowed by increased frequency of micturition due to physiological changes in last trimester.

Pro-inflammatory immune cytokines which are related to the progress of disease and anemia quite reliably quantify morbidities due to Schistosoma in pregnancy.

15.3.3 Adverse Pregnancy Outcome in Maternal Schistosomiasis

Schistosomiasis affects the uterine environment during pregnancy. Pregnant women develop severe anemia, have low-birth-weight infants and are at increased risk for infant and maternal mortality.

Schistosomiasis has been found in placenta, and newborns have been diagnosed with this condition, thus confirming congenital infection [39].

Pro-inflammatory cytokines, which are produced due to infection cause anemia associated with Schistosomiasis [40].

Two suggested mechanisms for causing anemia are:

- Decreased erythropoietin production due to increased levels of TNF-α affects red blood cell production from bone marrow as well as their life span [41].
- IL-6 (a cytokine produced due to Schistosomiasis) causes increased levels of hepcidin. This causes increased sequestration of iron in stored form (ferritin) finally leading to decreased bioavailability of iron and anemia [42].

Besides anemia, schistosomiasis can cause elevated levels of endotoxin in maternal and placental compartments which can have adverse effects on pregnancy. This has been suggested by a study among Philippine pregnant women [43].

Higher rate of spontaneous abortions and a higher risk for ectopic pregnancies are observed in schistosomiasis infected pregnant women. Additionally, an increase in infection load has also been attributed to the increased pelvic blood flow during pregnancy. Urogenital schistosomiasis in pregnant women results in hematuria due to bladder lesions caused by submucosal deposition of the parasite's spiny eggs [44].

15.3.3.1 Transplacental Transmission and Effect on Neonates

If an infection can cross placenta, it can be easily transmitted through this route and infect the developing fetus if its load is high. A few studies point towards transplacental transmission of schistosoma, although no definite link has been found yet [45].

15.3.4 Diagnosis

Rapid detection of schistosoma infection is very important in pregnant women as it helps to avoid adverse outcomes.

Diagnosis of Schistosomiasis can be done in the following ways:

- Detection of parasite eggs in stool or urine specimens.
- Detection of antibodies and/or antigens in blood or urine samples.
- In case of urogenital schistosomiasis, the standard diagnostic technique is a filtration technique using nylon, paper, or polycarbonate filters.
- Kato–Katz technique (methylene blue-stained cellophane soaked in glycerin) is used to detect eggs of intestinal schistosomiasis in fecal specimens. In *S. mansoni* transmission areas, CCA (Circulating Cathodic Antigen) test can also be used.
- Serological and immunological tests may be useful in showing exposure to infection and the need for thorough examination, treatment, and follow-up among people living in nonendemic and low exposure areas.

15.3.4.1 In Pregnancy

Rapid detection of schistosomiasis is very important in order to avert the adverse outcomes in pregnancy. Diagnosis of schistosomiasis during early pregnancy should be made an important part of antenatal care particularly in areas endemic with schistosomiasis.

- Urine analysis is recommended for screening during antenatal visits. This may help in early diagnosis of complications related with pregnancy.
- Macrohematuria (visible blood in urine) is used as an indirect rapid diagnostic marker for urogenital schistosomiasis.
- Microhematuria (by using urine chemical reagent strips) has also been suggested to be a reliable marker in endemic areas. However, other possible causes of microhematuria, such as idiopathic hematuria, changes in urogenital tract during pregnancy, and urinary tract infections should always be considered.
- Microscopy can be used to confirm the association of pregnancy associated proteinuria (diagnosed by using the urine chemical reagent strips) and schistosomiasis.

15.3.5 Management

WHO recommends the use of praziquantel (40 mg/kg) in a single dose during pregnancy in order to prevent the harmful effects of Schistosomal infection on maternal and fetal wellness. In pregnant women with obstructive uropathy due to polyps or granulomas, surgical intervention is required.

15.3.6 Prevention and Control

The control of schistosomiasis is based on:

- Extensive treatment of people living in endemic areas with Praziquantel. Such people include:
  - School going children

  - Adults
  - Entire communities
  - People who work in infected water bodies
- Availability of clean water
- Sanitary and hygienic conditions
- Educating the people
- Controlling the population of snail in these areas.

15.4 Leishmaniasis

Leishmaniasis is enlisted as a Neglected Tropical Disease (NTD) [46]. It occurs most frequently in the tropics and subtropics of Africa, Asia, America, and southern Europe. It is caused by the protozoa, Leishmania and spreads by the bite of certain types of sandflies. The risk factors of this disease include malnutrition, poverty, urbanization, and deforestation. There can be three main presentations of Leishmaniasis—cutaneous, mucocutaneous, or visceral [46].

The cutaneous form presents with skin ulcers. Ulcers of the nose, mouth, and skin are features of mucocutaneous form [47]. The visceral form first presents with ulcers on skin and later, the infected person suffers from fever, reduced red blood cells count, enlarged liver and spleen. More than 20 species of Leishmania are responsible for causing infections among humans [46, 47].

15.4.1 Transmission of the Disease

Leishmaniasis is a parasitic disease which is caused by 20 different species of *kinetoplastid protozoa* belonging to the genus *Leishmania* [48].

Visceral Leishmaniasis: It is usually caused by *Leishmania infantum* or *Leishmania donovani*.

Tegumentary Leishmaniasis (TL): The subtypes of TL include:

- Cutaneous Leishmaniasis (CL)—It presents as non-healing localized ulcers or nodules and is associated with over 15 geographically widespread species of Leishmania. Diffused form of cutaneous leishmaniasis is mostly associated with *Leishmania amazonensis* and *Leishmania mexicana* in the Americas and *Leishmania aethiopica* in Africa.
- Mucocutaneous Leishmaniasis (MCL)—It is mostly attributed to infection due to *Leishmania braziliensis*.

15.4.1.1 Vector

Only one genus of sandfly is responsible for human transmissions of Leishmania in the new World—Lutzomyia. The sandfly inhabits the areas in and around of human habitats. Here, it feeds on the blood of mammals like dogs and humans and birds as well. Females are anthropophilic. They need blood for the development of their eggs. Elsewhere, it is the genus Phlebotomus, which behaves as a vector of leishmaniasis [49].

15.4.1.2 Life Cycle of Leishmania

During a new blood meal the sandfly deposits promastigotes (infectious form of parasite) along with its saliva, inside the dermis of another host. These promastigotes invade macrophages and form amastigotes inside parasitophorous vacuoles. Here they multiply until rupture of vacuoles and get ready to infect new macrophages (Fig. 15.2).

Hematogenic dissemination to bone marrow, spleen, liver, and lymph nodes has also been observed because these are rich in cells of the mononuclear phagocyte system [50–52].

15.4.2 Clinical Features

The clinical manifestations, due to infection, can be attributed to the interaction between the tissue mainly attacked by the parasite and the host's immune response towards their presence.

In VL, parasites mainly colonize the mononuclear phagocyte system (MPS) of the spleen, liver, and bone marrow [52], while in TL parasites primarily reside in MPS cells in skin or mucosal tissue. Pregnancy induces a state of relative immune tolerance. This may permit increased parasitic spread and colonization of other organs and tissues. Clinical states such as post-kala-azar

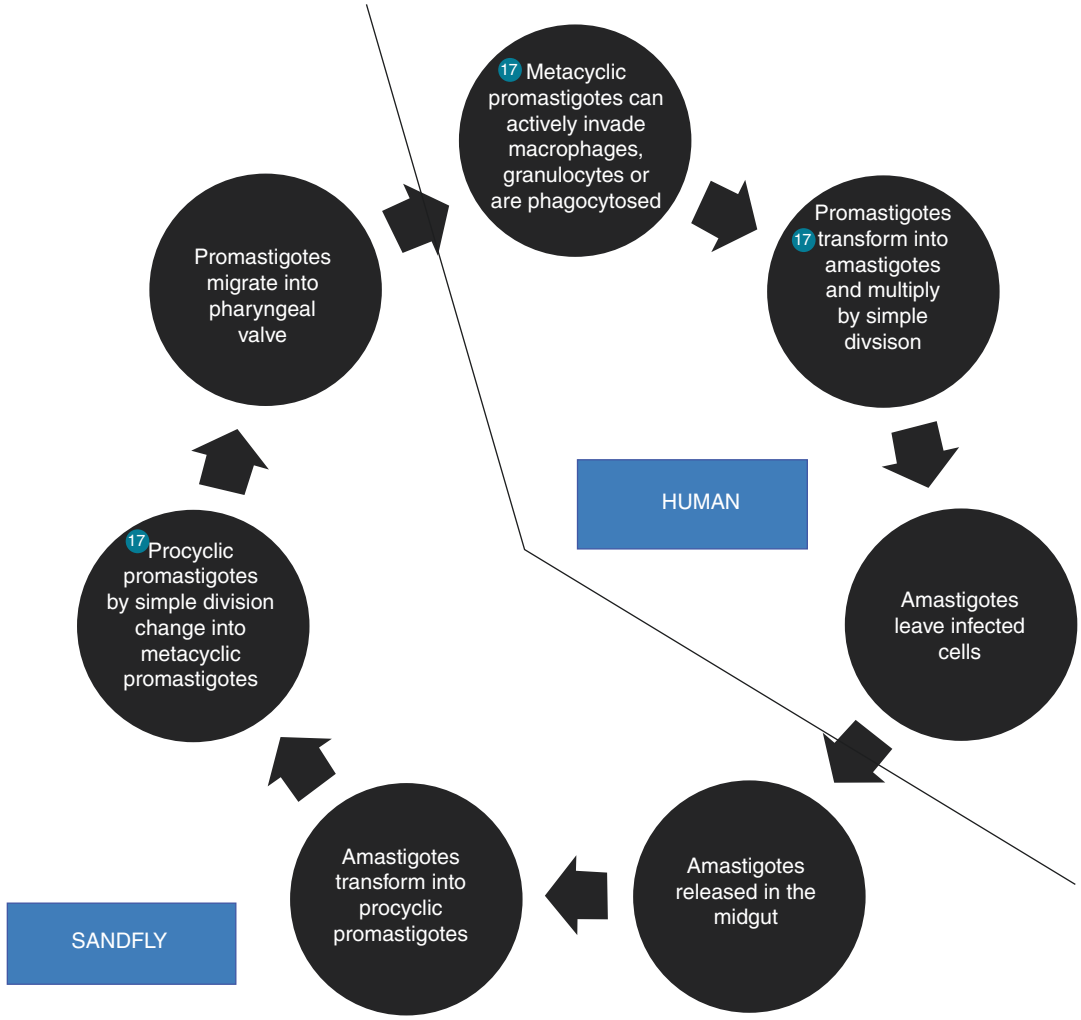

Fig. 15.2 Life cycle of Leishmania

dermal leishmaniasis and visceral symptomatology attributable to TL-associated Leishmania species in immunodeficient individuals highlight the host–Leishmania relationship [53, 54].

15.4.2.1 Congenital Transmission

In humans, transplacental route is responsible for congenital transmission of VL-associated Leishmania. Congenital transmission of TL-associated parasites has been documented in animal models only till now. The maternal T cell response to Leishmania infection has been shown to be associated with adverse fetal outcomes in animal models.

Given the affinity of Leishmania for the cells of the MPS, it is hypothesized that Hofbauer cells, the macrophages of the placenta, are the primary placental cell line targeted by Leishmania [55]. The role of timing of infection remains uncharted in case of Leishmaniasis.

Visceral Leishmaniasis (VL)

VL can be classified into different forms [50].

Inapparent infection: It is seen in patients with positive serology or positive Montenegro skin test (test for leishmania) or in such patients in whom parasites are detected in tissues without any clinical manifestations.

Oligosymptomatic: Patients suffer from low or absent fever intermittently; presence of hepatomegaly is observed, which may be accompanied with distinct splenomegaly. Adynamic state as well as cachexia is observed, but no reports of hemorrhage are present.

Acute: The onset can be abrupt or insidious. Mostly, high and continuous or intermittent fever appears to be the first symptom. This, however, can be, followed by diminution of symptoms within 1 or 2 weeks. In addition to anemia accompanied by hyperglobulinemia, adynamic state, hepatosplenomegaly, weight loss, and hemorrhage are observed,

Classic: It presents an image of protracted advancement in infection which leads to nutritional impairment accompanied with loss of hair, ciliary growth and brightness, and edematous lower limbs. Manifestations include fever, asthenia, adynamic state, anorexia, weight loss, and cachexia. Obvious hepatosplenomegaly, widespread micropolyadenopathy, and marked pallor of the skin and mucosa, as an outcome of severe anemia, are observed. Frequent hemorrhagic phenomena such as gingival bleeding, epistaxis, ecchymoses, and petechiae are also seen. Laboratory investigations reveal the picture of marked pancytopenia (anemia, leukopenia, thrombocytopenia), hypoalbuminemia, and hyperglobulinemia.

Refractory: This form of classic VL is unresponsive to antimony treatment. This form has evolved over time and owing to its refractoriness to standard treatment, is considered to be more severe clinically.

Cutaneous Leishmaniasis (CL)

The most frequent clinical type of cutaneous leishmaniasis (CL) usually lasts for less than a year. Affected parts of the body are those which are exposed and hence, can be easily bitten by the sandfly. The lesion begins, at the site of bite, with a non-specific erythematous papule. The variation in incubation period observed, is from 1 week to several months (average 1 week–3 months). This depends on several factors including the species of Leishmania and the size of the inoculum. In a week or two, many of the bite-like lesions resolve and only a few persist which develop into CL lesions. Over 4–12 weeks, persistent papules enlarge into nodular plaque. A seropurulent discharge develops which later dries up resulting in crust formation. Upon removal of this crust, a shallow ulcer/crater is revealed. This "volcanic" nodulo-ulcerative morphology is the most distinctive feature of acute CL.

The longitudinal axes of elongated cutaneous lesions are aligned with those of skin creases. This orientation is more apparent in mature lesions [56]. Different morphological patterns of lesions may be seen like plaque, eczematoid, warty, hyperkeratotic, erysipeloid, zosteriform, and sporotrichoid [57].

Satellite papules may be seen around the primary lesion. These represent a reaction to local dissemination of the parasite or its antigenic products. Nodular lymphangitis is observed as solitary or multiple nodules which develop subcutaneously and are proximal to the skin lesions. Regional (bubonic) lymphadenopathy may also be seen.

End result is formation of an atrophic and faded scar. Before the appearance of scar, fully matured lesions remain stable for several weeks and heal. This takes several months.

Diffuse CL

An uncommon variety of acute CL is frequently initiated in a form which is called *primary lesion*. This lesion then converts into several ulcerated nodules and plaques which extend over other areas of skin.

Pregnancies associated with visceral and cutaneous leishmaniasis present differently. These infections may be associated with increased fetal complications like miscarriages, preterm birth, and stillbirth [58]. Table 15.2 shows the various types and presentations of Leishmania infection.

15.4.3 Diagnosis

Multiple diagnostic tests are available; both non-specific tests and tests which are specific to the infection [59].

Table 15.2 Types and presentation of Leishmania infection

Types of Leishmania infection	Clinical Presentation
Visceral Leishmaniasis	Hepatosplenomegaly and fever along with immunosuppression. Also, blood disorders, owing to affliction of hematogenic organs.
Cutaneous Leishmaniasis	Non-healing lesions of epithelial surfaces; may be diffuse which is associated with multiple, exuberant lesions
Mucocutaneous Leishmaniasis	Mucosal tissues and cartilage (such as palate or nasal septum) are involved and damaged

15.4.3.1 Non-specific Tests

- Complete blood count: This helps to identify the presence of anemia, leucopenia, thrombocytopenia, pancytopenia, or relative lymphocytosis. Lack of eosinophils is a distinctive finding.
- Determination of albumin/globulin ratio: marked inversion of ratio observed. This may be as much as what is observed in cases of multiple myeloma.
- Montenegro skin test: used mainly for the assessment of a patient's cell-mediated immunity. This test involves giving an intradermal injection of Leishmania antigen (phenol killed amastigotes). Response is generated and measured after about 48 to 72 hours (quite similar to the tuberculin skin test). This test, however, is unable to tell apart a present infection from what occurred in the past.

15.4.3.2 Specific Tests

- Serological tests
  - Indirect immunofluorescence (IF), which permits the determination of IgG and IgM antibodies. The result is considered positive at dilutions equal to or higher than 1: 40.
  - Immunoenzymatic assays (ELISA) [60, 61] are increasingly used for determining IgG and IgM antibodies. The sensitivity and specificity rates are higher than 97%.
- PCR tests: With parasite detection rates of 97% and species identification, more rapid and sensitive than isoenzyme analysis, these tests have become a backbone for diagnosis and prognosis. Determination of definite species is imperative for the treatment and prognosis as this tends to vary for each species. Quantifying of Leishmania organisms can also be done with the help of PCR studies and the data can be used for diagnostic and follow-up measurements. Further studies are required to evaluate the specificity of PCR studies in differentiating Leishmania species and subspecies [59].
- Parasitological examination (amastigotes, Leishman–Donovan bodies are directly visualized) on buffy-coat preparations of peripheral blood or aspirates preferentially obtained from bone marrow, spleen, lymph nodes, or skin lesions using Leishmania or Giemsa stain. Biopsy from spleen should be obtained in hospitals under surgical supervision. In case of pregnant patients, sternal bone marrow is preferred for biopsies over spleen and lymph node.
- Culture: The organism is cultured using RMPI media and NNN media.
- Monoclonal antibodies: This technique is mainly reserved for research purposes and is more sensitive and specific than routine staining. This method uses several antibodies which can be utilized for the identification of amastigotes (in smears or biopsy specimens) and promastigotes (in culture) because they are directed against genus or species-specific Leishmania antigens [62–64].

15.4.4 Differential Diagnosis

Differential diagnosis of Leishmaniasis consists of:

- Malaria Brucellosis
- Typhoid Acute Chagas disease
- Leprosy Sarcoidosis
- Hepatosplenic schistosomiasis lymphoma
- Multiple myeloma Sickle cell anemia
- Leukemia

15.4.5 Treatment

Principles of treatment in pregnant women include:

- Treating the patient and preventing vertical transmission
- Likely teratogenic and toxic effects of drugs should be kept in mind while treating.

15.4.5.1 Visceral Leishmaniasis

Pentavalent antimonial organic compounds are the drugs of choice in case of VL and have been used in clinical practice since years. Information on their safety profile in pregnancy is still minimal. According to some authors, these should be avoided since their teratogenic effects are not well proven in pregnancy, while others are of the opinion that carcinogenic, mutagenic, and teratogenic risks of antimony compounds are not very significant and so they may be used during pregnancy without any fear of maternal or fetal harm. A clinical report has also shown no adverse effects of pentavalent antimony on fetus when it was administered during the second trimester accompanied with uneventful full-term delivery and a healthy baby [61, 62, 64].

An experiment consisting of repetitive administration of meglumine antimoniate and Glucantime in rats embryo was conducted, which was observed to be lethal and teratogenic. However, no maternal toxicity or diminution of fetal weight was noted in the treated groups.

Amphotericin B is the second drug of preference for treating VL among women who are not pregnant. However, strict care is needed during its usage owing to high cardio and nephrotoxicity. Though Amphotericin B crosses the placenta, still its concentrations in fetal plasma are less than one-third of those observed in maternal plasma. Based on the high cure rates of kala-azar with use of Amphotericin B, its safe use in pregnancy women without any repercussions on fetus has been reported [65–67].

Several other drugs have been in use in the treatment of VL. Aminosidine is another option for treatment during pregnancy. The precautions and restrictions are the same, which apply to the use of aminoglycosides during pregnancy. The response to aminosidine is generally slower than that observed during treatment with the first and second choice drugs. Renal functions monitoring is mandatory during the treatment with these drugs.

During lactation, if the mother is being treated with pentavalent antimony compounds, the newborn should be breast-fed 5 to 6 hours after drug administration to the mother. By this time, levels of drugs in the milk become negligible. If amphotericin B is used, no significant recommendations concerning lactation are considered necessary [68].

15.4.5.2 Cutaneous Leishmaniasis

The treatment of uncomplicated cutaneous leishmaniasis can be both local and pharmacological with heat or cryotherapy and intralesional injection of pentavalent antimonial or topical paromomycin, respectively. Methylbenzethonium chloride (MBCL) is a quaternary ammonium salt that exhibits antileishmanial activity in high concentrations. It is often used synergistically with the aminoglycoside antibiotic paromomycin (PR) in a combination of 15% PR/12% MBCL ointment (not FDA approved). Consequently, there are no clear guidelines for treatment of CL in pregnancy. In addition, the vertical transmission of the Leishmania parasite in the context of CL is still debatable. Transplacental CL transmission has not been reported in humans till date.

15.5 Conclusion

The parasitic infections discussed above form important differential diagnosis of common presentations seen in pregnancy- anemia, fever, headache and seizure disorder. These parasitic infections are now not limited to endemic areas and knowledge regarding their presentation and dignostic evaluation is crucial for correct diagnosis and management in pregnant women to avoid maternal and fetal complications.

Key Points

1. Cysticercosis is an infection caused by the larvae (*Cysticercus cellulosae*) of the parasite *Taenia solium* (pork tape worm) which are transmitted by consumption of improperly cooked food or drinking water contaminated with *T. solium* eggs.
2. Taeniasis is mostly characterized by non-specific gastro-intestinal symptoms, while features of cysticercosis depend upon the location of cysticerci. Due attention must be paid to the family history, occupational history, food habits, and history of migration from endemic sites to clinch the diagnosis.
3. NCC in pregnancy presents with features mimicking those of eclampsia; treatment with antihelminthic drugs should be deferred until the seizure is controlled or until postpartum unless the severity of clinical condition necessitates its use.
4. Schistosomiasis is quite prevalent in poor communities of tropical and subtropical areas, where people are unable to access safe drinking water and proper sanitation and is an important cause of severe anemia in pregnancy.
5. Anemia associated with Schistosomiasis is alleged to be the consequence of pro-inflammatory cytokines produced in reaction to disease causing agents.
6. Leishmaniasis is an infection caused by the protozoa Leishmania species and is spread by sandflies.
7. Leishmaniasis is characterized by visceral as well as cutaneous symptoms depending on the type of the disease; Antimony compounds are the recommended first-line drugs used for the treatment of both visceral and cutaneous leishmaniasis.

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Impact of Helminthic Infections in Pregnancy

16

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16.1 Introduction

Helminthic infections during pregnancy have been found to be an important public health problem in developing world and are predisposed by poverty, inadequate sanitation, poor public and personal hygiene and lack of education [1]. These infections have adverse effects on pregnant women and influence their obstetric outcomes. Helminthic infections can be asymptomatic, or present as anaemia, increased risk of co-infection, nutritional deficiencies, immune-modulation, elephantiasis and organ blockages, thereby adversely affecting the foetus and resulting in foetal growth restriction (FGR), preterm deliveries and immunomodulation of the infant [2]. In view of maternal and foetal complications, World Health Organization (WHO) also recommends the treatment of pregnant women for helminth infections [2]. In areas where prevalence of hookworm infection is more than 20–30%, WHO recommends antenatal deworming of pregnant women after first trimester. In the present chapter, we will discuss various helminthic infections including intestinal nematodes, cestodes, trematodes, tissue nematodes and their impact on pregnancy.

16.2 Disease Burden and Prevalence

Globally, 1.7 billion people are infected with one or other Soil Transmitted Helminths (STH). Survey done in 2003, found prevalence of A. lumbricoides to be more than 1.2 billion(China had >50% of cases), T. trichiura 795 million and hookworm 740 million worldwide. The prevalence rate of A. lumbricoides had decreased to 819 million, T. trichiura to 464 million and hookworm to 439 million in a survey done later in 2010. Asia contributes 67% of the global prevalence of STH and in Asia, the highest prevalence is seen in India (21%) followed by China (18%) [3]. Overall, the STH prevalence decreased to 30% in 2010 from 38.6% in 1990. In India, hookworm prevalence is estimated to be 71 million cases and A. lumbricoides contributes 140 million and T. trichiura 73 million cases [3]. The various types of helminthic infections are shown in Table 16.1.

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Table 16.1 Classification of Helminthic infections [4]

Category	Organisms
Soil-transmitted nematodes	Ancylostoma duodenale (hookworm) Ascaris lumbricoides (roundworm) Trichuris trichiura(whipworm)
Filarial nematodes	Wuchereria bancrofti Onchocerca volvulus Mansonella perstans
Cestodes	Taenia saginata (beef tapeworm) Taenia solium (pork tapeworm) T. Saginata asiatica Diphyllobothrium latum (fish tapeworm)
Schistosoma (blood flukes)	Schistosoma mansoni Schistosoma haematobium Schistosoma japonicum

Source: Arias F, Bhide AG, S A, Damania K, Daftary SN. Arias' Practical Guide to High-Risk Pregnancy and Delivery—E-Book: A South Asian Perspective: Elsevier Health Sciences; 2015

16.3 Soil-Transmitted Nematodes

16.3.1 Hookworm Infestation

Causative organisms are Ancylostoma duodenale (old world hookworm), Necator americanus (new world hookworm) and Ancylostoma ceylanicum (rare infestation). It is transmitted by direct barefoot exposure to contaminated soil and ingestion of raw farm products containing larvae. Transplacental transmission of Anycyostoma duodenale has also been reported [5]. After barefoot exposure to contaminated soil, the filariform larvae penetrate the skin and enter the blood circulation to reach alveoli and travel to trachea and pharynx, and finally enter into the gastrointestinal tract. In the duodenum and upper jejunum, the adult A. duodenale of around 1 cm in length lays about 15,000–20,000 eggs daily for 6–8 years and sucks about 0.2 ml of blood daily. N. Americanus lays fewer eggs (6000–10,000/day), for 2–4 years and sucks about 0.03 ml blood daily. The eggs are passed out in the faeces to start a new life cycle [6] (Fig. 16.1).

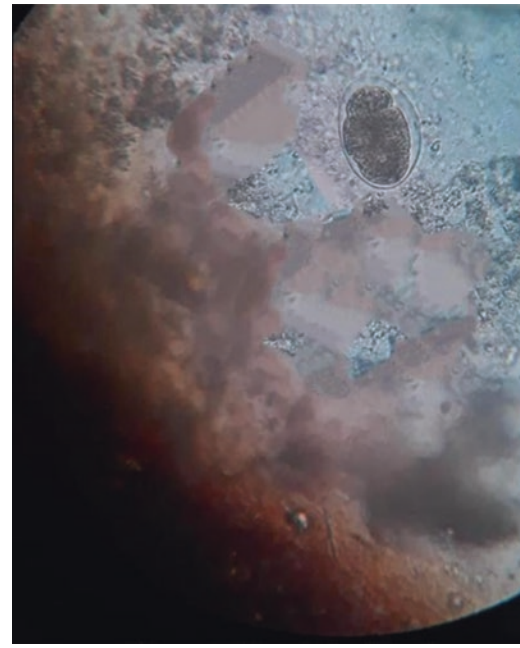

Fig. 16.1 Wet mount of stool showing eggs of Ancyclostoma duodenale containing unsegmented blastomeres (×40)

16.3.1.1 Clinical Features

An erythematous maculopapular rash with itching and blister is observed at the larval penetration site. The patient can present with wheezing, breathlessness, cough, and fever during migration of larvae from the pulmonary alveoli to the trachea. Subsequently, dyspepsia and gastroenteritis due to intestinal colonization occur and this is followed by lethargy, fatigue, pallor and oedema, due to chronic blood loss and progressively increasing anaemia. Increased demand during pregnancy aggravates iron and protein deficiency. The infestation is diagnosed by microscopic examination of stools, which shows a typical four to eight celled hookworm morula.

16.3.1.2 Effects on Pregnancy

Hookworm infestation causes anaemia and its sequelae, chronic ill health, risk of preterm delivery and foetal growth restriction (FGR). Transplacental transfer (as hypobiotic larva), has been also reported [7], causing infantile disease and increased mortality in affected infants [5].

16.3.1.3 Treatment

Anti-helminthics should be started in the second trimester (avoided in the first trimester as a general rule). The anthelmintic of choice is pyrantel pamoate which should be given as a single oral dose of 10 mg/kg body weight with a maximum dose up to 1.0 g. Supportive treatment with iron supplements, folic acid, vitamin B12 and high protein diet is given. Mebendazole and albendazole can be used in pregnancy, and these could be effective in reducing maternal anaemia and improving birth weight in hookworm endemic regions [8].

16.3.2 Ascariasis (Roundworm Infection)

The causative organism is A. lumbricoides with around 25% of the world's population at risk of its infection [9]. It is transmitted orally by ingestion of food contaminated with eggs of A. lumbricoides. Ingested embryonated eggs mature into larvae in the small intestine. The larvae then penetrate the gut wall to reach the circulation and travel to the liver and lungs. After a period of 10 days, these larvae reach the bronchi and trachea up to the epiglottis and then are swallowed to reach the intestine, where they mature into adult worms over a period of 60 days. Female worm in the gut releases about 24,000 eggs daily for a period of 6–18 months. These eggs pass out in the faeces and become infective after incubation in soil for 2–3 weeks and remain infective up to about 6 years. (Figs. 16.2 and 16.3).

16.3.2.1 Clinical Features

Patients may suffer from a wide variety of symptoms because of migration of the larvae and adult worms. Patients can be either asymptomatic or can present with a persistent cough, bronchopneumonia, intestinal cramps, vomiting, chronic indigestion, malnutrition (protein, carbohydrate and vitamin deficiency), volvulus, intestinal obstruction, intussusceptions, biliary colic and liver abscess. The disease is diagnosed by stool examination which shows fertile and non-fertile eggs, blood count suggestive of eosinophilia and ultrasonography suggestive of a coiled up mass of worms. Other tests for helping diagnosis are ascaris complement testing and cutaneous hypersensitivity tests.

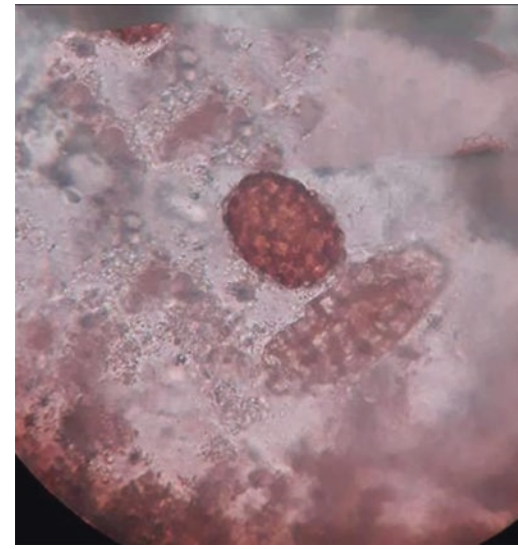

Fig. 16.2 Unfertilized eggs of Ascaris lumbricoides in stool (Wet mount; ×40)

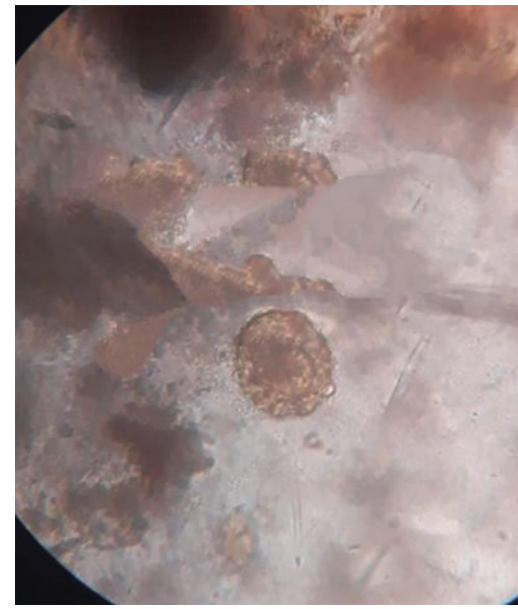

Fig. 16.3 Wet mount of faeces showing fertilized eggs of Ascaris lumbricoides (×40)

16.3.2.2 Effects on Pregnancy

Chronic malnutrition, indigestion, abdominal cramps, rarely acute abdomen, low birth weight and preterm birth.

16.3.2.3 Treatment

Pyrantel pamoate is administered as a single dose, 10 mg/kg body weight and should be given in the second trimester. Piperazine citrate is not preferred because of toxicity. Albendazole and mebendazole should be avoided in the first trimester of pregnancy. Surgical intervention may be called for in case of acute abdomen.

16.3.3 Enterobiasis (Threadworm, Pinworm)

The causative organism is E. vermicularis, affecting around 300 million people worldwide. It is transmitted orally by ingestion of infective eggs in faecal contaminated items. After ingestion, these eggs are transformed into larvae in the duodenum and mature into adult forms in the gut lumen (Fig. 16.4). Fertilized female worms migrate through the anal canal at night to deposit their eggs on the perianal skin before they die. These eggs become infective after a few hours of deposition. Autoinfection is widespread and spreads rapidly among other family members and contacts. There is no multiplication of worms inside the body and the average lifespan of adult worms is approximately 2 months.

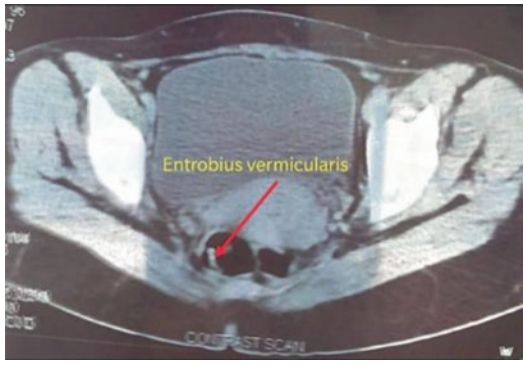

Fig. 16.4 CT image (in non-pregnant) showing Enterobious vermicularis mimicking as a foreign body

16.3.3.1 Clinical Features

Infection with E. vermicularis causes perianal and vulval pruritus. Occasionally, the adult worms migrate into the vagina, causing vaginitis. Microscopic examination of perianal scrapings and undersurface of fingernails reveals the typical eggs of Enterobius vermicularis. Adult worms can be found on gross examination of stools.

16.3.3.2 Effect on Pregnancy

E. vermicularis infection generally does not affect the pregnancy significantly but perianal and vulval pruritis may aggravate in pregnancy.

16.3.3.3 Treatment

Treatment of choice is oral Pyrantel pamoate 10 mg per kilogram of body weight with a maximum dose up to 1.0 g.

16.3.4 Strongyloides (S. stercoralis)

Causative organism is S. stercoralis. Immunocompromised individuals are more susceptible and have severe symptoms. Filariform larvae enter the circulation by penetration of the skin. After penetration, larvae reach the lungs and trachea-bronchial tree and finally reach the gut by swallowing. The adult worm lays its eggs in the duodenum and jejunum and these eggs release the rhabditiform larvae which are expelled in faeces and become infective filariform larvae. There are also alternative modes of spread with autoinfection by developing into filariform larvae in the gut and sexual reproduction in the soil.

16.3.4.1 Clinical Features

Cases with low parasitic load are asymptomatic while others may present with cough, breathlessness, malabsorption, protein losing enteropathy, iron deficiency anaemia, indigestion, flatulence, belching and cutaneous manifestations like urticaria, petechiae and ulcers. Infection is diagnosed by microscopic examination of fresh samples of stool, duodenal aspirates, jejunal biopsy and sputum. Stool culture using Agar plate and Charcoal culture method is done when larvae are scanty in stools. Serological tests include Complement

fixation test, indirect haemagglutination and enzyme-linked immunosorbent assay (ELISA) larval antigen test can also be done.

16.3.4.2 Effects on Pregnancy

Infection with S. stercoralis can cause malnutrition, anaemia, gastrointestinal symptoms, low birth weight and FGR.

16.3.4.3 Treatment

Albendazole 400 mg is given twice daily for 3 days during pregnancy. Thiabendazole 25 mg/kg twice daily for 2–3 days after delivery can also be given.

16.3.5 Trichuriasis (Whipworm)

Causative organism is T.trichiura. It is transmitted orally by food contaminated with embryonated eggs. There is no extra-intestinal migration and worms stay in the caecum and appendix. The entire cycle takes 3 months to complete and the female worm lays about 5000 eggs/day (Fig. 16.5).

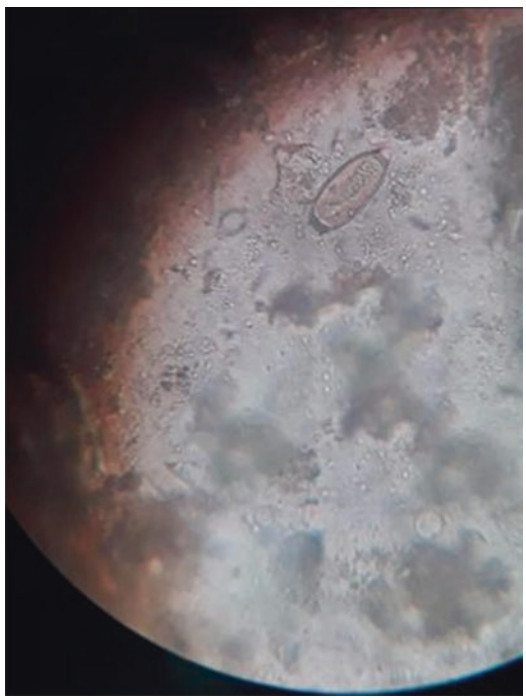

Fig. 16.5 Stool wet mount showing eggs of Trichuris trichiura with mucus plug at both ends.

16.3.5.1 Clinical Features

Infection causes malnutrition, anaemia, gastrointestinal symptoms (diarrhoea, tenesmus and vomiting) and in some cases severe dysentery. It is diagnosed by stool examination which may reveal presence of adult worms grossly and typical barrel-shaped eggs microscopically. Blood count may show eosinophilia.

16.3.5.2 Effects on Pregnancy

Infection with T.trichiura causes malnutrition, anaemia and low birth weight.

16.3.5.3 Treatment

Pyrantel pamoate as a single dose, 10 mg/kg of body weight with a maximum dose of 1.0 g, preferably after completion of the first trimester. Albendazole and mebendazole 400 mg as a single dose may be given in second trimester.

16.4 Cestodes

16.4.1 Cestode (Tapeworm)

Causative organisms are Taenia saginata (beef tapeworm), Taenia solium (pork tapeworm), T. saginata asiatica and Diphyllobothrium latum (fish tapeworm). These are difficult to treat and recurrence rates are high. Humans are both a definitive and intermediate host and the infection is transmitted by undercooked and raw non-vegetarian food.

16.4.1.1 Clinical Features

Infection can be asymptomatic or present with gastrointestinal symptoms like abdominal pain, anorexia, nausea and vomiting, diarrhoea, weight loss, while in some cases, proglottids(segments) may cause obstruction of the bile duct, pancreatic duct or the appendix. Infection with the larval stage of T. solium (cysticercosis) can cause ectopic parasitism with involvement of the central nervous system, striated muscles, eyeball and rarely other tissues. D. latum is known to cause megaloblastic anaemia because of competitive utilization of available folic acid and vitamin B12.

Infection is diagnosed by presence of gravid proglottids in clothing, bedding and in fresh stool

samples. Perianal cellophane tape test reveals eggs. For species differentiation, enzyme electrophoresis of glucose phosphate isomerase can be done.

16.4.1.2 Effects on Pregnancy

Infection with cestodes can cause nutritional deficiencies and anaemia.

16.4.1.3 Treatment

Praziquantel 10 mg/kg single dose and niclosamide 2.0 g is the treatment of choice for all species. Moderate purgative ingestion 2–3 h after treatment is required for T. solium. Niclosamide is safe in pregnancy. Praziquantel is more effective for treatment of H. nana. Folic acid and vitamin B12 supplementation is recommended in D. latum infection. Albendazole 15 mg/kg day (in 2–3 divided doses) for 8–28 days is recommended for cysticercosis but should be avoided in the first trimester.

16.4.2 Hydatid Disease (Echinococcosis)

The causative organisms are echinococcus granulosis (cystic hydatid disease) and echinococcus multilocularis (alveolar hydatid disease). This is a zoonotic disease and human echinococcosis is caused by infection by the larval stage. Humans act as the intermediate host for the larval stage of the parasite. The hydatid cyst may persist in the host for many years. Common sites for hydatid cysts include liver (65%) and lungs (25%) and less common sites are the brain, kidney, bones, skeletal muscles and pelvic organs.

16.4.2.1 Clinical Features

Hydatid disease can manifest as cholangitis, reactive hepatitis, hepatic cirrhosis, obstructive jaundice and portal hypertension due to mechanical pressure on surrounding structures. Pulmonary echinococcosis may present with respiratory symptoms, i.e. cough, breathlessness, chest pain and in some cases haemoptysis.

Diagnosis is by X-ray chest which shows a thin eggshell calcification and USG (ultrasound abdomen is a safer option during pregnancy). Ultrasonographic features include a hydatid cyst with well-defined wall and presence of daughter cysts placed peripherally and there is varied echogenicity between the cysts. These cysts can be classified according to presence of septations, daughter cysts and calcifications. Cautious aspiration of cyst under USG guidance should be done. Immunoblot test is 98% specific and 91% sensitive for liver cysts, indirect haemagglutination test is positive in 60–90% cases; ELISA and immunofluorescence are useful screening tests. Hemogram suggests eosinophilia.

16.4.2.2 Effects on Pregnancy

Echinococcosis can cause malnutrition, dystocia in case of pelvic cysts, low birth weight and preterm birth.

16.4.2.3 Treatment

Surgical excision of hydatid cysts is the definitive treatment. Albendazole and mebendazole should be used cautiously in the first trimester and only for acute emergency situations. Medical treatment consists of albendazole 800 mg daily (in divided doses) for 1–3 months or mebendazole 50 mg/kg daily in three divided doses for 3 months.

16.4.3 Trematodes (Schistosomiasis)

The causative organisms for schistosomiasis are Schistosoma haematobium, Schistosoma japonicum and Schistosoma mansoni. It is transmitted by contaminated water and snails serve as intermediate hosts. The adult worms of S. japonicum and S. Mansoni habitats in the mesenteric and haemorrhoidal veins, involving the liver and gastrointestinal tract while the adult worm of S. haematobium habitats and matures in the pelvis and bladder venous plexus, involving the pelvic organs, bladder and lower gastrointestinal tract.

16.4.3.1 Clinical Features

Mucous diarrhoea, hepatosplenomegaly and colonic polyposis are caused by S. japonicum and S. mansoni; these patients are often carriers of chronic salmonella. S. Haematobium can cause haematuria, hepatosplenomegaly and in

some patients mucus diarrhoea, bladder polyposis and carcinoma. The infection is also associated with salpingo-oophoritis, infertility, ectopic pregnancy and abortion.

Schistosomiasis is diagnosed by:

- Microscopic examination of urine, stools and vaginal discharge for eggs.
- Biopsy from bladder, rectum or liver.
- Intravenous pyelography.
- Cystoscopy reveals sandy patches ulceration.
- Barium enema shows spiculating ulcers.
- CT scan may reveal turtleback calcification which is pathognomonic of S. haematobium.
- Western blot is also a good and accurate test with sensitivity >90% and specificity >70% [10].

16.4.3.2 Effects on Pregnancy

Infection leads to chronic proteinuria, haematuria, weakness, anaemia, malnutrition and recurrent UTI. Placental involvement, FGR and low birth weight have also been reported.

16.4.3.3 Treatment

Praziquantel 40 mg/kg in a single dose is the treatment of choice. Surgical intervention is required for obstructing granulomas and polyps causing obstructive uropathy.

16.4.4 Tissue Nematodes (Filariasis)

The causative organisms are Wuchereria bancrofti which is found in India and Brugiamalayi is common in Southeast Asia. The infection is transmitted by mosquito bite, and the microfilariae inhabit lymphatics and lymph nodes, causing acute and chronic obstruction which subsequently leads to fibrosis, granuloma formation and irreversible lymphoedema.

16.4.5 Clinical Features

In the acute phase, patient may have fever with rigors and lymphangitis. Chronic disease is characterized by lymphatic obstruction in the lower limbs, upper limbs, abdomen, pelvic organs and external genitals causing non-pitting oedema and elephantiasis of limbs, vulva and abdominal wall. Other manifestations are chyluria and chylous ascites.

The diagnosis is established by detecting microfilariae in venous blood ideally drawn between 9.00 pm and 1.00 am. Diethylcarbamazine (DEC) provocation test is performed by oral administration of 100 mg of DEC and collecting the venous blood half an hour later which is filtered through a fine-mesh filter membrane; stained microfilariae can then be identified. Indirect fluorescence and ELISA tests can detect antibodies (IgG and IgE) in 95% of active cases and 70% of chronic cases. Immunological tests and high eosinophilia are suggestive of filariasis.

16.4.5.1 Effects on Pregnancy

When lower genital tract and vulva are affected by the disease, there can be difficulty during labour [11]. Sometimes, the granulomas need to be excised to release the obstruction.

16.4.5.2 Treatment

Treatment should be deferred till delivery. Diethylcarbamazine is the drug of choice which is given as 5.0 mg/kg in three divided doses for 14–21 days. The allergic reactions can be controlled by concomitant administration of steroids or antihistaminics. Sensitivity can be tested by administering a single dose of 25–50 mg DEC. Caesarean section is indicated for obstructive vulval growths.

16.5 Impact of Helminthic Infections on Pregnancy

16.5.1 Helminthic Infections and Anaemia

Anaemia is the most common manifestation of helminthic infestation specifically geohelminths and schistosomes due to persistent blood loss in the intestine or urinary tract, particularly when helminthic infections are associated with other concomitant factors like nutritional deficiencies and co-infection with HIV or malaria. In presence of nutritional deficiencies, more specifically

hookworm infestation, iron deficiency may be exacerbated [12, 13]. Other geohelminths and schistosomes infestation is associated with mild iron deficiency, which only occurs when parasite burdens are high [12, 14–16]. Co-infection with malarial parasite is also associated with an increased risk of anaemia and other negative outcomes during pregnancy [16, 17], although the effects of helminths alone are often less clear.

Severe anaemia is associated with adverse obstetric outcomes such as maternal mortality, preterm birth, low birth weight and neonatal anaemia [18–22]. With limited risks associated with mild anaemia, it is suggested that anemia due to helminths is of more concern when it is associated with high worm burden and other factors like chronic iron deficiency, malnutrition and malaria etc [18, 23].

16.5.2 Malnutrition

Helminths, mainly gut nematodes can cause malnutrition during pregnancy. Loss of appetite is the most important mechanism through which gut nematode infections can lower nutritional status. Also, decreased nutrient absorption and increase nutrient loss due to mechanical effects and gut inflammation can occur due to gut nematodes.

16.5.3 Helminthic Infections and Co-Infection

Helminthic infections are associated with an increased risk of co-infection and disease progression by affecting immunity and causing malnutrition. Various studies have suggested the association between geohelminths and malaria and it has been found that helminths may increase susceptibility to malaria [22, 24, 25]. Hookworm has been shown to have a strong association with malaria [17]. However, few studies have also found that some species, like A. lumbricoides are associated with a reduced risk of malaria [26], and it has been reported that Schistosoma haematobium can limit parasitaemia [27, 28].

Helminthic infections and HIV can cause depletion in CD4+ T cells and treatment of helminths reduces HIV progression and improves CD4 counts. Helminths are also associated with increased mother-to-infant transmission of HIV [29].

16.5.4 Immune Response Modulation Due to Helminthic Infections

16.5.4.1 Maternal Immune Response Modulation

Helminthic infections are associated with modulation of the host immune response of pregnant women with a shift towards Type 2 immunity and release of anti-inflammatory cytokines. The immune response during a normal pregnancy and due to chronic helminthic infections is similar with increased activity of CD4C T cells and helper T cell type 2 (Th2) and release of anti-inflammatory cytokines like IL-4, IL-5, IL-9 and IL-10 and transforming growth factor-b (TGF-b) increase while T-helper 1 (Th1) cells and their inflammatory cytokines (as well as inflammatory macrophages and natural killer cells) decrease [30, 31]. This leads to a weaker immunological response to other infections and increases susceptibility to heterologous infections such as malaria. These associations might also be confounded by environmental and behavioural factors.

Immunomodulation may also have an impact on glucose metabolism. Eosinophils, which are a source of IL-4 in the adipose tissue for the induction of alternatively activated macrophages are increased in helminthic infections. Therefore, this may be beneficial to pregnant women with gestational diabetes as it leads to a sustained improvement in glucose tolerance [32].

16.5.4.2 Infant Immune Response Modulation

Helminth antigens that are transferred to the foetus can be mistaken as self-antigens by the developing foetal immune system and these, in turn, induce tolerance or sensitization in the infant. This may cause suppression of the immune

response to helminthic antigens. These infants modulate their immune response by downregulating type 1 immune response, increasing the Th2 responses to helminth antigens and decreasing Th1 responses to non-helminthic antigens [32]. Infants of helminth infected mothers are less likely to develop eczema and allergic diseases, suggesting attenuation in inflammatory responses [33, 34].

16.5.5 Premature Birth and Low Birth Weight

Helminthic infections can cause lower birth weight and preterm delivery, although other confounding factors such as HIV, malaria, undernourishment and anaemia were also found to be associated with helminths. In a study by Egwunyenga et al., malaria and helminthic coinfection were associated with lower birth weight than malaria infection alone [35]. The various maternal and neonatal effects of helminthic infections are enumerated in Table 16.2.

16.6 Conclusion

Helminthic infections contribute to significant morbidity and mortality among the general population and pregnant women in particular. Anaemia, malnutrition and adverse foetal out-

Table 16.2 Maternal and neonatal impact of helminthic infection during pregnancy

Classification	Impact on mother	Impact on infant
1. Soil-transmitted nematodes		
(a). Ancylostoma duodenale *(hookworm)*	Anaemia Reduced maternal fertility Higher malaria parasitaemia or prevalence Higher HIV viral load	Poorer motor skills and lower cognitive ability Lower rate of eczema
(b). Ascaris lumbricoides *(roundworm)*	Geophagy Higher maternal fertility Higher malaria prevalence	
(c). Trichuris trichiura *(whipworm)*	Anaemia Increased odds of P. falciparum Higher HIV viral load	Low birth weight
2. Filarial nematodes		
(a). Wuchereria bancrofti	Elephantiasis in hyper-responsive individuals	Increased maternal/infant HIV transmission Lower response to W. Bancrofti antigen 17–19 years later Increased infection in children of infected mothers
(b). Onchocerca volvulus	Onchocerciasis (river blindness)	Children of infected mothers are also more likely to be infected Children of infected mothers have higher TH2 cytokines and lower TH1 cytokines
(c). Mansonella perstans	Higher malaria parasitaemia and prevalence	Maternal infection associated with higher IL-10 to BCG and tetanus immunogens
3. Schistosoma (blood flukes)		
(a). Schistosoma mansoni	Intestinal schistosomiasis Anaemia and undernutrition	Increase in total IgE and tuberculosis-specific IgG transfer from mothers
(b) Schistosoma haematobium	Urinary schistosomiasis Anaemia	Preterm deliveries Lower birth weight
(c). Schistosoma japonicum	Intestinal schistosomiasis Anaemia	Lower birth weight

comes warrant timely treatment of helminthic infestation which has also been mandated by WHO. All helminthic infections are treatable with available drugs which are low cost and accessible to the general population. However, improvement of sanitation and hygiene, health education and treatment facilities also need improvement across countries with moderate to high burden.

Courtesy

- Figure 16.1: Dr. Aparna Parmar, Sr Professor & Head, Dept. of Microbiology, Pt BDS PGIMS Rohtak, India
- Figures 16.2, 16.3, and 16.5: Dr. Nidhi Negi, Associate Professor, Dept. of Microbiology, Doon Medical College, Dehradun, India.
- Figure 16.4: Dr. Praveen Malhotra, Senior Professor & Head, Dept. of Gastroenterology, PGIMS, Rohtak, India

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Part V

Obstetrical Considerations of Vector-Borne Infections

17 Maternal Malaria, Dengue, and Chikungunya

Ashish Rohatgi and Anshul Grover

17.1 Introduction

Arthropod borne infections are very common globally, especially in developing countries. Mosquito borne illness is the most important cause of acute febrile illness during the monsoon season in South Eastern countries as well as some Central African and South American Countries. These febrile illnesses affecting pregnant women are associated with increased incidence of maternal morbidity and fetal morbidity. The chapter discusses malaria, dengue, and chikungunya infections in pregnant women in detail.

17.2 Malaria Infection in Pregnancy

The term malaria (mal—meaning bad and aria—meaning air) originated in the eighteenth century in Italy where it was believed to cause the disease as a result of bad air arising from marshy soil. Malaria is a life-threatening febrile illness responsible for more than a million mortalities per year. It is caused by the bite of the infected female anopheles mosquito resulting in transmission of the malarial parasite (Plasmodium spp.). It is a severe public health issue mainly affecting tropical and subtropical countries of the world and WHO defines it as the disease of poverty with the African continent bearing the maximum burden of the disease. Young children, pregnant women, and non-immune travelers visiting malaria endemic areas are the most vulnerable population. Malaria infection during pregnancy can be responsible for both maternal and fetal affection such as maternal anemia, low birth weight infants, congenital malaria, and increased risk of both maternal and infant mortality. Malaria is a preventable disease with appropriate drugs and effective preventive measures. WHO has initiated a global malaria program which aims to bring about a decline in the incidence of malaria by 90% by 2030 and eliminate malaria from at least 35 countries in the world.

17.2.1 Global Burden

According to WHO estimates (2019), the global burden of malaria is 229 million cases and it accounts for 409,000 malarial deaths worldwide [1]. The children under 5 years still remain the most susceptible population as far as the morbidity and mortality is concerned. The African region leads worldwide in being affected and accounts for 94% of all malarial deaths worldwide followed by Asian region. The infections in these regions are indigenous while in the United

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States most infections are by infected travelers from endemic areas. In India, 90% of people live in malaria transmission zones with two-thirds of infections being caused by *P. falciparum*; there are estimated 13 million cases and 24,000 deaths every year [2]. 50 million pregnancies are subject to risk of contracting malaria annually in endemic areas, of which 200,000 women develop anemia and 200,000 infants are born with low birth weight. Malaria is responsible for 10,000 perinatal mortalities in these low birth weight infants annually [3].

Primipara are at greater risk of infection as compared to multipara and co-infection with HIV increases the morbidity and mortality from malaria during pregnancy [4]. Data obtained from malaria intervention trials suggest that prevention and treatment significantly reduces the incidence of severe maternal anemia by 38%, risk of low birth weight infants by 43%, and perinatal mortality by 27% among first and second gravida [3, 5].

17.2.2 Malarial Parasite and Vector

17.2.2.1 Malarial Parasite [6]

The malarial parasite is a member of the genus Plasmodium which belongs to the phylum Apicomplexa. They are unicellular eukaryotes, which are obligate parasites of vertebrates and insects. Of the 100 known species of Plasmodium, four are recognized to infect humans: vivax, falciparum, ovale, and malariae. Recently, another species which naturally infects macaques—*P. knowlesi*—has been identified as a cause of zoonotic malaria in humans.

- *P. falciparum*—is the most predominant species in Africa. Globally it is seen to survive in tropical and subtropical areas. It is known to cause severe disease due to its propensity to rapidly multiply and destroy red blood cells, causing severe anemia. It can also cause cerebral malaria which can be fatal.
- *P. vivax*—has a wider geographical distribution due to its ability to survive in lower temperatures and higher altitudes. It is the most predominant species in Asia. It is characterized by its ability to lie dormant in the liver as "hypnozoites" which can re-activate and cause a relapse, months and years after the bite of the infected mosquito. The characteristic feature of *P. vivax* is that it does not infect people who lack the Duffy glycoprotein on the blood cells. The Duffy glycoprotein also acts as a receptor for *Plasmodium vivax*.
- *P. ovale*—It is the predominant malaria parasite affecting West Africa and western Pacific region. This species is morphologically and biologically similar to *P. vivax*, and also has the capability to differentiate into "hypnozoites" and cause relapses.
- *P. malariae*—It is prevalent worldwide and causes chronic infection which can last a lifetime.
- *P. knowlesi*—The natural hosts of this parasite are the pig-tailed and long-tailed macaques found in Southeast Asia. It has been recently recognized as the major cause of zoonotic malaria in that region, especially in Malaysia. *P. knowlesi* has a short replication cycle of 24 h, thus explaining its rapid progression from an uncomplicated to a severe infection.

17.2.2.2 Vector

Anopheles mosquito is the vector for transmission of malaria in humans. They are mainly found in rural habitats and are crepuscular, i.e. they are active at dusk or dawn or are nocturnal and this characterizes their biting habits. The primary malaria vectors are *Anopheles gambiae* and Anopheles funestus, which are strongly anthropophilic (feed on humans). Similar to any other insect, the Anopheles mosquito undergoes four stages in their life cycle. The first three stages of its life cycle; the egg, larva, and pupa are aquatic. The fourth stage or the adult stage is the female Anopheles mosquito which is the malaria vector for transmission. The adult females can survive on an average for not more than 2 weeks in nature. The eggs are laid in water and between every egg lying cycle, the adult mosquito feeds multiple times on a human host, thus linking the survival of the mosquito to the parasitic cycle. After ingestion by the mosquito, the malarial parasites undergo an intrinsic development within the mosquito thus rendering it infectious to humans. The cycle of development in the mos-

quito is called the extrinsic incubation period which ranges from 10 to 21 days. Unlike the human host, the mosquito host is not affected by the presence of the parasites [7].

17.2.2.3 Life Cycle of the Malarial Parasite

The life cycle of Plasmodium involves two separate hosts. The mosquito is a definite host where the parasite undergoes sexual reproduction and vertebrates act as alternative hosts where it undergoes asexual reproduction. The parasites enter a vertebrate host by the bite of a mosquito. In the vertebrate, the first tissue to be infected is the liver tissue, where the parasite undergoes replication to form the merozoites. In the *P. vivax* and *P. ovale* species, a few parasites differentiate into "hypnozoite." These hypnozoites remain dormant in the liver cells and are responsible for relapses. The merozoites then infect the erythrocytes and undergo continuous cycles of infection. A small fraction of parasites differentiate into a sexual stage called a gametocyte. These gametocytes are ingested by the insect host during a blood meal. In the midgut of the mosquito, the gametocytes transform into gametes. The gametes undergo fertilization to form a zygote. The zygote transforms into an ookinete and then into sporozoites. The sporozoites migrate to the salivary glands of the mosquito, which are transferred into a new host during the mosquito bite, thus starting a new cycle of infection [8] (Fig. 17.1).

17.2.3 Transmission and Pathophysiology

17.2.3.1 Transmission

Malaria can be transmitted only by the bite of the infected female Anopheles mosquito. The transmission is vector, human host, and environment dependent. Certain individuals who are negative for Duffy blood group are preferentially infected by *P. ovale*; 90% of the Sub-Saharan African population are Duffy negative or lack the Duffy antigen receptor for chemokines (DARC). Individuals who have Duffy negative blood group have genetic protection from *P. vivax* infection [9]. Individuals heterozygous for sickle cell disease (SCD) are conferred protection from severe *P. falciparum* malaria. The hypoxic RBCs in SCD provide an inhospitable environment for the

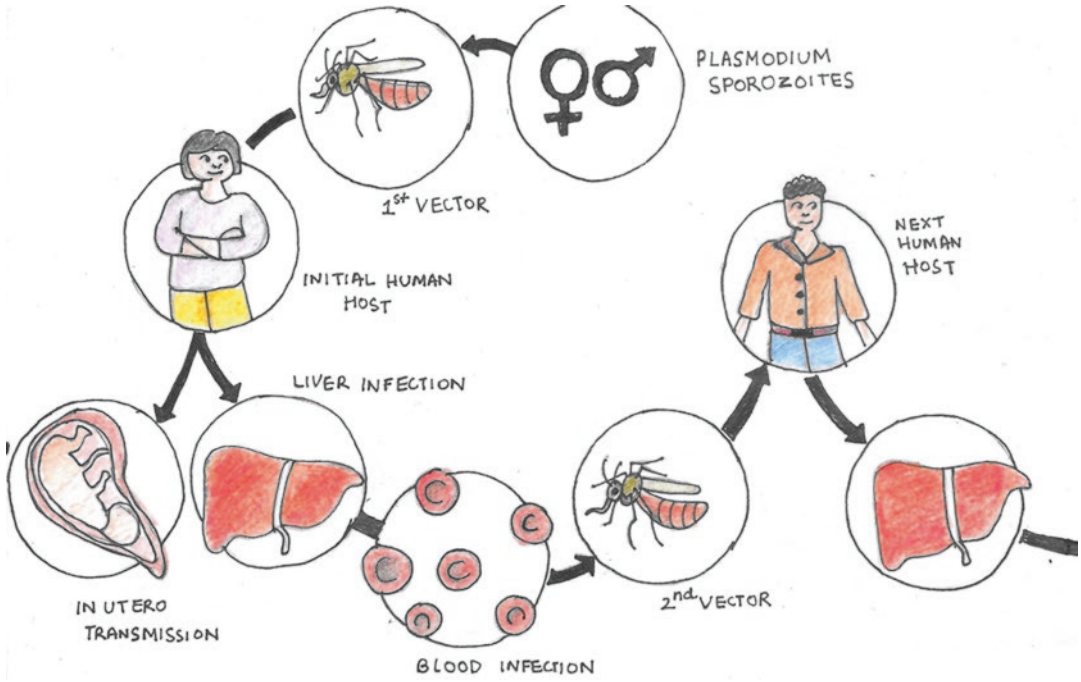

Fig. 17.1 Life cycle of malarial parasite

growth of the parasite. Co-infection with HIV may result in increased risk of transmission due to decline in immunity [10]. The number and survival of mosquitoes is affected by the temperature, rainfall patterns, and humidity of an area. It is observed that the transmission is highest during and just after the rainy season in many areas while in the tropics and subtropics the vector population is constant throughout the year, therefore it is endemic. Malaria epidemics occur in the rest of the world when the climatic conditions intensify transmission.

17.2.3.2 Pathophysiology

Products of erythrocytic schizogony are responsible for the clinical manifestations in malaria. These parasitic antigens result in a local and systemic response by the host immunogenic system. Also, the parasitized erythrocytes cause obstruction in the blood vessels leading to tissue hypoxia and reduced oxygen delivery. Liver, the primary organ of affection is congested and enlarged, the Kupffer cells are increased and filled with parasites. The liver parenchymal cells show evidence of fatty degeneration, atrophy, and centrilobular necrosis. In acute infection, the spleen is soft and congested. The kidneys are enlarged due to presence of malarial pigment in the glomeruli and hemoglobin cast in the tubules. In case of falciparum malaria the brain gets congested as capillaries are plugged with parasitized RBCs. The subcortical white matter may show evidence of punctate hemorrhage. Complement mediated autoimmune hemolysis, bone marrow suppression due to TNF toxicity, and phagocytosis of infected as well normal RBCs are the various mechanisms which result in development of anemia.

17.2.4 Clinical Features

The typical clinical feature of malaria is development of periodic bouts of high-grade fever with chills and rigors. The typical febrile paroxysms which last for 8–12 h comprise three stages; the "cold stage"—when the patient feels severe cold and has chills with rigors, lasts for 15–60 min. There is associated lassitude, headache, and nausea. This is followed by a "hot stage" when the patient's temperature rises up to 41 °C and may be associated with persistent headache, nausea, and vomiting. The duration of the "hot stage" is 2–6 h. This is followed by the "stage of sweating." This is the final stage, in which the temperature comes down and the skin is cool and moist; this stage lasts for 2–4 h. The periodic febrile response, in all types of malaria, is due to the rupture of mature schizonts. The periodicity of the paroxysm varies according to the maturation cycle of the schizonts in different species, which helps to identify the type of malaria. Other common symptoms include myalgia, diarrhea, abdominal pain, and cough.

Splenomegaly is evident usually only after 1 week. The enlarged spleen is soft and prone to traumatic rupture. Infection with *P. falciparum* generally does not cause splenomegaly. With recurrent bouts of malaria as seen with *P. vivax* and *P. ovale*, the spleen becomes fibrotic, firm, and palpable; classically known as the tropical splenomegaly (Table 17.1).

17.2.4.1 Severe Malaria

It is defined as the demonstration of asexual forms of the malaria parasites in the blood of a patient with a potentially fatal manifestation or complication of malaria, in whom other diagnoses have been excluded. It is a complication unique to malarial infection caused by *P. falciparum* species. It develops as a result of the parasite to cause massive parasitemia in a very short span. It is a multiorgan affection by a severe inflammatory response which leads to sequestration of infected RBC's into the tissues, resulting in impaired tissue perfusion and lactic acidosis. Severe malaria can present as cerebral malaria, acute renal failure, pulmonary edema, or severe anemia due to hemolysis. The most common metabolic complications associated with it are acidosis and hypoglycemia. The rapid progression of the disease process can result in death within hours or days if not diagnosed and treated [11]. Risk factors for development of severe malaria include age >65 years, co-existing medical condition, pregnancy, nonimmune status, and absence of antimalarial pro-

Table 17.1 Clinical features of different malarial parasite species

Species	Incubation period	Erythrocytic preference	Pattern of fever	Disease characteristic	Severity of disease	Fatality
P. falciparum	9–14 days	Nascent RBC's	Tertian/ Subtertian	Severe disease Can lead to cerebral malaria	6%	2%
P. vivax	12–17 days or 6–12 months	Reticulocytes	Tertian	Do not compromise vital organs Can cause relapses Infect individuals negative for Duffy blood group	3%	0.8%
P. ovale	16–18 days	Reticulocytes	Tertian (48 h cycle)	Do not compromise vital organs Can cause Relapses	Very rare	Very rare or none
P. malariae	18–40 days	Old RBCs	Quartan (72 h cycle)	Low level of parasitemia Immune complex mediated nephrosis and nephritis	Very rare	Very rare or none
P. knowlesi	9–14 days	–	Quotidian (24 h cycle)	High-level parasitemia Associated thrombo-cytopenia	6–10%	1–2%

phylaxis [12, 13]. The diagnosis of the disease requires a very high index of suspicion.

17.2.5 Pregnancy and Malaria

Malaria and pregnancy both have synergistic effect on each other. The physiological changes during pregnancy and the pathological changes as a result of malaria are mutually aggravating. The incidence of malaria in pregnant woman is more common than general population and it is directly responsible for 25% of maternal mortality in endemic areas. Women during pregnancy have a threefold higher risk of developing severe malaria and its complications such as pulmonary edema, hypoglycemia, and placental infarction [14]. The mortality rate of severe malaria is also seen to double in pregnant women as compared to non-pregnant women [15]. This increased susceptibility can be attributed to the relative immune-compromised state during pregnancy due to reduced lymphoproliferative response, reduced Type 1 cytokine response, and elevated levels of serum cortisol. These adaptations are measures to prevent rejection of the fetus but probably also lead to increased susceptibility to the disease. The parasitemia in pregnancy is also tenfold greater, explaining the greater severity of the disease as compared to nonpregnant population. Adolescents are more at risk of developing infection [16]. In endemic areas, the multigravida has some partial immunity and is usually asymptomatic and present with anemia. This partial immunity is absent in areas of low transmissions and therefore parity is not a risk factor in these areas.

17.2.5.1 Placental Preference of *P. falciparum*

The predilection of Plasmodium falciparum malarial parasite towards pregnant women is attributed to the safe haven that the parasites find in the placental tissue [17]. The parasites stimulates expression of a surface protein on the red cells—VAR2CSA which binds to the placental receptor Chondroitin sulfate A (CSA). The parasites thus gain entry along the surface of the placental membrane, specifically the trophoblastic villi, the syncytial bridges, and extravillous trophoblasts. The parasites in the intervillous spaces of the placenta are protected from the immune clearance and filtration in the spleen, thus promoting asexual reproduction and severe disease [18]. The villi undergo hypertrophy and fibrinoid necrosis and the placental tissue shows presence

of malarial pigment. The presence of large number of parasites, malarial pigment, hemorrhages and macrophages in the intervillous spaces cause hindrance to the nutrient and oxygen transfer to the fetus leading to fetal complications.

17.2.5.2 Effect of Pregnancy on Malaria

The presentations in pregnancy are more atypical. This can be as a result of hematological, immunological, and hormonal changes of pregnancy especially in the second half. The fever pattern is variable. It can range from afebrile state to continuous pyrexia which may be low grade or high grade. The paroxysm may be more frequent due to immunosuppression, leading to greater parasitemia.

In endemic areas, partially immune multigravidas may present with only anemia and no fever. Pregnancy is already associated with physiological anemia which may be compounded by helminthiasis and malnutrition in low resource countries and it may be difficult to identify patients. Therefore, malarial parasite in blood smears should be tested during evaluation of anemia in pregnancy. In non-endemic areas, a very high index of suspicion has to be kept for any type of febrile illness in pregnancy; a travel history to endemic area in the last 6 weeks is important.

17.2.5.3 Maternal Complications

Apart from the febrile illness, the pregnant women can develop certain complications such as anemia, hypoglycemia, and pulmonary edema.

Anemia: Malaria can cause or aggravate anemia due to hemolysis of the parasitized RBCs; marked hemolysis also aggravates folate deficiency. The increased demands of erythropoiesis and hemodilution during pregnancy along with breakdown of infected RBC's in the spleen increase the severity of anemia.

In endemic areas, prior recurrent infections lead to chronic anemia in the population. In a study on *P. falciparum* malaria treated women in pregnancy in areas of low natural immunity, about 90% were found to be moderately anemic (hemoglobin <10 g/dl), either at the time of admission or during follow-up [19]. The severity of anemia is maximum between 16 and 24 weeks, coinciding with the peak of physiological changes of pregnancy. In severe malaria, the marked parasitemia leads to sudden onset of anemia. Along with management of the disease, pregnant women may require transfusion of packed red cell concentrates for correction of anemia. Anemia also increases the risk of developing pulmonary edema and post-partum hemorrhage, thereby increasing maternal morbidity and mortality.

Acute pulmonary edema: This is a complication more commonly seen to affect pregnant women as compared to non-pregnant women. It generally presents in the late second/third trimester or immediate postpartum corresponding to the physiological rise in cardiac output in pregnancy. Acute parasitemia during labor is a result of return of a large number of parasitized RBC's from the placental circulation to the intravascular compartment. This leads to a sudden rise in peripheral vascular resistance and increased cardiac output leading to pulmonary edema. It accounts for a high mortality of approximately 50% [20].

Hypoglycemia: Hypoglycemia results due to hypercatabolic state created by infected parasites, recurrent vomiting, and decreased oral intake during viremia. It is aggravated by treatment with quinine which stimulates pancreatic beta cell production and hyperinsulinemia. Symptoms of hypoglycemia can be missed, as they simulate the symptoms of malaria—sweating, tachycardia, giddiness. Some patients may present with abnormal behavior, altered sensorium, sudden loss of consciousness or even convulsions which can mimic symptoms of cerebral malaria. Thus, all pregnant women receiving quinine should undergo blood sugar monitoring every 4–6 h [21].

Secondary bacterial infections: Like pneumonia or urinary tract infection are more commonly seen with malaria in pregnancy. If not recognized and treated, patient can develop algid malaria or septicemic shock. Appropriate antibiotics, fluid management, and monitoring help to avert catastrophes.

17.2.5.4 Fetal Complications

Malaria with pregnancy is associated with spontaneous abortion, premature birth, growth restricted fetuses, fetal distress, and low birth weight infants. High-grade fever, placental insuf-

ficiency, hypoglycemia, and chronic anemia can adversely affect the fetus. Both *P. vivax* and *P. falciparum* are implicated for prenatal and neonatal mortality in up to 15–70% cases. Transplacental spread of the infection to the fetus can result in congenital malaria.

Congenital Malaria

Congenital malaria is defined as the demonstration of the malarial parasites in the peripheral smear of the newborn within twenty four hours and up to 7 days of life [22]. It can be acquired by vertical transmission of parasites from the mother to the fetus during pregnancy or perinatally during labor. The incidence of congenital malaria ranges from 8 to 33% in both endemic and non-endemic areas [23, 24]. All four species of plasmodium are known to cause congenital infection; *P. vivax* is prevalent in Europe while *P. falciparum* is an important cause of congenital malaria in the Indian and African subcontinent. The diagnosis of congenital malaria is difficult as the symptoms are nonspecific and generally manifest after 2–8 weeks correlating with the half-life of the IgG antibody. Transplacentally acquired maternal IgG immunity and the high proportion of fetal RBCs present in the neonatal circulation initially do not allow malarial parasites to develop. In instances where the mother is symptomatic immediately prior to or during delivery, the neonates may present with symptoms in less than a week as maternal protective antibodies have not developed till that time. Neonates present with anorexia, fever, lethargy, anemia, and hepatosplenomegaly or with features simulating neonatal sepsis. Pregnant women with malaria and HIV co-infection present with an increased burden of placental malaria due to impaired antibody responses, thus increasing the risk of congenital infection [25]. Differential diagnoses of congenital malaria include Rh incompatibility, infections with CMV, herpes, rubella, toxoplasmosis, and syphilis.

17.2.6 Laboratory Diagnosis

WHO guidelines recommend that in all suspected cases of malaria, a diagnosis should be made either by parasitological confirmation using microscopy or by Rapid Diagnostic Test (RDT) before treatment is initiated [26, 27].

Blood Smear—Demonstration of the malarial parasite by Giemsa staining of thin and thick preparation of blood smear, still remains the traditional method for diagnosis (Fig. 17.2). Smear examination helps in knowing the species of infection as well as the level of parasitemia. Thick blood smear consists of a thick layer of lysed (dehemoglobinized) RBC's. By definition, if placed wet on a newsprint, it should barely allow one to read the print. With an ability to detect 10–50 trophozoites/micro-liter, the sensitivity of the thick smear is 20–40 times more than thin smears. Thus they are preferred tests for screening.

Thin blood smears are a layer of blood spread on a slide with progressively decreasing thickness from one end to the other. This results in a monolayer of cells, such that they do not touch one another. They are used to identify the species of the parasite, determine the stage of the disease (i.e., gametocytes, schizonts), and to identify the presence of malarial pigment in the monocytes and the neutrophils. Parasitemia can be defined

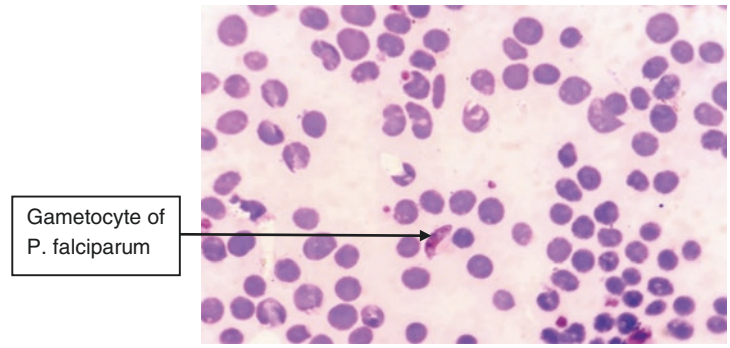

Fig. 17.2 Gametocytes of *plasmodium falciparum* on Giemsa stain in thin peripheral blood smear

either as the number of parasites per micro-liter of blood or as a percentage of parasitized erythrocytes. Parasitemia in falciparum malaria is more than 50% while in non-falciparum malaria it rarely exceeds 2%.

At least 200 oil immersion visual field analysis at ×1000 magnification should be examined in both thin and thick smears, before documenting a negative result. This increases the sensitivity of the test to 90%. A minimum of three negative smear examinations at least 12–24 h apart is required to rule out the diagnosis of malaria in a febrile patient.

Newer methods like fluorescence microscopy are available now. This technique utilizes dyes such as benzothiocarboxy purine and acridine that can stain parasites present in the red blood cells only.

Rapid antigen detection [28, 29]—These tests are based on antigen detection by immunochromatographic methods and can be in dipstick or card form. Currently, immunochromatographic tests manufactured are using the histidine-rich protein 2(PfHRP2) of *P. falciparum*, a pan-malarial *Plasmodium* aldolase (PMA), and the parasite specific lactate dehydrogenase (pLDH). The RDT's do not require any special equipment, electricity or the presence of a laboratory.

It is an increasingly popular test not only due to its high sensitivity and specificity but also as it yields results within 15 min.

The disadvantages of RDT are that they might be negative in low parasitemia, and they cannot differentiate between mono-falciparum infection and mixed infection and between active and past infection. Both positive and negative results need confirmation with smear microscopy.

Polymerase Chain Reaction (PCR)—PCR is a highly sensitive test and picks up very low levels of parasitemia. PCR is increasingly used for species detection as well as drug resistance. Quantitative PCR can be helpful in diagnosis of low density infections [30]. Loop-mediated isothermal amplification (LAMP) has similar sensitivity to PCR but is more rapid and potentially applicable at the point of care testing [31]. These tests are not used for screening but in research settings.

Placental histology—Placental evaluation with histopathology helps to identify both active and past infections. In patients with anemia, perinatal mishaps, fetal growth restriction, low birth weight infants, placental histopathology helps to make an accurate diagnosis as few patients may have absent peripheral parasitemia in the presence of placental parasitemia. Active infection is characterized by intervillous leucocytic infiltrates with predominant monocytosis. Presence of malarial pigment hemozoin in the fibrin deposits is a feature of past infection, as may be evident in multigravida in endemic zones [32].

Blood Investigations The most common abnormality in blood picture associated with malaria is thrombocytopenia (60%). In majority of the cases the total leukocyte count is normal or low, but neutrophilia is evident with presence of band forms (left shift). Anemia is present in 30% cases, while 40% patients may have hyperbilirubinemia and 25% have increased aminotransferases. Inflammatory markers, erythrocyte sedimentation rate, C-reactive protein, and procalcitonin are raised. In 90% of pregnant women anemia (Hb < 10 gm/dl) is a presenting feature [33]. Figure 17.3 discusses the investigation approach to a pregnant woman with suspected malaria.

17.2.7 Differential Diagnosis

- Dengue
- Typhoid fever
- Schistosomiasis
- Tick-borne rickettsial diseases
- Filariasis
- Histoplasmosis

17.2.8 Management of Malaria in Pregnancy

Malaria in pregnancy should be treated as an emergency. Hospitalization is recommended in all pregnant patients with malaria and patients with severe disease should be admitted in intensive care unit [20]. Non-falciparum malaria can be treated on an outpatient basis but admission ensures compliance, helps to manage vomiting, and monitors patient for any deterioration of symptoms. It is strongly advised that a proper

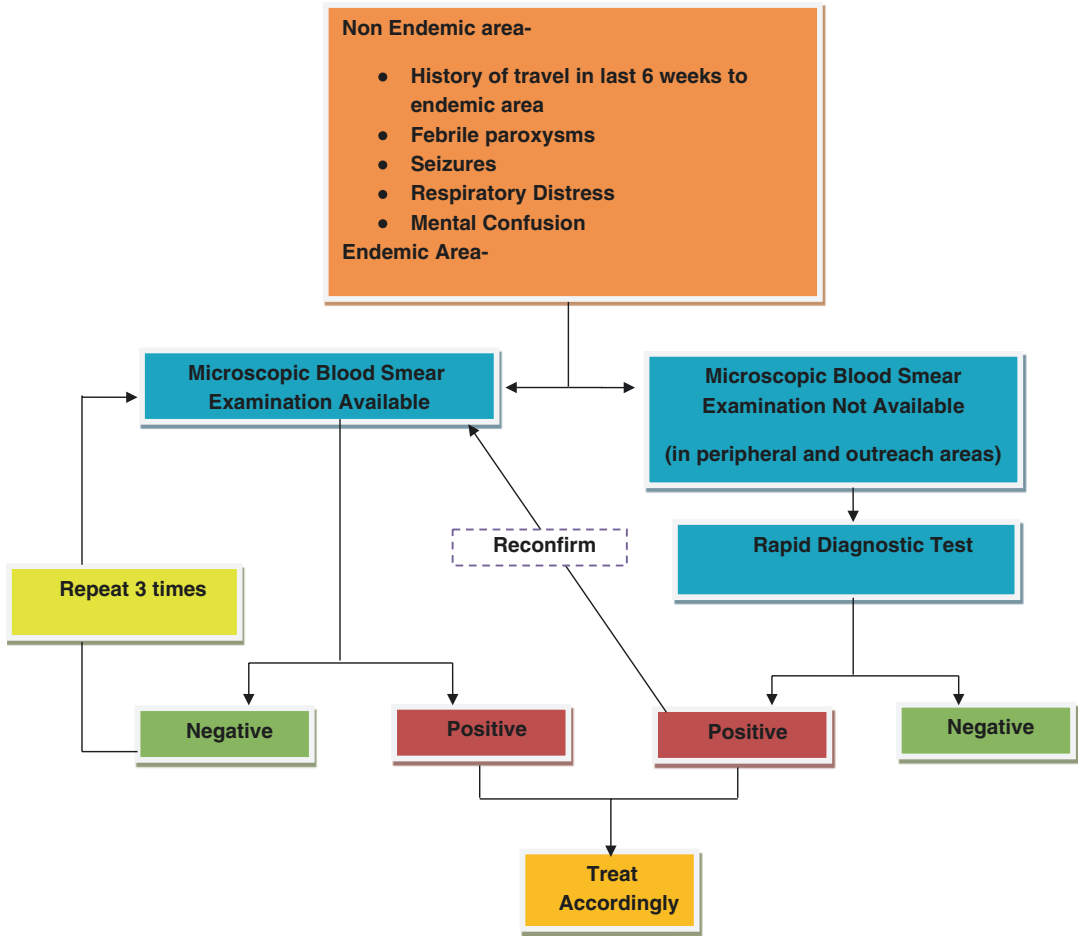

Fig. 17.3 Approach to investigation of a pregnant woman with suspected malaria

plan for treatment and follow-up of these patients should be documented so as to detect any relapse of malaria that can be picked up early. The assessment of the patient should be made for severity of the disease as case fatality of severe malaria in pregnancy is high (15–20% in non-pregnant women compared with 50% in pregnancy).

For convenience of management and treatment, the disease has been divided into

- Uncomplicated malaria—defined as fewer than 2% parasitized red blood cells in a woman with no signs of severity and complications.
- Severe and complicated malaria—Pregnant women with 2% or more parasitized red blood cells are at higher risk of developing severe malaria. The signs of severe malaria are non-specific and other causes must be excluded before assigning the signs and symptoms to malaria.

17.2.8.1 General Management

Uncomplicated Malaria

- Fever—Paracetamol infusion 1 g every 4–6 hourly (maximum of 4g/24 h) and tepid sponging and fanning is to be done. High-grade fever can result in spontaneous abortion, fetal distress, and onset of preterm labor.
- Vomiting—Anti-emetics are prescribed along with quinine derivatives. If patient has severe persistent vomiting, she should be shifted to injectable therapy as this is an important reason for treatment failure.
- Assessment of anemia—severe anemia is corrected by blood transfusion under cover of a

diuretic to avoid fluid overload. Iron and folic acid supplementation is required for correction of moderate anemia after the immediate management.

Severe Malaria

It is a medical emergency and requires admission and treatment in a high-dependency or intensive care unit. Multi-disciplinary approach with involvement of infectious disease specialist, intensive care specialist, and obstetrician is required for management of severe malaria. Appropriate and timely treatment for complications like pulmonary edema, cerebral edema, and acute renal failure should be initiated to avoid mortality.

17.2.8.2 Antimalarials

Antimalarial medicines which are considered safe in the first trimester of pregnancy are quinine, chloroquine, clindamycin, pyrimethamine, proguanil and sulfadoxine–pyrimethamine. Of these available options, quinine still remains the most effective and can be used safely in all trimesters of pregnancy including the first trimester [20]. Some of the guidelines for treatment include:

- Chloroquine should be used in case of infection with *P. vivax*, *P. ovale*, and *P. malariae*.
- A combination of quinine and clindamycin should be used in uncomplicated *P. falciparum* and mixed infections.
- The drug of choice in severe falciparum malaria is Injectable artesunate. Quinine can be used as an alternative if artesunate is not available.
- Mefloquine is not recommended due to its association with stillbirth.

Artemisinin derivatives (ACTs)—Artemisinin derivatives have been extensively studied regarding their association with embryotoxicity as evident in animal models but no such association in human trials has been demonstrated [34]. Therefore, as per Malaria Policy Advisory Committee of WHO, artesunate derivatives are recommended for treatment of uncomplicated falciparum malaria in the second and third trimester of pregnancy, but not endorsed for usage in the first trimester [35, 36]. Four different ACTs, artemether-lumefantrine, amodiaquine-artesunate, mefloquine-artesunate, or dihydroartemisinin piperaquine (DHA-PQ), were evaluated for treatment of uncomplicated malaria in the second and third trimesters of pregnancy, and were found to be highly effective (95% or more). The artemether-lumefantrine combination was associated with the fewest adverse events while DHA-PQ had the greatest post-exposure prophylaxis. This evidence strongly supports the use of ACTs as first-line treatment for malaria in the second and third trimester [36]. ACT's are generally tolerated well and side effects include nausea, vomiting, pruritus, and fever; bleeding and cardiac arrhythmias rarely occur. Figures 17.4 and 17.5 show the management of uncomplicated *P. falciparum* malaria in first and second/third trimester, respectively. Treatment of uncomplicated non-falciparum malaria is shown in Fig. 17.6.

Treatment of Recurrences

P. falciparum is most commonly associated with recurrences due to its ability to sequester in the placenta. Most recurrences present by 28–42 days and weekly screening by blood film until delivery is recommended. WHO recommended regimen for recurrences is 7 days of artesunate (2 mg/kg/day or 100 mg daily for 7 days) and clindamycin (450 mg three times daily for 7 days).

Treatment Considerations in HIV Positive Women

The risk of contracting malaria in pregnancy is increased if the women already are infected with HIV. Treatment in such patients should have the following consideration.

- HIV infected women are commonly prescribed co-trimoxazole to decrease opportunistic infections, so they should not be given intermittent preventive treatment of malaria with sulfadoxine-pyrimethamine (SP) because this combination increases the risk of severe skin reactions such as Stevens–Johnson syndrome.
- Mefloquine decreases malaria prevalence in HIV-infected women but it seems to increase the risk of materno-fetal transmission of HIV [21].
- There is concern regarding the drug to drug interactions between antimalarials and antiret-

First Line Therapy

Tab Quinine 10mg/kg twice a day for 7days

Tab Clindamycin 10mg/kg twice a day for 7days

Alternative Therapy

Monotherapy with Quinine

Artemisinin-based combination therapy (ACT) is advised only if first line therapy fails or

Quinine is not available

Side Effects

Quinine - tinnitus or fullness in the ears, headache, nausea, diarrhea, blurred vision, altered

Fig. 17.4 Management of uncomplicated *P. falciparum* malaria in first trimester (Source: Guidelines for the treatment of malaria, third edition. Geneva: World Health Organization, 2015)

rovirals [22], which may require change in doses or even omission of certain medicine.

To date, little is known about the impact of antiretroviral therapy or immune system reconstitution on the interactions between malaria and HIV.

17.2.8.3 Monitoring Response to Treatment

Parasite Count—Parasitemia may rise initially after starting treatment in the first 12–24 h, as there is release of merozoites into the circulation following rupture of the schizonts. Increasing parasitemia 36–48 h after the start of antimalarial treatment indicates treatment failure. This may be due to drug resistance, requiring change of anti-malarial. Treatment failure is seen in 5–10% of patients with falciparum malaria, with recurrence of symptoms within 1 month. A repeat blood smear examination at 7 and 28 days after completion of therapy is recommended to monitor for relapse of severe falciparum malaria.

Electrocardiograph (ECG) Monitoring—Both quinine and quinidine are cardiotoxic drugs. Intravenous quinine is prescribed for treatment of severe malaria but in the USA, quinidine gluconate is available which is twice as potent and more cardiotoxic than quinine. Associated acute renal failure in patients of severe malaria increases the chances of toxicity. Monitoring of plasma quinine concentrations does not predict cardiotoxicity; an electrocardiography is a more accurate approach to monitor such patients. Lengthening of the QRS complex by more than 25% beyond baseline or the QTc interval increase to more than 500 ms, is suggestive of toxicity. Other common electrocardiographic abnormalities associated with quinine and quinidine include ventricular and supraventricular ectopic beats, sinus bradycardia (<50 beats/min), and ventricular tachycardia.

Blood sugar levels—Patients on quinine should be monitored for quinine induced hypoglycemia 4–6 hourly.

17.2.8.4 Follow-Up After Acute Phase

After recovery from the acute event, pregnancy should be monitored regularly for anemia, thrombocytopenia, hypoglycemia, and fetal growth.

First line

1. Artemether + Lumefantrine (AL)

4 tabs (20 mg + 120 mg) given at 0, 8, 24, 36, 48, and 60 h over 3 consecutive days

OR

2. Artesunate + Amodiaquine (AS–AQ)

2 tabs (100 mg + 270 mg) given once daily for 3 consecutive days

OR

3. Dihydroartemisinin + Piperaquine (DHA–PPQ)

4 tabs (40 mg + 320 mg) given once daily for 3 consecutive days

Special mention

- Artemether + Lumefantrine to be given with a milk/ fat rich diet to enhance its bioavailability
- DHA-PPQ regimen more efficacious in Papua, Indonesia as other combinations were shown to develop resistance

In case of vomiting in Uncomplicated/complicated falciparum malaria

- Injectable Quinine 10 mg/kg dose IV in 5% dextrose over 4 hours every 8 hours
- Injectable Clindamycin 450 mg IV every 8 hours

Fig. 17.5 Management of uncomplicated *P. falciparum* malaria in second/third trimester of pregnancy (Source: Guidelines for the treatment of malaria, third edition. Geneva: World Health Organization, 2015)

Infection with *P. vivax* and *P. ovale* is known to relapse or recur. The pregnant women should be advised weekly chloroquine till delivery and during lactation. Thrombocytopenia is seen with severe malaria but 90% patients recover by 7 days and 100% by 14 days irrespective of the treatment. It has not been found to be associated with postpartum hemorrhage.

Risk of congenital malaria should be explained to the mother. Cord blood sample and placental histopathology is advised at birth. The baby should be monitored with weekly thick and thin blood smears up to 28 days.

17.2.9 Prevention of Malaria

Malaria is one of the most common preventable causes of poor outcomes in pregnancy. The malaria prevention strategies include:

P. vivax, P. ovale, P. malariae

Treatment of blood Infection

Oral chloroquine (base) 600 mg followed by 300 mg 48 hours later. Then 300 mg on day 2 and again on day 3.

Resistant P. vivax

As for uncomplicated malaria P. falciparum - ACT based

Treatment of Exo-erythrocytic cycle (Relapse Prevention)

During pregnancy

Chloroquine oral 300 mg weekly until delivery

After Delivery

Postpone until 3 months after delivery and do G6PD testing

P. ovale -Oral primaquine 15 mg single daily dose for 14 days

P. vivax -Oral primaquine 30 mg single daily dose for 14 days

Fig. 17.6 Treatment of uncomplicated non-falciparum malaria in pregnancy (Source: Guidelines for the treatment of malaria, third edition. Geneva: World Health Organization, 2015)

- Insecticide-treated nets (ITNs)
- Intermittent preventive treatment of malaria in pregnant women (IPTp)
- Indoor residual spraying (IRS)

Insecticide-treated nets (ITNs)—They are an effective cheap and sustainable means of personal as well as community protection that have shown to reduce malaria illness, severe disease, and death due to malaria. Pyrroles and pyrethroids are the two insecticides classes approved for use on ITNs. The nets need to be retreated every 6–12 months or more frequently if washed. The need for frequent retreatment and the lack of understanding its importance has been a major barrier in its usage in the African countries.

Intermittent preventive treatment in pregnancy (IPTp)—This refers to a course of antimalarial medicine given to pregnant women at routine antenatal care visits, irrespective of their infection status. IPTp has been documented to reduce the incidence of maternal malaria especially in areas of high transmission. This results in a decline in maternal anemia, placental parasitemia, low birth weight, and neonatal mortality. There is little evidence to support effectiveness of IPTp in vivax Malaria [37]. There is also lack of evidence to support IPTp benefits in lower transmission zones and at present WHO recommends IPTp with sulfadoxine-pyrimethamine (IPTp-SP) in all areas with moderate to high malaria transmission in Africa [38, 39]. The preventive treatment is started as early as possible in the second

trimester and is administered at monthly intervals up to delivery with a rapid diagnostic test done during each antenatal visit.

Intermittent screening and treatment during pregnancy (ISTp)—ISTp during pregnancy involves screening of women for malaria using a rapid diagnostic test (RDT) on each ANC visit, regardless of symptoms and treatment, if found to be positive. This strategy has not been proven to be cost effective and therefore not promoted by WHO as an alternative to IPTp-SP.

Indoor residual spraying (IRS)—It is a core vector control intervention that involves the application of a residual insecticide to internal walls and ceilings of housing structures where malaria vectors may come into contact with the insecticide. Environmental hazard of the insecticides has put this strategy into disrepute.

17.2.10 Malaria Vaccine

In 2002, the scientists successfully sequenced the *P. falciparum* genome, thus opening frontiers for further research to control it [40]. Vaccine development remains the best long-term and permanent hope for complete protection. The complicated life cycle of plasmodium has been the biggest challenge in the vaccine development. The most widely tested vaccine is RTS,S AS01 which has demonstrated efficacy in phase III trial although the protection is only partial [41]. The revised Malaria Vaccine Technology Roadmap to 2030 now talks of for a next-generation vaccine to achieve 75% efficacy over 2 years against *P. falciparum* and/or *P. vivax* [42].

17.3 Dengue Fever

17.3.1 Introduction

Dengue fever is one of the most common mosquito-borne viral disease. It is caused by one of four dengue flaviviruses. The Aedes mosquito is the vector for virus transmission while ingesting a blood meal and the infection occurs with any of the four serotypes. The intriguing fact about the different serotypes is that primary infection with one serotype does not confer immunity to the other serotypes. The secondary infection is more severe due to the anamnestic response of the immune system caused by genetic similarity of the various serotypes. With a rise in the adult dengue fever globally, the number of infected pregnant women has also increased. Dengue fever during pregnancy has been associated with many pregnancy complications like abortions, preterm delivery, and low birth weight infants. Timely intervention and treatment can improve both maternal and fetal outcome. In this section we discuss the clinical course of the disease, pregnancy affection, and appropriate treatment.

17.3.2 Global Burden

Dengue fever is a major public health concern with increasing incidence; almost 30-fold rise in last 50 years [21]. The disease is increasing its footprints in over 100 countries, mostly in South America and southeast Asia. It is still encroaching upon newer countries including Europe [43]. The disease is prevalent mainly in the tropics and largely influenced by the temperature, rainfall, and the degree of urbanization. It is estimated that incidence of infections is about 390 million per year. Asia contributes to 70% of the infection, of which 33% are contributed by India alone. America accounts for 14% of the infection of which more than half the cases are localized to Brazil and Mexico. A large burden of the disease in Africa is masked due to under reporting and confusion with symptomatically similar diseases [44, 45].

17.3.3 Viral Genome and Vector

Dengue virus is an arthropod borne Arbovirus, belonging to flavivirus family and genus flaviviridae. It is a single stranded, enveloped, positive sense RNA virus which encodes 3 structural and 7 nonstructural (NS1, NS2a, NS2b, NS3, NS4a, NS4b, NS5) proteins [46]. It has genetically similar and antigenically distinct four serotypes,

referred to as DENV1–4 [47], which are defined by their inability of individually elicited antibodies to cross-neutralize. The virus can be inactivated by heat and disinfectants containing detergents and lipid solvents.

Dengue virus can be transmitted to humans through the bites of infected Aedes mosquitoes. The main vector species implicated is the *Aedes aegypti*. This mosquito is primarily a tropical and subtropical species but is distributed around the world, mostly between latitudes 35^0N and 35^0S. The immature forms have predilection for water-filled habitats, mainly in artificial containers in and around human dwellings and mainly indoors. Dengue outbreaks have also been attributed to *Aedes albopictus*, *Aedes polynesiensis*, and several species of the *Aedes scutellaris* complex. In recent years, *Aedes albopictus* has spread across continents from Asia to Africa, America and Europe, attributable to increased international travel.

17.3.4 Transmission and Pathophysiology

The primary mode of transmission of dengue virus in humans is through a vector—the infected female *Aedes aegypti* mosquito. The *Aedes albopictus* has also been implicated as a vector in certain areas. The mosquito is infected when it feeds on a dengue virus infected individual. The virus then undergoes replication in the mosquito midgut before it reaches other organs like the salivary glands, which is instrumental in transmitting the virus to the new host during a bite. The time taken from ingesting the virus to actual transmission to a new host is termed the extrinsic incubation period (EIP). The EIP is around 8–12 days when the ambient temperature is between 25 and 28 °C [48]. The extrinsic incubation period is not only affected by ambient temperature; but a number of factors such as the magnitude of daily temperature fluctuations, initial viral concentration and virus genotype, can also alter the time it takes for a mosquito to transmit virus. The mosquito once infectious is capable of transmitting the virus for the rest of its life [49, 50].

Human-to-mosquito transmission—Mosquitoes can become infected from people who are already infected with dengue virus following a bite. The human host can be asymptomatic, symptomatic or in the prodromal phase [51]. Human-to-mosquito transmission can develop up to 2 days before someone shows symptoms of the illness till about 2 days after the fever has resolved [52].

Other modes of transmission—A possible vertical transmission has been postulated in pregnant women who acquire the infection in the latter half of pregnancy. While the incidence of vertical transmission appears low, and only a few isolated cases have been reported in literature, it has been associated with increased risk of neonatal mortality.

17.3.4.1 Pathophysiology

The virus gains entry into the human body through the skin, binds to the Langerhans cells to reach the nearest lymph nodes where they replicate. In dengue hemorrhagic fever, there is marked increase in production of chemokines or cytokines along with activation of T-lymphocytes. These are responsible for the capillary plasma leakage and circulatory disturbances. An increase in apoptosis and endothelial cell dysfunction is also noted. Thrombocytopenia in dengue is multifactorial; initially it is due to the bone marrow hypocellularity and thereafter immune mediated destruction of platelets contributes to it.

17.3.5 Clinical Features

Nearly 40–80% of dengue infections are asymptomatic. Most of the patients with symptomatic infection generally present with nonspecific, mild to moderate, acute febrile illness; about 5% progress to severe, life-threatening disease. Early detection of warning symptoms and timely treatment helps to reduce the associated mortality by 20 fold. The World Health Organization (WHO) previously classified dengue using three disease categories: dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome [53]. Re-evaluation of treatment strategies highlighted the shortcomings in the classification

scheme, most notably the underestimation of disease severity in some patients. Therefore, in 2009, WHO revised their guidelines and dengue cases are now classified as either dengue with or without warning signs or severe dengue [54] (Table 17.2). *The presence of a warning sign predicts the severity of the disease.*

Clinical course of dengue fever has been divided in three phases:

Febrile phase—lasts 4–5 days. The characteristic features include

- High-grade fever which is associated with facial flushing, skin erythema, conjunctival congestion, myalgias, and arthralgias
- Severe headache with retro-orbital pain
- Anorexia associated with nausea and vomiting
- General systemic examination is normal
- A positive Tourniquet test- The test is performed by inflating the BP cuff to the midpoint between systolic BP and diastolic BP for 5 minutes. Appearance of petechial hemorrhage in a one square inch area are looked for. The test is considered positive if more than 10 petechiae appear over a one inch squre area
- A low white blood cell (WBC) count should alert the treating doctor to a higher probability of the patient having dengue fever

Table 17.2 WHO classification of dengue

Dengue without warning signs	Dengue with warning signs	Severe dengue
Combination of ≥2 clinical findings in a febrile person who traveled to or lives in a dengue-endemic area • Nausea • Vomiting • Rash • Aches and pains • Positive tourniquet test • Leukopenia	• Abdominal pain or tenderness • Persistent vomiting • Clinical fluid accumulation • Mucosal bleeding • Lethargy, restlessness • Liver enlargement • Postural hypotension	• Severe plasma leakage leading to shock • Fluid accumulation with respiratory distress • Severe bleeding • Severe organ impairment such as elevated transaminases ≥1000 IU/L • Impaired consciousness • Heart impairment

Source: Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control. 2009, Geneva: World Health Organization. 1–147

Critical phase—develops after the fever subsides and warning signs develop in this phase. This phase is marked by significant plasma leak from the intravascular to the extravascular compartment which may lead to shock and fatal outcome if timely intervention is not performed.

Features of impending shock include lethargy, confused and restless state, cold and cyanosed peripheries, tachypnea, tachycardia, increased capillary refilling of more than 2 s, generalized anasarca, ascites, and tender hepatosplenomegaly.

Serial CBC examination may show a progressive fall in WBC and platelet count due to hemoconcentration followed by rise in packed cell volume and the liver enzymes are raised.

Recovery phase—After 2–3 days of critical phase there is a gradual re-absorption of fluid from the extra vascular compartment and the general condition improves. The major complication in this phase is due to hypervolemia which may be due to inappropriate and excessive fluid therapy and may even lead to pulmonary edema. The WBC and platelet count starts rising.

17.3.6 Dengue in Pregnancy

With the rise of dengue cases globally, the disease is bound to effect pregnant women also. But very limited evidence is available in literature regarding the effect of dengue on pregnancy. Pregnant women form a high-risk group due to an immunocompromised state. The disease predominates during mid to late gestation, correlating with the peak of physiological and immunologic changes in pregnancy which increase the dengue virus susceptibility. This can also be a cause of asymptomatic infections in endemic areas going unnoticed [55]. Dengue infection in the first trimester can be complicated by spontaneous abortion and neurological congenital anomaly in the fetus while infection in the third trimester can lead to preterm labor [56]. Various researches have documented tropism of the virus for neural tissues and its abil-

ity to cross the blood brain barrier and placental barrier [57]. There is evidence that pregnant women are at an increased risk of severe dengue as well hospitalization compared to non-pregnant females [58]. Preterm birth and low birthweight are the most common adverse fetal outcomes. Various studies have also reported an increased risk of hemorrhage, cesarean section rates, and maternal mortality [59, 60]. A recent Brazilian study of dengue in pregnancy found a four- to fivefold increased risk of dengue hemorrhagic fever and threefold risk of maternal mortality in these women [57]. The stillbirth rates vary from 6.6 to 47% [61, 62]. DHF may be confused with pre-eclampsia, HELLP syndrome because of features of thrombocytopenia, liver dysfunction, edema, ascites, and oliguria [63].

17.3.7 Laboratory Diagnosis

Virus Isolation—It is the standard method for diagnosing dengue infection. The virus is grown either in mosquito cell lines, mammalian cell lines, or in live mosquitoes [64, 65]. The sample is collected during the viremic phase (within 5 days of onset of febrile disease). In secondary affected individuals, isolation of the virus is difficult due to rapid production of cross-reactive antibodies early during the acute phase of disease that form immune-complexes along with the circulating virus [66]. It can be isolated from serum, plasma, anticoagulated blood, CSF, and mosquito.

RT-PCR—It is a highly sensitive test in comparison to virus isolation. It involves nucleic acid extraction, purification, and amplification followed by detection and characterization. The test is fast, less complicated, and cheaper compared to virus isolation [67]. Four serotype specific oligonucleotide primers in a single reaction tube are used for amplification of the virus and the products of these are read by electrophoresis. Real time PCR and Nucleic Acid Sequence Based Amplification (NSABA) are modifications which are being used nowadays.

NSI antigen capture [67, 68]—Detection of NS1 antigen from a patient's blood using an antigen capture ELISA approach was first described in 2000. The NS1 viral structural protein is secreted from the viral infected cells and correlates with the viral titer. It can be detected from the onset of symptoms up to 9 days or longer after disease onset, at least in primary infections. In secondary infection, the rapid anamnestic rise of NS1 cross-reacting antibodies during the initial viremia may give false negative response. The NS1 antigen kits have a sensitivity of 86% and a specificity of 100%.

Serology—Detection of antibodies against dengue infection can be performed by the various available methods—hemagglutination inhibition (HI) assays, complement fixation tests, dot-blot assay, Western blotting, indirect immunofluorescent antibody tests, and plaque reduction neutralization tests, as well as IgM and IgG antibody-capture ELISAs. IgM antibodies begin to form in the first week of onset of symptoms. In 50% patients it is detected by 3–5 days while in 100% patients by day 10. It peaks by 2 weeks and is detectable in serum for 2–3 weeks. IgG develops after the first week and rises slowly and persists for months or even lifelong. During secondary infection IgG antibody is produced as early as 3–5 days due to anamnestic response. Presence of antibodies (IgG) from a previous infection can interefere with interpretation of results in the present infection. To diagnose acute infection, paired sera (acute and convalescent phase) are required. Therefore single sample IgG is not considered diagnostic. In the DENCO trial (Dengue and Control trial 2006–2007), a single value of IgG of 1280 or more was considered diagnostic. Detection of dengue infection by serology becomes complicated in regions where more than one flaviviruses exist—yellow fever, Japanese encephalitis, and, more recently, Zika virus. This is due to the shared cross-reactive epitopes on the flavivirus E protein, and hence cross-reactivity of the antibody response.

17.3.7.1 Interpretation of Tests

Suspected

- IgM positive in single sera
- IgG positive in single sera in high titer of 1280 or more (Adapted from DENCO trial)

Confirmed

- RT-PCR positive
- Virus isolation is positive
- Paired sera show IgM seroconversion
- IgG seroconversion in paired sera/fourfold rise in paired sera.

17.3.8 Treatment of Dengue in Pregnancy

There are no specific guidelines for dengue management in pregnancy. All patients with pregnancy coming with fever should be suspected for dengue. A baseline CBC of the patient should be done and if the WBC count is normal or low, dengue should be considered as a differential. A CBC count should be repeated after 24 h; one further fall of WBC count or platelet or rise in PCV (more than 10%) is considered to be significant.

All patients should be admitted to the hospital as they require strict monitoring. The management strongly depends on the presence of complications.

17.3.8.1 Dengue Fever Without Warning Signs

- Oral paracetamol 500–650 mg doses every 4–6 h is the drug of choice for pyrexia
- No other NSAID like ibuprofen or diclofenac sodium should be given
- Withhold aspirin, if patient is receiving it for any other medical condition
- Fluid intake should be at least 2–3 L. Fluids such as juices and coconut water should be encouraged
- Monitor vitals like temperature pulse, blood pressure, and pulse pressure every 4 hourly
- Maintain a strict input output record. Ensure good urine output of at least 100 ml every 4 h
- Daily complete blood count should be sent to monitor fall in platelet count and rise in PCV by 10%
- If patient is having severe nausea or vomiting due to pregnancy or otherwise, initiate IV fluids @100 ml per hour at least
- The treating physician should be watchful for warning signs such as lethargy, narrowing of pulse pressure (<20), or delay in capillary filling (>2 min) especially when the fever is subsiding. These patients required immediate institution of intravenous fluid therapy so that they do not progress to severe dengue.

17.3.8.2 Dengue Fever with Warning Signs

These patients require very close monitoring once the fever starts subsiding to avoid further complications.

- Look for warning signs (Table 17.2) as they are hallmarks of capillary leakage
- Monitor vitals—blood pressure, pulse pressure, capillary refilling time, and urine output every hour
- Initiate fluid resuscitation with normal saline—5–10 ml/kg/h over first 2 h followed by 3–5 ml/kg/h as maintenance dose
- CBC including hematocrit, liver function tests to be monitored for any deterioration
- Induction of labor or a planned surgery should be avoided in this phase.

17.3.8.3 Dengue Fever with Shock on Admission

These patients should be managed in the ICU. Quick and appropriate fluid management can practically prevent further complications. At the time of admission a complete CBC including hematocrit, serum electrolytes, and liver function test should be done. Patient should receive a bolus of at least 1 l of fluids over 15 min followed by another bolus of one liter of saline over the next one hour. Resuscitation should be followed by assessment of the fetal wellbeing and other supportive measures.

17.3.8.4 Management in Recovery Phase

As the patient is recovering, WBC count platelet and hematocrit start stabilizing. It is important to keep a strict watch for signs of fluid overload as large volume of fluid is shifting from extravascular to the intravascular compartment.

Patient may be discharged from the hospital once the patient has normal hematocrit, improved appetite, and is afebrile without antipyretics for more than 24 h.

Choice of fluid for replacement—Normal Saline 0.9% should be the fluid of choice over dextrose saline or ringer lactate as they will increase the hematocrit further. Colloids should be avoided as they can enhance bleeding though they may be used for initial fluid bolus in a patient of shock.

Platelet transfusion as a prophylactic measure should not be done unless delivery is inevitable. The recommended safe level of platelet count for conducting normal delivery is ≥50,000/cc and for operative delivery is ≥75,000/cc. In a clinically stable patient without any signs of bleeding, platelet transfusion should be avoided unless and until the platelet count <10,000/cc.

17.3.8.5 Obstetric Care

Dengue fever is not an indication for termination of pregnancy. Steroids, immunoglobulins, or prophylactic antibiotics have no role for management of dengue infection in pregnancy. Operative deliveries should be done for obstetric indications only. A planned induction or cesarean section should be avoided during the critical phase of dengue with associated thrombocytopenia, as this may lead to substantial risk of severe hemorrhage. If delivery is inevitable, adequate arrangements must be made for transfusion of blood and blood products. Use of tocolytic agents to postpone labor can be considered during the critical phase of dengue illness; however, there is little evidence to support such practices. Delivery should always be preferred in hospital where blood and blood components and team of experienced obstetricians and neonatologist are available (Table 17.3).

Table 17.3 Important points in care of pregnant women with dengue

DOs
• In all patients with acute febrile illness, dengue should be suspected
• Admit probable dengue cases with pregnancy for close monitoring
• CBC with hematocrit is the sole lab parameter needed for monitoring
• Watch vigilantly for warning signs
• Diagnose shock early and treat with intense fluid management (normal saline only)
• In case of imminent delivery, blood and platelets should be kept ready
• Newborn should be evaluated for congenital dengue
DON'Ts
• No intramuscular injections
• No hypotonic IV fluids
• No steroids or antibiotics
• Avoid IV fluids if oral intake is adequate

17.4 Chikungunya

17.4.1 Introduction

Chikungunya fever is a mosquito-borne, self-limiting, viral disease. The causative agent of the disease is a RNA virus belonging to the alphavirus genus of the Togaviridae family [69]. The potential vector for the virus is the Aedes spp. mosquito—*A. aegypti* and *A. albopictus*. The human infection manifests as an inflammation of the musculoskeletal system with symptoms of headache, rash, myalgia, fever, and polyarthralgia. The term "Chikungunya" originates from the Makonde language (local language of South Africa), meaning "to lie doubled up" or "to become contorted" [70], describing the crippling, stooped position of the patient during the viremia. Infection during pregnancy subjects the growing fetus to potential risk but data regarding this association is scarce. Neonatal infections as a result of vertical transmission have been reported thus generating interest of both obstetrician and neonatologist in this arthropod borne disease.

17.4.2 Viral Genome

Chikungunya (CHIKV) is a single-stranded, spherical, enveloped, RNA virus. The viral genome is of 11.6 kb. It is divided into 4 nonstructural (nsP1, nsP2, nsP3, and nsP4) and 5 structural proteins (C, E3, E2, 6 K, and E1). The E1 glycoprotein plays an important role in membrane fusion and the E2 glycoprotein is required

for incorporation of the virus into the cell by endocytosis. Thus, these two form the important proteins for viral replication [69, 71, 72].

Phylogenetic analysis of CHIKV classifies them into four different genotypes according to the geographical regions in which they are prevalent [73, 74].

1. West African genotype—isolated from Senegal and Nigeria in western Africa
2. East/Central/South African (ECSA)—enzootic in Africa
3. Asian genotype—isolated from Asian countries
4. Indian Ocean Lineage (IOL) genotype—identified first from the Comoros islands in 2004 and resulted in severe epidemics in Southeast Asia and India during the years 2005–2008.

17.4.3 Epidemiology

Chikungunya virus (CHIKV) is a reemerging arthropod borne virus. Initially the disease was confined to Africa and South East Asia but resurgence in 2004 has led to world-wide spread of the disease. The 2004 epidemic in Kenya was followed by spread of the virus to nearby regions including Seychelles, Mauritius, Comoros, and La Réunion Island. In the 2005–2006 outbreak, over one third of the inhabitants of the La Réunion Island were affected [75, 76]. During the same time (2005), the epidemic in India involved 1.39 million people and 20 Indian states [77]. In 2007, the first outbreak with local transmission was reported from Italy in Europe [78]. In 2013, the first documented Chikungunya outbreak from the Americas was due to autochthonous transmission [79].

The reasons for global spread of the disease as noted by the epidemiologists include

- Increased international travel has led to the importation of the virus to newer geographical areas through infected people
- Autochthonous CHIKV outbreak which was responsible for spread in Europe and America
- Genetic mutations in the viral genome for better adaptation to *A. albopictus* which is its only vector in certain parts of the country.

17.4.4 Vector and Transmission

Aedes spp. mosquitoes, *A. aegypti* and *A. albopictus* are the main vectors implicated for transmission of the disease during the epidemics. *Aedes aegypti* is found mainly in the tropics and sub-tropics, while *Aedes albopictus* is found in the temperate and colder climates. Lately reports of isolation of *Aedes albopictus* from Africa, Europe, and America have suggested geographic spread of the virus. Both these species predominantly bite during the day hours with early morning and late afternoon peak. Both the species bite outdoors but *Aedes aegypti* also bites indoors. These species have been found to breed in stagnant water bodies and artificial containers like tires, saucers, and plant pots with water.

Chikungunya virus is transmitted to humans by mosquitoes. When an uninfected mosquito bites an infected individual, the mosquito ingests the virus in its blood meal. The virus then replicates in the midgut of the mosquito and amplifies. The virus after replication is spread to other organs of the mosquito including the salivary glands, where it has been demonstrated within 2–3 days of the bite. When the mosquito bites again it transfers the virus to another host and thus the viral transmission continues. A mosquito once infectious is said to be capable of transmitting the virus lifelong [80].

The natural cycle of the viral transmission is human-mosquito-human. Humans serve as reservoirs during epidemics but evidence suggests that epizootic cycles in vertebrates like monkey, rodents, and birds maintain the disease in the inter-epidemic periods. They act as reservoirs of the virus. These are responsible for re-emergence of the disease after periods of dormancy in humans [81]. Both species can transmit dengue and Zika virus also.

Vertical transmission is a less common mode of transmission from the infected mother to the

child during delivery. Theoretically, transmission through infected blood products and organ donation is possible during times of outbreak, but no such cases have yet been documented.

17.4.5 Clinical Features

The three most common clinical presentation of chikungunya infection are fever, myalgia, and arthralgia. The classical maculopapular rash develops in due course. The symptoms coincide with viremia and it is during this stage that the infection can be transmitted via the vector to another host or to the neonate in case the infected adult is a parturient. The disease has an incubation period of 2–12 days.

The disease manifestations can be classified into three phases; acute, post-acute, and chronic phase [82].

Acute Phase—This phase correlates with the phase of viremia. It lasts for 2–3 weeks and is characterized by:

- High-grade fever of 39–40 °C (80–90%)
- Arthralgia—(85–90%), which presents as bilateral joint involvement, though not always symmetric. Joints commonly involved are the knees, ankles, and joints of the upper extremities—interphalangeal, metacarpophalangeal, and metatarsal joints, shoulders, and elbows
- Arthritis associated with tenderness and joint swelling (about 30%)
- Maculopapular, pruritic rash (40–60%)
- Headache, nausea, anorexia, vomiting, and abdominal pain
- Hemorrhagic manifestations—seen in less than 5%.

Post-acute phase—This phase is documented in only 50% of the patients. It lasts for 4 weeks to 3 months. It is characterized by persistent joint pains.

Chronic phase—(>3 months to years) occurs in a minority of patients. It is characterized by persistence of the musculoskeletal features like joint pains and muscle aches. These symptoms respond to NSAIDs, analgesics, and physiotherapy. About 5% develop chronic inflammatory rheumatism.

Atypical, severe presentations in the form of encephalopathy, encephalitis, myocarditis, and hepatitis can be seen in less than 5% of cases. Neurological and cardiac involvement is a rare occurrence [83].

17.4.6 Chikungunya in Pregnancy

17.4.6.1 Effect of Pregnancy on CHIKV Infection

The course of the CHIKV infection is not affected by the pregnant condition per se.

17.4.6.2 Effect of CHIKV Infection on Pregnancy

The first case of vertical transmission in pregnancy was documented from La Reunion Island. Data from studies conducted in La Reunion island do not suggest association of first trimester chikungunya infection with miscarriages or congenital infection [84–87].

Very few cases of second trimester affection of CHIKV resulting in fetal demise have been reported in literature. The mechanism of such infections causing fetal demise is not clearly defined. It is hypothesized that viremia may have coincided with the period of deep infiltration of the trophoblastic tissue. The Th1 cytokine response and Toll-like receptor expression may affect the remodeling of the spiral arteries thus leading to fetal losses as studied in mouse models [88, 89].

Fritel et al. from his study in La Reunion island concluded that CHIKV does not infect the placenta, so as to be responsible for miscarriage, premature deliveries, low birth weight, gestational diabetes, hypertensive disorders of pregnancy, or stillborn [86]. In vitro mouse model studies have documented that human syncytiotrophoblast is refractory to the viral infection [90], thereby CHIKV cannot be implicated for antepartum complications. An Indian study on 150 pregnant women with CHIKV infection reported an incidence 20% adverse pregnancy outcome, with 80% affection in third trimester and 20% affection during second trimester. The adverse pregnancy outcomes reported

were oligohydramnios, preterm labor pains, premature rupture of membranes, decreased fetal movements, and intrauterine death [91].

Vertical transmission is documented in 50% of infections during the intrapartum period [79, 87]. The theory postulated for vertical transmission is that the fetal blood cells are infected by the free viral particles via breaches (break in syncytiotrophoblast due to uterine contraction) in the placenta during labor. They disseminate into the fetal circulation to reach the target organs and replicate [88]. Ominous fetal heart tracings and meconium staining of liquor have been reported but elective cesarean section has not been found to be effective in reducing such complications, neonatal outcomes or transmission [84, 92]. Most newborns affected are asymptomatic at birth but 12% with severe infection present with symptoms. The severity of infection is directly proportional to high viral load in the mother, low levels of neonatal Toll-like receptor induced interferon production, the proportion of neonatal fibroblasts, rate of cell division and neonatal immune ontogeny [93, 94].

17.4.6.3 Chikungunya in Neonates

Most neonates present with symptoms within 3–5 days of birth, which is the time taken for the virus to replicate in the neonate. This rules out placental infection prior to birth, as in that case the viremia of the neonatal circulation would parallel the maternal viral load. Also this rules out neonatal infection at birth as the manifestations appear before the incubation period of 2–12 days. Neonates present with fever, febrile seizures, suckling difficulties, diarrhea, limb edema, maculopapular skin rash, intertriginous aphthous ulcers, slate coloration or hyperpigmentation of nose, lips, trunk, abdomen, and knuckles [84, 92].

Life-threatening complications appear in 50% of the neonates who either develop encephalitis or multiorgan failure. In a prospective study by Gérardin P et al., neonatal infection was found to have long-term effects in the form of reduced developmental quotient scores at 2 years of age in 12.1% children infected by vertical transmission.

17.4.7 Laboratory Diagnosis

Hematological Investigations—are non-specific. Patients generally have lymphopenia without leukopenia, mild thrombocytopenia, mild transaminase level elevations (transaminase levels are 2–3 times the upper limit of normal), and an increased C-reactive protein level.

Viral Culture—It is the gold standard for viral detection and isolation. This technique is no longer used for routine diagnosis of the infection. It has the disadvantage of requiring specialized equipment, skilled laboratory technicians, and is time consuming. Its use is restricted in virology research for amplification of virus, isolation of strains and to identify contemporaneous strains.

Molecular Techniques—RT-PCR (Reverse Transcriptase) is a technique which utilizes nested primer pairs to amplify several Chikungunya-specific genes from whole blood or CSF. This process leads to generation of thousands to millions of copies of the genes for identification. This test is most appropriate during the early days of symptom onset, coinciding with the period of viremia (≤8 days after symptom onset). RT-PCR can also be used to quantify the viral load in the blood with the results being available within 1–2 days.

Serologic diagnosis—The antibody tests are performed after the first week of symptom onset and onward, coinciding with the development of the antibodies. Ig M antibodies develop after 4–5 days of onset of symptoms and last for several weeks to 3 months. IgG antibodies develop after 10–15 days and persist for several years (Table 17.4). ELISA test has a good specificity with very little cross-reactivity to the related alphaviruses. MAC-ELISA which is IgM antibody capture enzyme-linked immunosorbent assay is a commonly used test, whose results are available within the same day.

In view of cross-reaction with other alphavirus, CDC recommends Plaque Reduction Neutralization Tests (PRNT) assays for conformation or in patients with inconclusive tests [95].

Table 17.4 Interpretation of serological tests for CHIKV

Test	Result	Interpretation
IgM negative/ IgG negative	No infection	Retest after 10 days
IgM negative/ IgG positive	Past infection	
IgM positive/ IgG negative	Acute or recent infection	Retest after 2 weeks for detection of IgG antibody
IgM positive/ IgG positive	Recent or past infection	A fourfold rise in antibodies in a sample collected after 3 weeks is suggestive of recent infection

17.4.8 WHO Criteria for Confirmed Case

Any patient who meets one or more of the following findings irrespective of the clinical presentation:

- Virus isolation in cell culture or animal inoculation from acute phase sera
- Presence of viral RNA in acute phase sera by RT-PCR
- Presence of virus-specific IgM antibodies in single serum sample in acute or convalescent stage; Fourfold increase in virus-specific IgG antibody titer in samples collected at least 3 weeks apart.

In view of the presence of vertical transmission to infants, there should be continuous monitoring of IgM and IgG levels in the initial 3–4 weeks of birth. It should be noted that neonates may not have maternal antibodies for protection initially and generation of complete response might take 3–4 weeks. In symptomatic infants such monitoring helps in decreasing long-term neurodevelopmental complications [84, 96].

17.4.9 Differential Diagnosis

- Dengue Fever—The associated hemorrhagic findings distinguish it from CHIKV.
- Malaria—Periodicity of fever, alteration in the level of consciousness, and presence of seizures point towards a diagnosis for malaria.
- Leptospirosis—Patients have history of contact with contaminated water. They present with severe myalgia localized to calf muscles and associated conjunctival congestion/or subconjunctival hemorrhage; some patients may present with oliguria and jaundice.
- Rheumatic Fever—It is found commonly in children who manifest with fleeting polyarthritis involving the large joints with associated sore throat; raised ASO titers are present.
- Rickettsial disease—The presentation is similar and diagnosis is confirmed by serology.

17.4.10 Treatment

There is no specific antiviral treatment for chikungunya infection. The management mainly relies on relief of symptoms, including the joint pains. Anti-pyretic, optimal analgesics, drinking plenty of fluids, and general rest are the mainstay of its treatment [92].

17.4.10.1 During Pregnancy

Pregnant women and women planning pregnancy should avoid travel to endemic areas. In case of infection during pregnancy, medicines such as paracetamol (safe in pregnancy) or acetaminophen (FDA category B) are the mainstay for pain relief and reducing fever. Fever control and hydration help to avoid fetal complications also. In case of infection prior to delivery, the risk of vertical transmission is about 50%. Delaying delivery by use of tocolytics with the hypothesis that maternal antibodies may get transferred to the fetus and provide protection against neonatal affection needs further research [96]. Terminating pregnancy with cesarean section also has not

been seen to help in reducing the transmission [97]. The newborn should be monitored for development of infection and evaluated with appropriate tests.

As symptoms between chikungunya and dengue are overlapping and common, in areas where both viruses circulate, suspected chikungunya patients should avoid using aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) until diagnosis for dengue has been ruled out as these drugs can increase the risk of bleeding in dengue infection.

At present there is no commercial available vaccine to protect against chikungunya virus infection.

17.5 Prevention and Control of Mosquito Breeding

In the absence of specific treatment and effective vaccination, the best preventive measure is avoidance of mosquito bites and to limit the breeding of the potential vector.

- Individuals should avoid further mosquito bites in the first week of infection which corresponds to the period of viremia. This helps to break the vicious cycle of transmission.
- During outbreaks and monsoon season, insecticide application and spraying on the surfaces of containers where mosquitoes land is helpful. Different agents (mentioned below) can be used to treat water in the containers to kill the immature larvae.
- Prevention of breeding of mosquitoes in water filled containers can be accomplished by emptying and cleaning of artificial and natural water containing containers on a weekly basis.
- Use of insecticide treated nets for people sleeping, especially during daytime.
- Promoting use of screens at doors and windows to prevent mosquito entry.
- Promoting use of full sleeve shirt and trousers that decrease skin exposure during time of outbreaks.
- Use of repellents to clothing or on exposed skin should be as per instructions on the container.

Repellents should contain Environmental Protection Agency approved mosquito repellents which include:

- DEET (N, N-diethyl-3-methylbenzamide)
- IR3535 (3-[N-acetyl-N-butyl]-aminopropionic acid ethyl ester)
- Picaridin (1-piperidinecarboxylic acid, 2-(2-hydroxyethyl)-1-methylpropylester)
- Lemon eucalyptus oil
- Para-menthane-diol (PMD).

17.6 Conclusion

Arthropod infections are a common cause of acute febrile illness in tropical and sub-tropical countries. Malaria which is caused by the bite of an infected female anopheles mosquito is a major public health problem in these regions and infection in pregnant women is responsible for maternal morbidities including anemia, low birth weight infants and perinatal mortality. Dengue fever is one of the most common mosquito-borne viral diseases caused by one of four dengue flaviviruses and it can cause spontaneous abortion or lead to preterm labor in pregnant women. Pregnancy does not alter the course of the disease and treatment is the same as in non-pregnant, but vigilant watch should be kept for warning signs to appropriately treat severe disease. Chikungunya fever is another mosquito borne, self-limiting, viral disease caused by an RNA virus belonging to the alphavirus genus of the Togaviridae family. The human infection manifests as an inflammation of the musculoskeletal system with symptoms of headache, rash, myalgia, fever, and polyarthralgia. Neonatal infection as a result of vertical transmission has been reported thus generating interest of both obstetrician and neonatologist in this arthropod borne disease.

Key Points

- Arthropod borne diseases are very common infections especially in developing countries of the world.
- Fifty million pregnancies are subject to risk of malaria annually in endemic areas, of which 200,000 women develop anemia and 200,000 infants are born with low birth weight with 10,000 perinatal mortalities annually in these low birth weight infants.
- Four recognized species of Plasmodium are known to infect humans: vivax, falciparum, ovale, and malariae and the vector for transmission is female anopheles mosquito.
- Malaria in pregnancy should be treated as an emergency and all patients must be hospitalized.
- Chloroquine should be used in case of infection with *P. vivax*, *P. ovale*, 3 and *P. malariae*.
- Quinine and Clindamycin combination should be used in uncomplicated *P. falciparum* and mixed infections; Injectable artesunate is the drug of choice in severe falciparum malaria.
- Dengue fever is one of the most common mosquito-borne viral disease caused by one of four dengue flaviviruses. The Aedes mosquito transmits the virus while ingesting a blood meal.
- Nearly 40–80% of dengue infections are asymptomatic. About 5% develop severe, life-threatening disease.
- Dengue infection in the first trimester of pregnancy can be complicated by spontaneous abortion and neurological congenital anomaly in the infant while infection in the third trimester can lead to preterm labor.
- WHO (2009) classifies dengue into dengue with or without warning signs or severe dengue.
- No specific management is required for treatment of dengue in pregnancy, but vigilant watch for warning signs to appropriately treat severe disease is important.
- Chikungunya fever is a mosquito-borne, self-limiting, viral disease caused by RNA virus belonging to the alphavirus genus of the Togaviridae family.
- The most common clinical presentation of chikungunya virus infection is fever, myalgia, and arthralgia.
- Limited literature is available to document its role in causing antepartum complications but vertical transmission is documented in 50% of infections during the intrapartum period which are responsible for life-threatening complications in 50% of the neonates.

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Zika, Lyme, and Chagas Disease

18

Rashmi and Nazia Parveen

18.1 Introduction

Vector-borne diseases are serious health problems in many parts of the world and most of these are acquired in humans from the animals (zoonotic diseases). Earlier these were confined to localized parts of the world but in the last few decades, they have become emerging or re-emerging infections either due to increased incidence or spread across national boundaries. Due to globalization and increased international travel in recent times, the infections are spreading in populations where they were non-existent earlier. Few are more relevant in obstetric populations because of concerns for transmission to the fetus/neonates. Lack of knowledge and awareness among health professionals about these infections can delay diagnosis and treatment resulting in adverse obstetric outcomes. Zika virus, Chagas, and Lyme disease are such conditions which are a threat to international travelers and will be discussed in detail in the chapter.

18.2 Zika Virus Infection

Zika virus (ZIKV) disease is arbovirus-borne infection, endemic in multiple countries having the potential of international spread. It has become a major international public health issue due to its temporal association with neurological complications including fetal brain damage/death and microcephaly in babies born to infected mothers and Guillain–Barre syndrome (GBS) in adults.

Zika virus is a single stranded RNA arbovirus belonging to genus *flavivirus* and family of *Flaviviridae*. It is mainly transmitted through bites of female Aedes mosquitoes especially *A. aegypti* and *A. albopictus*. ZIKV is closely related to dengue virus, West Nile virus, Japanese encephalitis, and yellow fever virus.

18.3 Epidemiology

This virus was first isolated in rhesus monkeys in 1947 in Zika forest, Uganda. Human infection was reported in Nigeria in 1954 and since then the geographical distribution of Zika infection has expanded to include equatorial Asia, Africa, and the Americas but this was limited to only occasional case reports or small outbreaks. The first large outbreak of Zika infection was seen in the Island of Yap in 2007, following which there have been outbreaks in several other countries.

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From January 2015 to 2017, more than 7 lakh confirmed cases of Zika have been reported with maximum being from Brazil (46%) followed by Colombia (14%) and Venezuela. Region wise, South America has the maximum number of infections (70%) followed by Caribbean (21%), Central America (9%), and North America (1%). Because of increased cases of ZIKV infections across continents and its association with clusters of microcephaly and other neurological disorders, WHO in 2016 declared ZIKV a Public Health Emergency of International Concern (PHEIC). ZIKV exists in three different lineages: East African, West African, and Asian on the basis of genome sequencing of the NS5-encoding gene. These lineages can have different clinical presentation and neurological sequelae.

In Asia, occasional cases and small outbreaks had been reported earlier but increased awareness for the Zika disease has resulted in increased detection and reporting from this region also. Countries including Thailand, Vietnam, and Singapore have reported small clusters of Zika infections since 2016–17. *Aedes aegypti* mosquitoes are distributed throughout India and there is apparent threat of ZIKV to Indian population. Serological evidence of ZIKV has been documented in India as early as the 1950s but, proven cases of ZIKV were reported in 2017 followed by major outbreaks wherein a total of 159 cases were detected in Rajasthan (including 63 pregnant women) and 130 in Madhya Pradesh (including 42 pregnant women) [1, 2]. Neurological complications were not seen in these outbreaks. The virus responsible for the Indian outbreaks was considered to be of local origin caused by s sub-type of the Asian lineage ZIKV and there was no travel history to an endemic area in any of the patients. The Government of India in collaboration with the Indian Council of Medical Research (ICMR) has established a laboratory-based Zika surveillance system to detect Zika virus infection in patients with febrile illness, developed as part of the National Zika Action plan.

18.4 Clinical Features

18.4.1 Mode of Transmission

Main route of transmission is through bite of infected female anopheles mosquitoes. Non-vector mediated human to human transmission, though less common, has been reported by sexual transmission, blood transfusion, vertical (transplacental) transmission, peripartum, monkey bite, and laboratory transmission. The viable virus has been found in semen, vaginal secretions, menstrual blood, and breast milk. Although virus can be detected in semen up to 188 days, but potentially infectious virus is reported only up to 69 days [3]. Risk of sexual transmission is low and mostly occurs from male to female, but cases of transmission from female to male have also been reported. Routes of transmission can be vaginal, oral, anal sex and sharing of sex toys. No cases in India were attributed to non-vector routes of transmission.

18.4.2 Clinical Presentation

The median incubation period is 3–14 days after insect bite. Around 80% of infected people remain asymptomatic, but still can develop severe complications like Guillain–Barre Syndrome (GBS). The acute symptomatic cases (25%) may have symptoms of acute onset fever with maculopapular pruritic rash, myalgia, arthralgia (usually of small joints of hands and feet), or non-purulent conjunctivitis. Other symptoms reported are headache, lower limb edema, retro-orbital pain, and lower backache. Absence of hemorrhage and leukopenia/thrombocytopenia makes ZIKV infection different from dengue and chikungunya. This is usually a mild illness and symptoms generally resolve in 2–7 days without any sequelae. But in some cases serious neurological complications may occur after 5–6 days of acute illness. GBS is the most common neurological sequelae of ZIKV infection with estimated risk of 0.24 per 1000 cases [4].

ZIKV infection should be suspected in patients reporting with above mentioned symptoms along with epidemiological exposure (history of travel to areas with ongoing transmission during the 2 weeks preceding symptoms or sexual contact with person with infection/exposure). Single infection is likely to protect against future infections as seen in other flavivirus infections.

18.5 ZIKV Infection in Pregnancy

Pregnant women are neither at greater risk of acquiring ZIKV nor are likely to have more serious complications as compared to non-pregnant population. The primary concern for ZIKV infection in pregnancy is risk of vertical transmission and congenital Zika virus syndrome. Transmission can occur transplacentally or intrapartum at time of labor and delivery. Risk of transmission is estimated to be 5–10% and can occur in all trimesters, in both symptomatic and asymptomatic cases. Fetal infection can result in congenital anomalies and growth restriction. Adverse effects have been seen in all trimesters, but infection in first and early second trimester is associated with higher risk of congenital anomalies and also more severe disease.

18.5.1 Congenital Zika Virus Syndrome

ZIKV is considered a teratogen with neurotropism. Fetal Zika infection may cause several congenital defects like severe microcephaly with partially collapsed skull, other complex brain abnormalities, chorioretinal scarring, congenital contractures or arthrogryposis, marked early hypertonia and extrapyramidal symptoms. ZIKV particularly targets neural progenitor cells. Infection during pregnancy can lead to placental infection and injury followed by the transmission of virus to fetal brain where it kills the progenitor cells resulting in various anomalies (Table 18.1).

Table 18.1 Fetal abnormalities reported in pregnancies complicated with Zika virus infection

Cranial abnormalities	Extra-cranial abnormalities
Microcephaly	Contractures (single or multiple joints)
Cerebral and/or ocular calcification	Fetal growth restriction
Ventriculomegaly	Oligohydramnios
Periventricular cysts	Extrapyramidal symptoms
Callosal abnormalities	
Microphthalmia	
Cerebellar atrophy (transverse diameter <5th percentile)	
Vermian agenesis	
Blake's cyst	
Mega cisterna magna (>95th percentile)	
Choroid plexus cyst	
Brain atrophy leading to microencephaly (abnormally small brain)	
Cortical and white matter abnormalities (e.g., agyria)	
Chorioretinal scarring	

Association of congenital anomalies mainly microcephaly and antenatal ZIKV infection was first detected during Brazil outbreak in 2015. Though microcephaly can be caused by various congenital and acquired causes, based on evidence, WHO and other scientific bodies have concluded that ZIKA virus infection in pregnancy can cause microcephaly. Microcephaly can be associated with various developmental delays like intellectual impairment, hearing and visual defects, and epilepsy. The risk of microcephaly in infants born to women with prenatal Zika virus infection is reported between 1% and 4% [5, 6].

Ocular abnormalities have been reported in as high as 35% of the cases with microcephaly [7]. Highest risk of microcephaly was seen in infections in first trimester. Other CNS abnormalities seen are ventriculomegaly and intracranial calcifications. The intracranial calcification seen in ZIKA virus infection occurs at the junction of

white and grey matter. Positional abnormalities like club foot (Talipes) and arthrogryposis have been reported and may be of neurogenic origin. Case reports of cardiac defects and diaphragmatic hernia have also been reported. The causal relation between Zika infection during pregnancy and spectrum of congenital defects known as Congenital Zika virus Syndrome (CZS) (Table 18.1) has been well established through various studies. ZIKA infection in pregnancy has also been associated with miscarriages, preterm delivery, still birth, and growth restriction.

Magnitude of risk of fetal anomalies is uncertain and varies due to different strains/lineages, mutations, baseline population risk, coinfections, etc. Asian strain of ZIKV has been found to replicate in the fetal brain and placenta. In Indian outbreaks no case of microcephaly or other fetal abnormality was reported. The mutation causing CZV was not seen in the strain in Indian outbreaks.

18.6 Prevention

Currently there is no vaccine available for ZIKV. There is no specific treatment for the infection or any method to prevent transplacental transmission. Primary prevention includes avoiding or limiting exposure. Pregnant women should avoid travel to any area where ZIKV transmission is identified. Travel restriction guidelines are issued and list of countries with ongoing or past transmission of ZIKV is constantly updated by WHO, CDC, and RCOG. If pregnant women have to travel in such areas, then various measures should be taken to prevent mosquito bite. Light-colored and loose-fitting clothes should be worn which cover the maximum exposed skin. Insecticides (permethrin) can be applied over clothes. N-diethyl meta toluamide (DEET) based repellents are more effective insect repellents and are safe in pregnant and breastfeeding women. Women should sleep under mosquito nets impregnated with permethrin.

Since the period of viral shedding by infected male partner is not clear, it is advised to abstain from sexual activity, or to use a condom consistently for the duration of pregnancy to reduce the sexual transmission to pregnant partner if male partner has exposure.

Table 18.2 Measures to prevent sexual transmission after possible ZIKV exposure

Traveling in areas with ZIKV transmission	Duration recommended to avoid sexual contact or use of condoms
If both partners have traveled	3 months till after last possible exposure
If only female partner has traveled	8 weeks/2 months
If only male partner has traveled	3 months

Those planning pregnancy should avoid travel to such areas or postpone pregnancy. Effective contraception should be used and barrier methods (condoms) should be used while vaginal, oral, or anal sex to prevent sexual transmission (Table 18.2) [8, 9].

18.7 Diagnosis

Diagnosing ZIKV infection is difficult due to most cases being asymptomatic, cross reactivity with other flaviviruses, short window of detecting acute infection, and lack of point of care diagnostic facilities. Screening in non-pregnant, asymptomatic travelers who return from a country with ongoing transmission of ZIKV is not recommended. ZIKV infection should be suspected in symptomatic women with onset of symptoms within 2 weeks of relevant epidemiological exposure. Epidemiological exposure or possible ZIKV exposure is defined as travel to or residence in an area with ongoing ZIKV transmission or sexual contact with a partner with such exposure. Symptoms of ZIKV infection are non-specific and overlap with many other acute febrile illnesses. The diagnosis is established by molecular or serological tests.

18.7.1 Molecular Testing: Serum RT-PCR

The diagnosis of ZIKV infection is established by detecting ZIKV RNA through reverse tran-

scription polymerase chain reaction (RT-PCR) performed on serum, plasma, or urine. Urine has better sensitivity for ZIKV detection than serum. ZIKV RNA can be usually detected in serum up to 7 days after symptom onset. ZIKV RNA can persist in serum for longer time in many cases. Prolonged detection (up to 107 days after symptom onset) in blood has been reported during pregnancy [10].

Serum and urine samples are tested by RT-PCR for ZIKV in symptomatic women within 2 weeks of onset of symptoms. RCOG recommends testing in urine up to 3 weeks of symptom onset [11]. CDC recommends testing with RT-PCR on serum and urine along with serological testing up to 12 weeks after symptom onset (Table 18.3) [13].

Detection of ZIKV RNA in serum/blood or urine is diagnostic of recent ZIKV infection. But negative test result does not rule out infection and requires serological testing.

18.7.2 Serological Testing

Serological tests for ZIKV are ELISA testing for IgM antibodies and Plaque Reduction Neutralization Test (PRNT). IgM antibodies are detectable within 2 weeks after ZIKV infection. IgM antibodies can remain elevated up to 4 months. Neutralizing antibodies start rising shortly after IgM response and are likely to remain high for many years.

Detection of serum IgM antibodies by enzyme-linked immunosorbent assay (ELISA) is possible after 4 days of onset of symptoms, but its diagnostic value is limited because of cross reactivity with other flaviviruses like dengue. IgM testing can be done in both serum and CSF. PRNT is a specific test and can differentiate antibodies of closely related viruses. However, this test is not widely available, and limited by cost factor. This involves handling of live virus and takes a long time to perform. CDC recommends performing PRNT for ZIKA and dengue viruses for NAT negative and IgM ELISA non-negative cases. PRNT can often identify the infecting virus in primary infections and can detect false positive IgM cases. But in previously flavivirus infected individuals, PRNT may not be able to differentiate ZIKV antibodies from cross reacting antibodies. So its role is limited in areas with high transmission of Dengue virus.

18.7.3 Testing During Pregnancy

1. In asymptomatic pregnant women with exposure but without any ongoing exposure, testing is not recommended.
2. But if there is ongoing possible ZIKV exposure, molecular testing is advised three times

Table 18.3 Zika Virus Testing Recommendations During Pregnancy

	CDC [12]	RCOG [13]	WHO [14]
	Pregnant women with possible exposure in current pregnancy and symptomatic or USG suggesting congenital ZIKV syndrome	Symptomatic women with onset of symptoms within 2 weeks of possible exposure	Pregnant women with exposure; symptomatic/asymptomatic/ fetal anomalies suggesting congenital Zika virus syndrome
Serum testing for ZIKV RNA	Up to 12 weeks after exposure/ symptom onset	Up to 2 weeks after symptom onset	Up to 7 days after symptom onset
Urine testing for ZIKV RNA	Up to 12 weeks after exposure/ symptom onset	Up to 3 weeks after symptom onset	Up to 21 days after symptom onset
Antibody testing	IgM up to 12 weeks along with molecular test PNRP if IgM positive and RNA test negative	IgM testing >2 weeks after symptom onset	IgM testing >7 days of symptom onset
Testing for asymptomatic women	Not recommended	Not recommended	Recommended

during pregnancy by CDC. Routine IgM testing is not recommended. Adverse outcomes can occur even if infection occurs in third trimester, so testing in all trimesters is recommended.
3. Testing is also recommended in pregnant women with possible exposure and ultrasound detection of anomalies consistent with congenital ZIKV syndrome.
4. Routine serological testing in non-pregnant women with ongoing exposure for preconception counseling is not recommended.

18.8 Treatment

Currently there is no specific antiviral treatment available for ZIKV infection. Since the disease is usually mild and resolves in 2–7 days, only supportive care and symptomatic management is advised that includes adequate fluids and rest. Control of fever and pain is done with paracetamol (not to exceed 4000 mg/day). Similar to other flavivirus infections, Acetylsalicylic acid and non-steroidal anti-inflammatory (NSAIDs) should be avoided due to potential risk of hemorrhage. Calamine lotion or menthol-based aqueous cream can be applied for pruritic rash. Tab loratadine 5 mg every 12 h may reduce symptoms of non-purulent conjunctivitis.

18.8.1 Fetal Evaluation and Pregnancy Management

Ultrasonographic evaluation should be done to assess fetal anatomy, mainly neuroanatomy and growth monitoring in all pregnant women with possible ZIKV infection. However, detection of prenatal features of congenital Zika syndrome may not be identified if ultrasonographic evaluation is performed soon after onset of infection. It might take as long as 29 weeks from infection onset and presentation of fetal abnormalities [15]. There is no clear recommendation about the optimal timing from exposure and first ultrasound screening in pregnant women with ZIKV infection.

ACOG recommends ultrasound evaluation every 3–4 weeks to look for congenital anomalies especially intracranial and fetal growth in cases with recent ZIKV infection in pregnancy. Abnormal USG findings in ZIKV infection may be microcephaly, absent corpus callosum, hydranencephaly, cerebral calcification, abnormal sulcation and gyration, ventricular dilatation, brain atrophy, micro-ophthalmia, eye calcifications, anhydramnios, hydrops fetalis, and fetal growth restriction.

If ultrasound is abnormal, amniocentesis may be considered in pregnancy >15 weeks, for detection of fetal infection though its usefulness in detecting congenital infection is uncertain and depends on timing of testing after initial infection. As viral DNA presence in amniotic fluid is transient after infection, negative result does not rule out congenital infection, thus limiting its role in management.

MRI is more sensitive in detecting brain abnormalities. Fetal brain MRI may be considered to detect further abnormalities which might not be detected on ultrasonography if it is likely to impact management.

Other causes of fetal abnormalities should also be ruled out like other congenital infections, toxin/drug exposures, genetic abnormalities, etc. Individualized care with proper counseling of the couple should be done. If there is confirmed significant brain abnormality or microcephaly in the presence of ZIKV infection, the option of termination of pregnancy may be discussed with the woman. If pregnancy is continued, proper support throughout pregnancy should be given especially to manage anxiety and stress.

Infected fetus is at risk of still birth though exact mechanism is not clear. Therefore, close monitoring with antepartum fetal surveillance should be done. Delivery timing and route is decided as per routine practice. Management of baby soon after birth should be planned and discussed with pediatrician and pediatric neonatologist if possible, especially in the presence of abnormalities.

18.8.2 Postnatal Management

All newborns with antenatal exposure should be tested by RT-PCR of serum and urine and Zika virus IgM antibodies in serum to rule out congenital infection. Also, they should be evaluated for growth parameters, vision, hearing, and developmental milestones.

Testing of placental and fetal tissues is not routinely recommended, but can be performed in certain situations (e.g., a woman without laboratory-confirmed infection who has a fetus or infant with possible Zika virus-associated abnormalities or pregnancies resulting in miscarriage or fetal death).

18.8.3 Breastfeeding

There are reports of viable virus detection by PCR in breast milk, but there is no confirmed case of Zika virus transmission by breastfeeding. As breast-feeding benefits outweigh the risks, it is recommended to continue breastfeeding in ZIKV infection in pregnancy [16].

18.9 Lyme Disease

Lyme disease (Borreliosis) is a zoonotic infection caused by spirochetal bacteria *Borrelia burgdorferi*, transmitted to humans via *Ixodes* ticks. Three species of Borrelia: *B. burgdorferi sensu stricto, B. afzelii, and B. garinii* are pathogenic in humans. The latter two are frequently found in Asia. Lyme disease is considered the most common tick-borne disease in the United States. Estimated 60,000–100,000 cases of Lyme disease occur annually across the world. The *Ixodes* ticks are prevalent in Himalayan region of India, suggesting the likelihood of Lyme disease in our country. High seroprevalence has been reported in Northeastern states and forests in South India [17, 18].

18.10 Clinical Features

Lyme disease has three clinical stages. *Early localized infection (Stage 1)* is characterized by erythema migrans rash (bull's eye rash) of skin, with associated symptoms of headache, fever, myalgia, arthralgia, lymphadenopathy, and conjunctivitis. The rash usually occurs within 1 week of infection, but may develop as late as 16 weeks after the tick bite. It is a red expanding rash, with or without central clearing. The lesions usually resolve within 3–4 weeks. It is seen in 50–80% of the cases. Hematogenous and lymphatic dissemination of the bacteria to distant sites occurs within days to a few weeks after infection, giving rise to stage 2. If detected early, it is completely treatable with antibiotics and serious complications can be avoided.

Early-disseminated stage (Stage 2) is characterized by involvement of musculoskeletal, cardiac, and neurological system. Musculoskeletal system involvement is seen in approximately 60% of patients in the form of arthralgia and myalgia in early course, and asymmetrical, oligoarticular arthritis mainly of large joints (e.g., knee) in later course of disease. Neurological Lyme disease can present in the form of meningitis, cranial nerve palsies, and radiculopathies. The cranial neuropathy in form of unilateral and bilateral facial paralysis is the most common neurological feature. Cardiac involvement can present as AV block.

Late-stage disease (Stage 3) is characterized by polyradiculoneuritis, chronic arthritis, and localized scleroderma-like lesions. Demyelination disorder, cognitive dysfunction, and fatigue may also occur.

Borrelia burgdorferi mainly causes chronic and refractory oligoarticular arthritis. *Borrelia garinii* has neurotropic manifestation while *Borrelia afzelii* has only cutaneous manifestations.

18.11 Lyme Disease in Pregnancy

There are concerns about adverse effects of Lyme disease in pregnancy due to similarities with Syphilis disease which has established congenital effects and adverse pregnancy outcomes. Multiple cases have been reported regarding the possibility of transplacental infection with *B. burgdorferi* [19–21].

Case reports of cardiac malformations, stillbirth, cerebral edema, and rash have suggested a possible association between Lyme disease in pregnancy and adverse fetal outcome [19, 21]. Multiorgan involvement of the fetus has been documented by presence of spirochetes in liver, adrenal, brain, heart, and placenta. Adverse pregnancy outcomes in congenital Borreliosis can be in the form of second trimester miscarriages, growth restriction, prematurity, still birth, and neonatal death. There are concerns of teratogenic effects resulting in congenital heart disease (aortic stenosis, septal defects, patent ductus arteriosus, coarctation of aorta) and other malformations. Neonatal hyperbilirubinemia, hepatosplenomegaly, neonatal rash have also been reported. A large prospective study by Strobino et al. in over 2000 pregnant women concluded that maternal exposure to Lyme disease before conception or during pregnancy was not associated with fetal death, congenital malformations, or prematurity [22]. Subsequently no association was found between congenital heart defect and maternal Lyme disease in a retrospective case–control study [23]. However, Dr. Tess Gardner in an extensive review of literature on congenital Borreliosis concluded that congenital Borreliosis though rare, may result in severe adverse outcomes, including neurological symptoms in 20% of infants [24]. Lakos and Solymosi found evidence of increased risk of fetal death and still birth in acute Borrelia infections in pregnancy [25].

Despite multiple case reports, case series, animal studies, epidemiological investigations, and histological studies, there continues to be a lack of consensus regarding causal relationship between *Borrelia* infection and adverse pregnancy outcomes [23, 26, 27].

Few cases are reported in literature pointing towards an association of pre-eclampsia with antenatal Borrelia infection. Cases of pre-eclampsia are reported in third and also second trimester with Borrelia infection detected post-partum by serology [20].

Subclinical neonatal Borreliosis acquired transplacentally has been suggested to cause unexplained sudden infant death syndrome (SIDS). In 10 cases of SIDS in an endemic region in United States, 2 were found to have Borrelia spirochetes in brain [20].

18.11.1 Postpartum Considerations

Irrespective of fetal outcome, pathological examination of the placenta should be done for detection of spirochetes in the placental tissue and cord blood in all cases of antenatal acute Borrelia infection. Neonatal serology is done to detect disease. As majority of infants can test negative despite infection, placental test results are taken into consideration for treating the infant. Maternal to fetal infection can be clinically silent and if not appropriately treated, infection can last lifelong with late activation or re activation. Women with Lyme disease during pregnancy should be monitored up to one year for symptoms that may represent late-stage disease.

18.11.2 Breast-Feeding

Borrelia DNA has been detected in breast milk of mothers who are acutely infected. However, since there is no confirmed case of *Borrelia* infection in infant from breast milk, this is only a relative contraindication to breast-feeding.

18.12 Diagnosis

Diagnosis is based on appearance of erythema migrans rash with a history of recent travel to an endemic area (with or without history of tick bite). Serology test using enzyme-linked immunosorbent assay (ELISA) is used to detect

the antibodies to *B. burgdorferi*. Due to high false positive rate, a positive/equivocal ELISA should be confirmed by Western blot. The patients with only cutaneous disease are not recommended for laboratory testing because the test may be negative in early stage. IgM antibodies appear after 2–4 weeks following the appearance of rash and decline to low levels in 4–6 months. IgG antibodies start appearing at 6–8 weeks and peak at 4–6 months and remain elevated indefinitely. The diagnosis of acute infection cannot be made on the serological tests alone.

In neurological involvement cases, classical findings in CSF are seen including lymphocytic pleocytosis, increased protein concentration, normal glucose concentration, elevated immunoglobulin G (IgG) index, and oligoclonal bands. For the definitive diagnosis, intrathecal anti-*B. burgdorferi* antibody production should be demonstrated.

18.13 Prevention

The best preventive measure is to avoid exposure to the vector ticks. It is recommended to use 20–30% DEET in endemic area. There is no evidence of any risk in pregnancy with its use. After outdoor activities in such areas, thorough examination should be done for any ticks. Ticks should be removed immediately and shower should be taken. After removal of attached ticks, patient should be kept under observation for appearance of clinical disease, e.g. skin rash or fever up to 30 days.

18.14 Treatment

When Lyme disease is suspected in pregnancy, serological testing should be done and treatment is started immediately in acute infection without waiting for test reports as fetal death can occur. Treatment is based on the stage of infection. The recommendations are to treat women with stage I disease with oral antibiotics and stage 2 & 3 with intravenous antibiotics. The standard antibiotic treatment is Amoxicillin 500 mg three times daily or Cefuroxime axetil 500 mg twice daily for women who are allergic to penicillin. Doxycycline is contraindicated in the obstetrical population. Oral antibiotics are given for 21 days. Injection Ceftriaxone 2–4 g daily or Penicillin G five million units four times a day for 14–21 days duration is recommended in stages II or III.

Termination of pregnancy is not warranted and if adequate treatment is given for acute infection, adverse fetal effects are avoided.

Ultrasound fetal surveillance is recommended if acute infection occurs in pregnancy. Evidence of congenital spirochetal infection can be fetal ascites, hepatosplenomegaly, and fetal anemia evidenced by increased middle cerebral artery blood flow, non-immune hydrops, and placentomegaly. If acute infection occurs in first trimester during cardiac organogenesis, fetal echocardiography should also be done.

18.15 Chagas Disease

Chagas Disease (CD) or American trypanosomiasis is a protozoan zoonotic disease caused by the hemoflagellate Trypanosoma cruzi. It is a vector-borne disease transmitted by blood-sucking triatomine vectors (reduviid bug), closely associated with poverty and considered as neglected tropical disease by WHO, affecting close to six to seven million people globally. It is a chronic disease and approximately 30% can develop chronic Chagas cardiomyopathy and other serious cardiac complications such as stroke, rhythm disturbances, and severe heart failure. It is a major cause of death due to parasitic diseases.

18.16 Epidemiology

Historically the disease was limited to endemic areas of Latin America but in the recent years large-scale migration of chronically infected and asymptomatic persons from rural to urban areas of Latin America and to other regions of the world has caused globalization of CD and now it has become an emerging global problem reported

from many non-endemic areas including United States, Europe, Canada, Japan, and Australia.

Human trypanosomiasis is of two types—*African trypanosomiasis* (sleeping sickness) endemic in Sub-Saharan Africa, caused by *Trypanosoma brucei* and *American trypanosomiasis* (Chagas disease). Neither of these, nor their vectors are found in India. In 2005, first confirmed case of atypical human trypanosomiasis caused by *T. evansi* was detected near Nagpur [28]. *T. evansi* causes a disease named "surra" in horses and other livestock in India. Subsequently, 4.5% of the screened population was sero positive in that village. This new zoonosis has been christened as Human Asian Trypanosomiasis. These are atypical human infections and their effect on pregnancies is unknown.

18.17 Transmission and Pathogenesis

The vector-borne transmission occurs through Triatomine bugs, mostly found in poor quality houses. These bugs usually bite on faces during night time, hence known as "kissing bugs." Infected bug passes the parasites in the feces (trypomastigotes). When they bite, they defecate on skin near to the bite site. The person can become infected with parasite if bug feces enter the body through mucous membranes or breaks in the skin, which happens quite often if sleeping person may accidentally scratch or rub the feces into the bite wound, eyes, or mouth.

Non-vector transmission of infection can occur by the following routes:

- Congenital transmission (vertical transmission pregnant woman to fetus)
- Blood transfusions
- Organ transplantation
- Orally through uncooked food and drink contaminated with triatomines or their feces
- Accidental laboratory exposure
- Sharing of needles between intravenous drug users.

Chagas disease is not transmitted from person-to-person or through casual contact with infected people or animals. Due to successful interventions interrupting vector and blood transfusion routes, congenital transmission has become proportionately more relevant. It is responsible for about one-third of new infections, representing the major mode of transmission in non-endemic areas [29].

Trypomastigotes after entering the cells near the site of inoculation, differentiate into amastigote forms. Amastigote divides and differentiates into trypomastigotes and is released into blood and infects new sites and gets transformed into intracellular amastigotes. In humans *T. cruzi* infection is mainly limited to myocardium and gut nerve fibers. Bugs get infected by sucking blood from infected host with circulating parasites.

18.18 Clinical Presentation

The incubation period of Chagas disease is 7–14 days for vector-based transmission and around 30–40 days in the case of transfusion-related transmission. The disease has two distinct phases.

Acute Chagas: The initial acute phase is characterized by high levels of parasitemia. Many cases remain asymptomatic or have nonspecific symptoms including fever, fatigue, rash, anorexia, headache, body aches, diarrhea, and vomiting. Clinical signs include hepatosplenomegaly, generalized or local edema, and lymphadenopathy. In vector-transmitted CD, specific signs of inoculation chancre and Romaña's sign (classic finding of unilateral painless edema of the palpebrae and periocular tissue) may be present. Chagoma which is an indurated area of erythema and swelling accompanied by local lymphadenopathy may be seen when the organism enters through a break in the skin. Severe acute disease occurs in less than 1–5% of cases carrying a mortality risk of 0.2–0.5%. It may present with hemorrhagic manifestations, jaundice, myocarditis, pericardial

effusion, tachycardia, arrhythmias, atrioventricular block, and, in a small percentage, meningoencephalitis [30].

If untreated, symptoms of acute phase mostly resolve spontaneously in 1–2 months and patients remain chronically infected.

Chronic phase—Acute phase is followed by an asymptomatic indeterminate phase. About one third cases develop chronic CD wherein parasite and immune response cause end organ damage mainly in the heart and digestive tract muscle. Few or no parasites are found in the blood. Most people remain asymptomatic for life. Cardiac disorders are seen in up to 30% patients in the form of life-threatening ventricular arrhythmias, cardiac arrest, and sudden death [31]. The gastroenterological manifestations in form of enlargement of esophagus or colon are seen in up to 10% cases.

18.19 Pregnancy with Chagas Disease

Congenital transmission rates of *T. cruzi* infection range from 0% to 28.6% [32]. Mothers living in endemic areas or migrants, congenital infection in siblings, coinfection with HIV/Malaria increase the chances of congenital Chagas. Congenital transmission may occur during any phase of disease. The transmission can get repeated during each pregnancy and during entire fertile period. High parasitic load in blood is a risk factor for transplacental transmission. Higher parasitemia is seen in acute phase of disease. In chronic phase, though parasitemia is low but during pregnancy parasitemia increases. Increased levels of IgM have been observed in chronically infected mother during pregnancy which suggests reactivation of disease. Factors which determine the risk of transmission include phase of the disease, immunological status, obstetrical history, parasite strain, and parasitic load. The transmission of blood parasites occurs more during the second and third trimesters of pregnancy and during delivery through placental breaches. A study reported higher parasitemia in third trimester as compared to first two trimesters [33].

Higher congenital transmission is reported in acute disease during pregnancy. Reactivation of chronic disease has been observed in immunosuppressed condition which explains high frequency and severity of congenital CD in patients with coinfection with HIV [33].

Adverse pregnancy outcomes like preterm delivery, still birth, growth restriction may occur due to inflammation of the placenta seen in these cases. But evidence for an overall increased risk of abortion or prematurity in seropositive women is inconclusive. Maternal chronic infection has no effect on the outcome of pregnancy or on the health of newborns as long as there is no maternal transmission of parasites to the unborn child.

Clinical features of Chagas disease in infants may include low birth weight, prematurity, hepatosplenomegaly, anemia, thrombocytopenia, and low Apgar score. Severe disease such as meningoencephalitis, pneumonitis, or anasarca and even death can occur in infected infants but is rare. *Congenital Chagas disease*: Congenitally infected newborns are frequently asymptomatic, but symptoms may appear within days or weeks after birth. This is attributed to late parasite transmission during pregnancy (during second and third trimester) and consequently less time for parasite multiplication in fetuses and clinically evident disease at birth. This is the reason of screening for congenital infection by laboratory diagnostic tests at birth in endemic areas.

Congenital *T. cruzi* infection is an acute infection in newborns. If not treated timely, infection will persist for life and these infants are at risk for developing clinical manifestations of chronic Chagas disease later in life like cardiomyopathy or digestive mega viscera by the age of 25–35 years. There is further risk of vertical transmission in next generation.

18.20 Prevention

18.20.1 Primary Prevention

Currently there is no vaccine available for Chagas disease. Primary prevention in endemic areas can be done by cleanliness, insecticide spray, use of bed nests, and good hygiene practices in food preparations. Screening of blood donors, organ/tissue donors, treatment of cases are recommended to control the transmission.

18.20.2 Preventing Congenital Transmission

The most effective strategy to prevent congenital transmission is screening all women of childbearing age in endemic areas or migrants from there and treating seropositive women with antiparasitic agents prior to pregnancy. The antitrypanosomal drugs are contraindicated during pregnancy, hence treatment of females of childbearing age is now recommended in major guidelines [34].

18.21 Diagnosis

In acute phase diagnosis can be made by direct parasitological detection of *T. cruzi* in blood smear. PCR can also be used in acute phase. In chronic phase diagnosis can be made by serological methods by enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescence, indirect hemagglutination, and Western blot. All the pregnant women at risk should be screened with 2 sequential serological tests.

The newborns of infected mothers should be screened and promptly treated as high cure rates are seen with early treatment. Infected newborns have high levels of parasitemia. Hence, screening is done by microscopic examination of cord blood after concentration (microhematocrit, Strout's method) and if microscopic test is negative, PCR should be done. If PCR is negative, serologic testing is performed at 9 months of age. Examination of the placenta is not recommended as screening method.

18.22 Treatment

Benznidazole and nifurtimox are the only drugs available for the treatment of CD and are given for 60–90 days [26].

Benznidazole: It is active against both the trypomastigote and amastigote forms. It is rapidly absorbed from the gastrointestinal tract with a biological half-life of 12 h. The recommended dose is 5–7 mg/kg/day in 2 divided doses for 60 days. It is commonly associated with dermatologic side effects which are seen in 30% patients. The dermatitis is usually mild to moderate and can be treated with topical steroids. Another side effect commonly seen with its use is peripheral neuropathy that is reversible but may take months to resolve.

Nifurtimox: It is also active against both the trypomastigote and amastigote forms. It is used in the dose of 8-10 mg/kg/day in 3 divided doses for 90 days. The drug is usually associated with gastrointestinal side effects like anorexia, nausea, vomiting, and weight loss.

Both are nearly 100% effective in curing the disease if given early in acute phase including congenital CD. The efficacy of the treatment decreases in people having prolonged exposure to the infection. The cardiac, digestive, or neurological manifestations of the disease require specific treatment. Benznidazole is preferred over nifurtimox due to better tolerability profile, tissue penetration and efficacy. Both the drugs are mutagenic and hence are contraindicated in pregnant women. All infected mothers should be treated after completion of breastfeeding. This helps to reduce the risk for vertical transmission in subsequent pregnancies and reduce their risk for developing cardiac complications.

18.22.1 Treatment of Neonates and Infants

Both benznidazole and nifurtimox can be used to treat congenital cases. Drugs should be orally administered, preferably in divided doses of two to three sub-doses. The recommended duration of treatment is 60 days. If administered within the first year of life, treatment is generally successful and without the adverse reactions seen in adults.

18.22.2 Breastfeeding

As Chagas disease can be transmitted by oral route, during the acute phase, breast-feeding may pose a significant risk for the infant and should be avoided. The discontinuing of breast-feeding by mothers with chronic Chagas disease is not recommended. If the mother has fissures or bleeding nipples, pasteurization or microwaving of expressed milk before feeding the infant may be a safe alternative.

18.23 Conclusion

Vector-borne diseases are serious health problems in many parts of the world, which are increasing in incidence worldwide. This is mainly attributable to the changing environment, increase in travel, and resource constraints in the areas endemic to such diseases. Lack of knowledge and awareness among health professionals about these infections can delay diagnosis and treatment and contribute significantly to maternal and fetal morbidity and mortality. Table 18.4 summarizes the transmission, clinical features, maternofetal outcomes and treatment of the three emerging important vector-borne diseases in pregnancy.

Table 18.4 Emergent vector born infections in pregnancy

	Zika virus	Lyme disease	Chagas disease
Vector	*Aedes aegypti*, *aedes albopictus*	*Ixodes* ticks	*Reduviid bug*
Infectious agent	Zika virus	Spirochetes of the genus *Borrelia burgdorferi sensu lato*	Hemoflagellate *Trypanosoma cruzi*
Sign and symptoms	Rash, mild fever, conjunctivitis, myalgia, arthralgia	Erythema migrans rash, fever, myalgia, arthralgia, lymphadenopathy, and conjunctivitis	***Acute***—fever, fatigue, rash, anorexia, headache, body aches, diarrhea, and vomiting ***Chronic—***ventricular arrhythmias, cardiomyopathy, megacolon
Onset time	2–12 days	7 days	7–14 days
Geographical distribution	Africa, Americas, Pacific island, and southeast Asia	United States	Latin America
Maternal and fetal outcomes	Microcephaly, cerebral calcification, growth restriction	Second trimester miscarriages, fetal growth restriction, prematurity, still birth, neonatal death	Preterm delivery, still birth, fetal growth restriction, hepatosplenomegaly, anemia, thrombocytopenia
Testing	RT-PCR	ELISA followed by Western Blot	ELISA
Management and prevention	Supportive/vector control and environmental measures	Vector control/oral amoxicillin, cefuroxime Intravenous ceftriaxone and penicillin G	Vector control Benznidazole and nifurtimox (Both drugs are contraindicated in pregnancy)
Termination of pregnancy	Can be considered	Not advised	Not advised

Key Points

1. ZIKV is an arbovirus-borne infection transmitted by Anopheles mosquitoes, causes mild disease, but has associated risk of microcephaly in fetuses of infected mothers and occurrence of Guillain–Barre syndrome (GBS) in adults.
2. Early testing and fetal evaluation of symptomatic pregnant women living in or traveled to Zika endemic areas is recommended.
3. There is no vaccine or specific treatment available for ZIKV; environmental and vector control measures are important for prevention of infection.
4. Lyme disease is caused by *Borrelia burgdorferi* transmitted by ticks. The disease has three distinctive phases of early localized, early disseminated, and late stage.
5. Lyme disease during pregnancy is associated with adverse pregnancy outcomes in the form of miscarriage, fetal growth restriction, prematurity, still birth, and neonatal death. Recommended management is early serological diagnosis and treatment with antibiotics.
6. Chagas disease is caused by protozoa *Trypanosoma cruzi* and is transmitted to humans either by blood-sucking triatomine vectors, blood transfusion, or congenital transmission.
7. Chagas disease is characterized by two phases of disease, acute and chronic. The chronic phase of the disease is characterized by involvement of myocardium and gut nerve fibers and occurrence of cardiomyopathy and megacolon.
8. Treatment of Chagas disease is contraindicated in pregnancy. Screening and treatment of reproductive age females in endemic areas has important role to reduce the risk of congenital transmission of infection.

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Part VI

Sexually Transmitted Diseases

19 Herpes, Gonorrhea, Chlamydia, and HPV Infection

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19.1 Herpes, Gonorrhea, Chlamydia, and HPV in Pregnancy (Prevention, Screening, Treatment, and Outcomes)

19.1.1 Introduction

Sexually transmitted diseases (STD) are very common in young females. They present with wide range of clinical manifestations. They can be asymptomatic, may cause mild discomfort, or may cause significant complications like infertility or ectopic pregnancy. STDs are of special concern during pregnancy due to their potential to cause adverse obstetric outcomes and neonatal infections. Screening and treatment of STDs during pregnancy represent an overlooked opportunity and is often underutilized.

In this chapter, we will discuss the four common STDs that are encountered during pregnancy, namely Herpes simplex virus (HSV), Human Papilloma Virus (HPV), Chlamydia, and Gonorrhea.

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19.1.2 Herpes

HSV infection is a common STD in the reproductive age group [1]. HSV is an enveloped, double-stranded DNA epitheliotropic virus related to the *Alphaherpesvirinae*, a subfamily of the *Herpesviridae* family [2].

As per the World Health Organization (WHO), globally, 3.7 billion people under the age of 50 years are infected with HSV-1 infection, and 491 million people aged 15–49 years are infected with HSV-2 infection [3]. The prevalence of HSV-2 in Asian countries varies from 10% to 30% [1]. Studies from different regions in India have shown HSV-2 seroprevalence from 5.8% to 18.9%. HSV-2 seroprevalence among pregnant women has been reported to be 8.7% in north India and approximately 11.3% in south India [4, 5].

19.1.2.1 Pathogenesis

HSV is a double-stranded DNA virus and has two types HSV-1 and HSV-2. Primary herpes infection refers to a new infection acquired for the first time in a person lacking both pre-existing HSV-1 and HSV-2 antibodies. When a person with pre-existing HSV antibodies (against type 1 or 2) is infected initially with the other HSV type, it is called the first non-primary episode. Primary HSV infection with both types is acquired across mucous membranes and nonintact skin.

After the primary infection, the virus remains latent in nerve ganglia and can cause recurrent

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lesions. HSV-1 remains latent in trigeminal ganglia and usually causes orolabial lesions. HSV-2 commonly infects lumbosacral ganglia and causes recurrent genital lesions. However, both types of viruses can infect orofacial and anogenital regions, and their management remains the same. Recurrent infections are associated with antibodies against the same HSV type [1, 2]. Both primary and recurrent infections with HSV can be asymptomatic.

19.1.2.2 Clinical Features

Maternal Manifestations

Incubation period of primary genital herpes is 2–20 days, and symptoms can last up to 21 days. Women usually present with painful blisters and ulcerative lesions over external genitals, cervix, inner thigh, buttocks, perineum, and perianal area. She may have dysuria, vulval pain, vaginal soreness and discharge, with or without inguinal lymphadenopathy. Prodromal symptoms can range from fever, headache, and myalgia to severe manifestations including meningitis and autonomic neuropathy.

Severe manifestations of HSV infection are more common in pregnancy. The pregnant woman is at higher risk for severe and frequent symptomatic episodes of orolabial and genital herpes and also of asymptomatic viral shedding at term [6]. Disseminated HSV infection during pregnancy is a rare but serious complication of primary HSV infection in the third trimester. It can manifest as disseminated skin lesions, encephalitis, hepatitis, thrombocytopenia, leucopenia, coagulopathy, with a maternal case fatality rate of up to 50% [1]. There is also a high rate of transmission of infection to the fetus.

During pregnancy, recurrent genital herpes is much more frequent than primary HSV infection. Most episodes of recurrent genital herpes during pregnancy are asymptomatic or present with mild symptoms and few localized lesions. Recurrent genital herpes is also associated with a much lower transmission risk to the fetus than primary genital HSV infection. The fetal infection rate with recurrent genital HSV is <1%, compared with 30–50% fetal transmission rates with primary genital HSV infection during pregnancy [1, 2]. Viral shedding is higher with HSV-2 infection as compared to HSV-1 and can occur even in the absence of symptoms and evident lesions. Type-specific antibodies to HSV are usually formed within the first 12 weeks after maternal infection and persist indefinitely. These maternal antibodies may reduce fetal infection by transplacental passage and by decreasing viral shedding in the maternal genital tract.

Maternal to neonatal HSV transmission mainly occurs during antenatal (5–8%) and perinatal (85–90%) period; postnatal transmission is rare. As mentioned above, in-utero HSV transmission is higher with primary HSV infections and HSV-2 infections, and also with maternal infection during the first 20 weeks of gestation. Fetal HSV infection can cause spontaneous abortions, congenital anomalies, fetal growth retardation, preterm labor, and still birth [2]. Rates of perinatal transmission of HSV infection are increased with primary or non-primary third trimester maternal infections, absence of maternal neutralizing antibodies, prolonged rupture of membranes, vaginal mode of delivery, and with invasive fetal monitoring [6].

Neonatal Manifestations

The infected newborn may present with congenital infection or with neonatal herpes. Congenital herpes is characterized by skin vesicles (appearing within 48 h of birth) or scarring, eye lesions (chorioretinitis, microphthalmia, and cataract), neurologic damage (intracranial calcifications, microcephaly, seizures, and encephalomalacia), growth retardation, or impairment in psychomotor development.

Neonatal herpes infection is usually acquired at the time of delivery or occasionally in the early postnatal period. It is classified into three groups:

1. Localized to skin, eyes, or mouth, representing 30% of neonatal herpes and has the best prognosis. Neurological and ocular morbidity after antiviral treatment is <2%.

2. HSV encephalitis, presenting between 10 days to 4 weeks of age. Mortality is around 6%, while neurological morbidity is 70%, even after antiviral treatment.
3. Disseminated infection with multiple organ involvement, occurring mostly in preterm infants of mothers with primary herpes infection. It carries the worst prognosis, with mortality rates of around 30% and neurological morbidity of around 17% even after treatment [6].

19.1.2.3 Diagnosis

Clinical diagnosis of genital herpes can be made when characteristic multiple vesicular lesions on an erythematous base are present. However, diagnosis may be difficult when herpetic lesions resemble other skin conditions or when the patient has non-specific symptoms. Laboratory tests are required to confirm the diagnosis, which can be done by virus isolation or by detecting an antibody response against it [7].

1. *Serological tests*—Patients develop antibodies to HSV within few weeks of acquiring infection, and these antibodies persist indefinitely. Serological assays can detect antibodies that are common for HSV-1 and 2 and also type-specific antibodies. Serological tests can be used to differentiate between primary or recurrent infection, identify asymptomatic carriers, and diagnose symptomatic patients with negative viral yield. Type-specific serological tests are based on the HSV-specific glycoprotein G2 (HSV-2) and glycoprotein G1 (HSV-1).
2. *Culture*—HSV can be grown in wide variety of cell lines. Sensitivity rates of HSV culture are approximately 75% and 50% for primary and recurrent infection, respectively, with 100% specificity rates [7]. Cell-cultures can differentiate between HSV-1 and HSV-2 infections. Samples for viral culture should be collected within 3 days of the appearance of lesions, as isolation rates are significantly reduced once lesions start crusting. Due to suboptimal sensitivity and difficulty in the transportation of specimens, viral culture is not the initial preferred diagnostic test.
3. *Amplification techniques*—Polymerase chain reaction (PCR) is a very sensitive test and can detect viral DNA even in low concentrations, and can also differentiate between the HSV types. It is the test of choice for diagnosing the central nervous system and systemic infections and neonatal herpes.
4. *Cytology*—Direct microscopic examination of material from base of lesion (Tzanck test) can be done. Smears taken from the lesion are stained by Geimsa, hematoxylin-eosin, or Papanicolaou stains; giant cells or intranuclear inclusions (Cowdry bodies type A) are characteristic. Although cytology results are rapid, the sensitivity is low and it cannot be used to differentiate between the two HSV types. Cytology is now seldom used to diagnose genital HSV infection in clinical practice. A direct immunofluorescence assay using fluorescein-tagged antibodies (commercially available as IMAGEN™) is commercially available to detect HSV antigens from genital lesions.

19.1.2.4 Screening

Universal screening for HSV in asymptomatic pregnant women is not recommended by most of the societies like the Centers for Disease Control and Prevention (CDC) and American College of Obstetricians and Gynecologists (ACOG). However, type-specific serologic tests might be useful to council at-risk pregnant women to prevent them from acquiring genital herpes during pregnancy. Serologic screening may also be used to identify women who have a past history of HSV infection so they can be offered suppressive antiviral therapy. In the absence of lesions, cultures for HSV are not indicated for women in the third trimester, even if they have a history of recurrent genital herpes.

19.1.2.5 Management

Management of Primary Genital Herpes in Pregnancy and Labor

Whenever a pregnant patient presents with symptoms of genital herpes, a history of any such previous infection should be inquired, and genital swabs should be taken to confirm the diagnosis by culture or PCR. The antiviral drugs, acyclovir, valacyclovir, and famciclovir, are all category B drugs and approved for use for HSV infection in pregnancy. Acyclovir is widely used and well tolerated in pregnancy without any dose adjustment. Acyclovir 400 mg orally three times a day for 7–10 days (intravenous for disseminated HSV) reduces the duration and severity of symptoms, and the duration of viral shedding. Fetal harm has not been reported with valacyclovir and famciclovir, but due to limited safety data, they are not used as first-line drugs during pregnancy. The treatment recommendations as given by ACOG are given in Table 19.1 [8]. Paracetamol and topical lidocaine 2% gel are used for symptomatic pain relief. If possible, delivery should be delayed by at least 6 weeks to ensure the transplacental passage of protective maternal antibodies to the fetus [1, 2, 6]. Patients who acquire infection in the first or second trimester may additionally be given suppressive dose of acyclovir 400 mg three times a day, daily from 36 weeks of gestation till delivery. This helps in reducing the maternal genital herpes lesions at term and need of cesarean section. Patients who acquire primary infection after 28 weeks of pregnancy need continuous treatment with daily suppressive dose of acyclovir 400 mg three times a day until delivery.

Table 19.1 Recommended treatment of maternal and neonatal herpes infection

Indication	Acyclovir	Valacyclovir
Primary infection	400 mg orally, thrice daily, for 7–10 days	1 g orally, twice daily, for 7–10 days
Symptomatic recurrent infection	400 mg orally, thrice daily, for 5 days or 800 mg orally, twice daily for 5 days	500 mg orally, twice daily, for 3 days or 1 g orally, daily for 5 days
Suppressive therapy	400 mg orally, thrice daily, from 36 weeks gestation until delivery	500 mg orally, twice daily, from 36 weeks gestation until delivery
Disseminated infection	5–10 mg/kg, intravenously, 8 hourly for 2–7 days, followed by oral therapy as in primary infection, total therapy for 10 days	
Neonatal infection	20 mg/kg, intravenously, 8 hourly	

Cesarean section is recommended in cases of primary and non-primary genital herpes, especially if infection has been acquired within 6 weeks of delivery. However, cesarean delivery does not have any protective effect if membranes have ruptured for more than 4 h. If the woman presents with herpetic lesions at onset of labor, swabs should be taken from the lesions and type-specific HSV antibody testing (IgG to HSV-1 or HSV-2) should be done, as it is difficult to distinguish between primary and recurrent lesions clinically. The presence of antibodies for the same type of HSV as isolated in the genital swab would confirm the recurrent episode, and an elective cesarean section may be avoided. If the patient presents in advanced stage of labor or chooses vaginal delivery, then intravenous acyclovir 5 mg/kg every 8 hours to mother and intravenous 20 mg/kg, 8 hourly subsequently to neonate after delivery should be started. However, definitive efficacy data for this approach is lacking. Any invasive procedure like fetal scalp electrodes application, fetal blood sampling, artificial rupture of membranes and instrumental deliveries should be avoided if possible [6].

Management of Recurrent Genital Herpes in Pregnancy and Labor

Majority of recurrent genital herpes episodes during pregnancy are mild and short lasting. Recurrent herpes lesions usually resolve within 7–10 days without any antiviral treatment. Symptomatic management with paracetamol is

sufficient, along with saline bathing. Risk of neonatal herpes is low (0–3%) due to transplacental maternal protective antibodies. Hence, cesarean delivery is indicated only for obstetric indications. However, these transplacental maternal antibodies do not protect the fetus against the neuro-ophthalmic complications. Daily suppressive dose of acyclovir 400 mg three times a day from 36 weeks of gestation until the onset of labor is recommended to reduce viral shedding and recurrence of genital lesions. Sequential PCR cultures are not indicated in this setting [1, 2, 6].

Special Circumstances

1. *Management of genital herpes in preterm premature rupture of membrane (PPROM)*—A woman with primary genital herpes presenting with PPROM (before 37 weeks of pregnancy), should be managed by a multidisciplinary team. If delivery is imminent, cesarean section is preferred over vaginal delivery to reduce the risk of neonatal herpes. If conservative management is planned, intravenous acyclovir 5 mg/kg, 8 hourly should be given to the mother, along with prophylactic corticosteroids to reduce the complications of prematurity in neonates. In a woman with recurrent genital herpes presenting with PPROM, risk of neonatal transmission is low. Management of these patients should be done according to standard PPROM guidelines, along with the addition of oral acyclovir 400 mg three times a day [6].
2. *Management of genital herpes in HIV positive mother*—HIV positive females are at an increased risk of more severe and recurrent episodes of genital herpes during pregnancy, and increased perinatal transmission of both HSV and HIV. Hence, suppressive acyclovir treatment should be started from 32 weeks (instead of 36 weeks) in a pregnant HIV seropositive woman with HSV infection. Suppressive treatment of HSV is not recommended in HIV seropositive pregnant patients without any history of genital herpes [6].

Management of Neonates of Mothers with Genital Herpes

Risk of vertical transmission is low in babies born by cesarean section to a woman with primary genital herpes. They are managed conservatively. If a baby is born by vaginal delivery within 6 weeks of primary herpes infection, risk of vertical transmission is very high. Swabs from skin, conjunctiva, oropharynx, and rectum of the neonate should be taken and sent for HSV PCR, even in the absence of any clinical manifestations. Lumbar puncture is not required in the absence of skin lesions. These neonates should receive intravenous acyclovir 20 mg/kg, 8 hourly as an empirical treatment [6].

Neonates born to mothers with recurrent herpes are managed conservatively, as risk of neonatal herpes is very low in these children. In the absence of herpetic lesions around the nipples, breast feeding can proceed as normal. Parents should be educated about hand hygiene to reduce risk of postnatal infection. They should report immediately if the baby develops any lesions over skin, eye, and mucous membrane, has lethargy, poor feeding or irritability.

If a neonate born to a mother with HSV infection presents with signs of sepsis or poor feeding, surface swabs and blood culture should be taken for herpes simplex culture and PCR, respectively. Intravenous acyclovir 20 mg/kg every 8 h should be started empirically. Further management should be done by neonatologist according to the clinical condition of the baby and culture report [6].

19.1.3 Human Papilloma Virus

HPV infection is the most common sexually transmitted viral infection in world, and is the main causative factor for carcinoma cervix and other anogenital neoplasms. It is also responsible for certain non-genital head and neck cancers (oral cavity, pharynx, and larynx).

HPV infection is common in reproductive age. Global prevalence of anogenital HPV in females

with normal cytology of cervix is around 11.7% [9]. In India, the prevalence of HPV type 16 or 18 in women is 5% with normal cytology, 28.2% with low-grade intraepithelial lesion (LSIL), 62.8% with high-grade intraepithelial lesion (HSIL), and 83.2% with cervical cancer. Around 14.6% to 64.2% of patients infected with HPV type 6 or 11 have visible genital warts. HPV prevalence in pregnant women ranges from 9.6% to 46.7%. Approximately 5% of pregnant females with HPV infection have abnormal cervical cytology [10, 11].

19.1.3.1 Pathogenesis

HPV belongs to *Papovaviridae* family of viruses. It has an icosahedral protein capsid and a tightly coiled circular double-stranded DNA of about 8000 base pair length. HPV genome is organized into three major functional regions, including an upstream regulatory region that regulates transcription from the early and late regions of the viral genome. The early region has genes encoding for proteins (E1, E2, E4, E5, E6, and E7) involved in viral replication, transcription control and cellular transformation. The late region includes genes that encode for structural capsid proteins L1 and L2.

Out of 184 types of HPV identified, 40 infect anogenital tract of males and females and are transmitted through sexual contact. HPVs are divided into three groups according to their neoplastic potential:

1. Low-risk types: Types 6, 11, 40, 42, 43, 44, 54, 61, 72, 73, and 81, are associated with genital warts, condyloma, and low-grade dysplastic lesions.
2. High-risk types: Types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 59, 68, and 82. Types 16 and 18 are the most common among this group and are responsible for precancerous lesions and cancers of cervix and other anogenital cancers.
3. Probable high-risk types; Types 26, 53, and 66 [12].

Young women of age 20–35 years are more susceptible to HPV infection. HPV is an epitheliotropic virus and its replication cycle is linked to epithelial cell differentiation. The infection is initiated when virus gains access to basal epithelial cells through micro-abrasions during sexual intercourse, and its circular DNA remains episomal inside the human cell nuclei. Upon entry into the dividing cells, there is initial replication of the viral genome, in concert with the differentiation of infected basal cells. These cells carry the viral genome with them as they move through the upper epithelial layers and aid in the transmission of infection.

Majority of HPV infections are cleared by host innate immunity. However, in certain cases, when HPV persists, and viral genome integrates with the host genome, over-expression of E6 and E7 genes takes place. Depending on the virus type and host factors, low-grade or high-grade lesions may be produced. There is increased production of E6 and E7 oncoproteins which bind and interfere with functions of tumor suppressor genes p53 and retinoblastoma protein (pRb), respectively, leading to abnormal and uncontrolled cellular proliferation and carcinogenesis [13].

19.1.3.2 Clinical Manifestations

A meta-analysis of 28 studies showed significantly increased risk of HPV infection in pregnant females as compared to non-pregnant females (16.8% vs. 12.3%) [14]. Pregnancy is a state of mild immunosuppression and the hormonal and immunological changes during pregnancy may be responsible for increased risk of HPV infection in pregnancy. The upstream regulatory region of HPV 16 contains a steroid hormone receptor binding element, which may contribute to increased HPV replication during pregnancy [15]. Restitution of the immune function in postpartum period can cause spontaneous regression of cervical intraepithelial lesions (CIN) in 37–74% cases [9, 13].

A meta-analysis of 45 studies that analyzed 14,470 pregnant females found higher prevalence of HPV infection in cases of spontaneous abortions and preterm deliveries. Various studies have detected HPV DNA in amniotic fluid, placenta,

fetal membranes, and umbilical cord blood [16]. HPV can infect trophoblastic cells of the placenta, and maternal HPV infection has been associated with spontaneous abortions and preterm delivery. However, the exact mechanism of adverse pregnancy outcomes is not yet clear.

The possible mode of vertical transmission of HPV infection from mother to fetus/neonate is still not clear. The most likely mode of transmission is passage through infected birth canal. Neonates born to mothers with HPV infection are at a higher risk of developing infantile genital and anal condyloma acuminatum and juvenile laryngeal papillomatosis (JLP). JLP is a rare infection with an incidence of 1.7–4.3 per 100,000 neonates. Risk factors associated with JLP are being a firstborn child, vaginal delivery with prolonged labor, and age of mother less than 20 years. JLP is commonly due to HPV type 6 and 11 [17].

For better understanding of HPV perinatal transmission and natural history of HPV infection, a large prospective cohort study- Human Papillomavirus perinatal transmission and risk of HPV persistence among children (HERITAGE) study is being done in Montreal, Canada. The preliminary data showed a high prevalence of HPV in pregnant women in the first trimester (45%), and of these, 80% remained positive in the third trimester. The overall prevalence of HPV infection was 14%. HPV positivity rates among children born of infected mothers was 11% from birth to 3 months of age. HPV was detected in children in multiple sites, including the conjunctiva [18].

19.1.3.3 Diagnosis

HPV infection may be diagnosed by characteristic clinical lesions or by molecular tests done on cervicovaginal specimens. As this virus cannot be grown in tissue culture, nucleic acid tests are employed to confirm the HPV infection.

1. Clinical examination—HPV associated condylomas and warts are visible with naked eye. (Fig. 19.1) Visual inspection with acetic acid (VIA), cytology, and colposcopy with biopsy give indirect evidence of HPV infection. (Fig. 19.2).

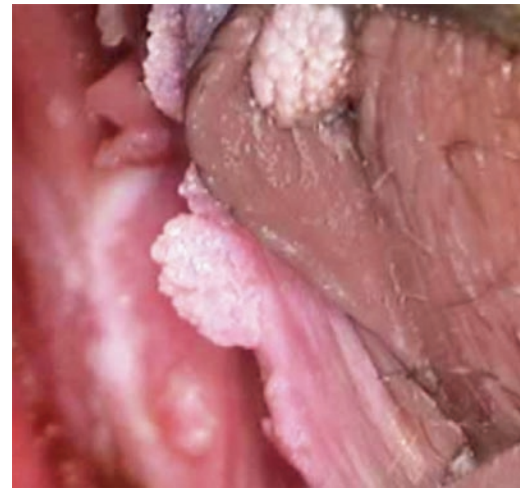

Fig. 19.1 Multiple exophytic condylomas in vulvovaginal area

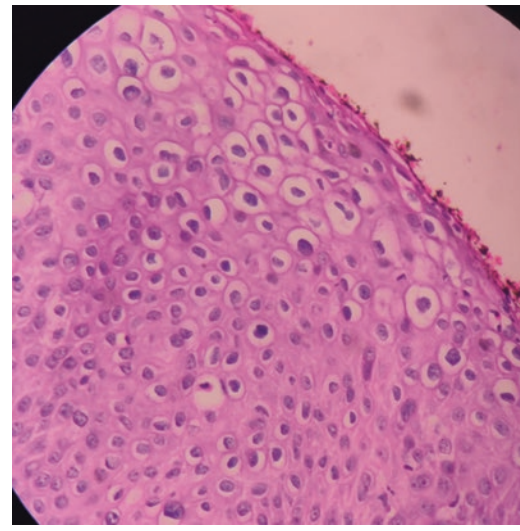

Fig. 19.2 Cervical biopsy showing stratified squamous epithelium with koilocytic changes due to human papilloma virus infection; H-E staining, 400x magnification

2. Non-amplified hybridization techniques—These include Southern blot for DNA, Northern blot for RNA, dot blot, and in-situ hybridization assays. They are not used commonly as these tests require large amount of purified nucleic acids, are poorly reproducible, and have low sensitivities.

3. Signal amplification assays—These are based on the amplification of DNA/RNA hybrids. Hybrid capture 2 (HC2) gives a semi-quantitative value using chemiluminescence. The available probes can detect the presence of the 13 high-risk types (types 16/18/31/33/35/39/45/51/52/56/58/59/68) but cannot identify the individual genotype. Similarly, a probe for low-risk types (types 6/11/42/43/44) can detect the presence of any of the five low-risk viruses but cannot specify the genotype.

4. Target amplification assays—These are PCR-based tests that amplify the target HPV DNA and also identify the specific HPV genotype. E6/E7 mRNA assay test is also based on target amplification of E6/E7 mRNA of high-risk HPV types. The most commonly used commercial target amplification test is the APTIMA™ HPV assay, which is FDA approved.

19.1.3.4 Screening

CDC, ACOG, and Federation of Obstetric and Gynecological Society of India (FOGSI) recommend cervical cancer screening by cytology every 3 years or by co-testing (HPV+ cytology) every 5 years for women aged 21–65 years. However, there are no specific recommendations and guidelines for HPV and cervical cancer screening during pregnancy.

Incidence of cervical cancer is low during pregnancy, around 3.3 to 26 cases per 100,000 births [19]. Still, cervical cancer screening should be a part of routine antenatal care in developing countries, where it may be the only opportunity for some women to be screened for cervical cancer. Broom brush, instead of endocervical brush should be used for cytology acquisition during pregnancy.

Recommendation for pregnancy with abnormal cervical screening: Pregnant women with positive high-risk oncogenic HPV (not type 16 or 18) and normal cytology or LSIL in cervical smear should have repeat HPV DNA testing after 12 months. Pregnant woman positive for high-risk oncogenic HPV (not type 16 or 18) along with HSIL or abnormal glandular cervical smear, or positive for oncogenic HPV (type 16 or 18) regardless of cytology results, need early colposcopic evaluation [19].

19.1.3.5 Management

There is no specific treatment for the virus itself. Postpartum regression of lesions has been documented in various studies, and expectant management is preferred for all low-grade lesions and high-grade lesions with no invasion. However, patients should be kept under follow-up, and undergo repeat colposcopy with biopsy 6 weeks postpartum. When indicated, colposcopy and directed biopsies are safe in pregnancy. Cervical biopsy is required when cytology is suspicious for malignancy or invasive carcinoma is suspected during colposcopy.

Management of Pregnant Woman with Genital Warts and Condylomas

In majority of cases, genital warts may increase during pregnancy and then regress spontaneously during puerperium. Definitive treatment is therefore usually delayed till delivery. Small lesions do not require any treatment, and larger lesions can be treated by keratolytic agents (80–90% trichloroacetic acid solution) or by cryotherapy. Occasionally, condylomas can show rapid growth during pregnancy and may become necrotic and macerated. These lesions may need surgical excision, which can be done in the second or third trimesters. 5-fluorouracil, podophyllin, and interferon should not be used during pregnancy.

Risk of perinatal transmission of HPV to oropharyngeal mucosa of newborn is low, and the presence of genital warts does not affect the mode of delivery, unless they are large and necrotic, or obscure the vaginal canal. In these cases, cesarean section is recommended [17].

Management of Pregnant Women with Invasive Disease

Pregnant women with suspected or confirmed cervical cancer should be referred to a gynecological oncologist. A multidisciplinary team should review and manage the patient based on the duration of pregnancy, stage of disease, and patient preference.

Management of Neonates

Anogenital warts and laryngeal papillomas are not seen commonly in neonates. Affected infants may present with weak cry, episodes of choking, or stridor. Treatment is directed towards removing papillomas, decreasing the spread of disease, and maintaining airway. The disease may resolve on its own or may require repeated surgical excision of the papillomas.

19.1.4 Chlamydia

Chlamydia trachomatis (CT) is the most common bacterial STD worldwide. In USA it accounted for 1,758,668 cases in 2018 [20]. Based on 2018 global STD surveillance from WHO, global estimation of new CT cases in 2016 was 127 million [21]. As CT infections are asymptomatic in majority of men, and women, the true burden of disease may be underestimated [22]. Detection of infection among women is twice as high as compared to men, probably due to increased screening in women. In India, the prevalence of CT infection is 0.9–25.5% among asymptomatic population, 10–50% among symptomatic women, and 0.1–2.5% among pregnant women [23].

19.1.4.1 Pathogenesis

Chlamydiae are gram-negative anaerobic, obligate intracellular bacteria. Chlamydia genus contains three species that infect humans: Chlamydia trachomatis (CT), Chlamydia psittaci, and Chlamydia pneumoniae.

Based on differences in their cell wall and outer membrane proteins, CT is divided into different serologically variant strains (serovars) and genotypes, which cause different illnesses. Serovars A, B, Ba, and C cause trachoma, which is the leading cause of preventable infectious blindness in the world. Serovars D-K cause genital tract infections, pelvic inflammatory disease, and neonatal infections. Serovars L1-L3 cause lymphogranuloma venereum (LGV) and genital ulcers.

Serovar identification is not important for therapeutic purpose except in cases of LGV, where longer treatment duration is indicated. Serovars can be identified by serologic typing or by molecular gene typing. Chlamydia possesses both DNA and RNA, has a cell wall and ribosomes. It lacks metabolic and synthetic pathways and depends on the host cell for intermediates, like ATP. Chlamydia has a complex reproductive cycle. It exists in two stages—the extracellular elementary bodies, which are the infectious form, and the intra-cytoplasmic reproductive forms called the reticulate bodies (RB). Elementary bodies are the metabolically inactive forms, and once taken up by the host cell, they differentiate into metabolically active RB within 6–8 h. RB undergoes binary fission within the host cells and re-organizes to form elementary body inclusions within 2–3 days. These inclusions rupture to infect other cells. The trachoma serovars mainly target squamocolumnar epithelial cells, whereas LGV serovars involve lymphoid cells.

The pathogenesis of host injury in CT disease involves direct cytotoxicity because of its intracellular replicative cycle, immune-mediated injury, and immune cross-reactivity between chlamydial and host cell antigens. The chlamydial heat-shock protein, which shares antigenic epitopes with similar proteins of other bacteria and with human heat-shock protein, may sensitize the host. CT causes chronic asymptomatic infections in the majority. However, persistent or recurrent CT infections can lead to scarring of mucous membranes and fibrosis.

CT transmission can occur through sexual contact (horizontal transmission), direct contact with the infected tissue, and by vertical transmission to the fetus during vaginal delivery. Genitoocular autoinoculation can also occur. The incubation period of sexually transmitted chlamydial infection is around 1–3 weeks.

19.1.4.2 Clinical Manifestations

In majority of pregnant women, chlamydial infections are asymptomatic. However, during pregnancy, cervical ectopy due to increased estrogen levels may aggravate the shedding of the bacteria. Symptoms of CT during pregnancy are similar to those seen in the non-pregnant state,

including mucopurulent cervicitis with vaginal discharge, lower abdominal pain, post-coital bleeding, increased urinary frequency, and dysuria. Urine analysis of women with urethritis will show sterile pyuria. Extra-genital presentations of CT can also occur during pregnancy, and include conjunctivitis, perihepatitis with right upper quadrant pain (Fitz-Hugh-Curtis syndrome), pharyngitis, and reactive arthritis. Ascending genital infections, either spontaneously or secondary to induced abortion, can lead to endometritis, chorioamnionitis, salpingitis and pelvic inflammatory disease (PID). Tubal scarring due to PID can lead to tubal infertility and ectopic pregnancy. CT infections are now considered a major risk factor for ectopic pregnancy.

Chlamydial infection during pregnancy can lead to adverse pregnancy outcomes like spontaneous or recurrent abortion, PROM, preterm labor, stillbirth, or low birth weight. Infections during early gestation (less than 24 weeks), in particular, increase the risk of preterm birth by two- to threefold. The exact mechanism is not well understood, but chlamydial DNA is frequently isolated from placenta of women with preterm deliveries before 32 weeks of gestation [24].

CT infection in pregnant women may lead to late postpartum endometritis, which develops between 2 days to 6 weeks after delivery. These women may present with secondary postpartum hemorrhage, with or without fever, lower abdominal pain, and vaginal discharge.

Chlamydial Infection in the Newborn

Newborn infants can acquire chlamydial infection during passage through the infected birth canal. Infection risk after cesarean delivery is considered to be lower than after vaginal delivery. The overall risk for infants born to women with untreated chlamydial infections is approximately 50–75% [25].

Chlamydia can cause ophthalmia neonatorum (neonatal conjunctivitis) in 20–50% of infected newborns [26]. Symptoms may present from first week until 3 months of age and include mild conjunctival redness with scant watery to severe mucopurulent discharge. Loss of vision is very rare, and majority of infections will resolve spontaneously; however, if left untreated conjunctival scarring may result. Nasopharynx is another common site of infection in neonates; these infections are usually self-limited and asymptomatic. Chlamydial pneumonia occurs in 5–20% of infants, typically between 1 and 3 months of age [25]. The pneumonia tends to be subacute; infants are usually afebrile with mild tachypnea and distinctive pertussis like non-productive cough (staccato cough). Chest radiograph reveals hyperinflation and bilateral diffuse infiltrates. Peripheral eosinophilia is frequent. Although mortality is rare, pneumonia can be more severe in premature infants and may require hospitalization. Untreated newborns may have apneic spells, feeding difficulties and may need ventilatory support. An association has been suggested between neonatal chlamydial infection and asthma and chronic lung disease later in life.

19.1.4.3 Diagnosis

Laboratory tests for chlamydia have evolved over the years. Nucleic acid amplification tests (NAAT) are the mainstay of the diagnosis currently and have largely replaced the initial gold standard test of cell culture. The various methods available for diagnosis are as listed below:

1. *Microscopy*: Direct microscopic examination of tissue scrapings with Giemsa or iodine staining or immunofluorescence is simple and cost-effective. The presence of characteristic inclusion bodies is pathognomic of CT infection. The test has high sensitivity for diagnosing neonatal conjunctivitis, but relatively less sensitive for diagnosing adult conjunctivitis and genital tract infections.
2. *Cell Culture*: Chlamydia cannot be cultured on artificial medium and need tissue media like McCoy, HeLa 229, or Buffalo Green Monkey Kidney cells for their growth. The characteristic intra-cytoplasmic inclusions can be detected after 48–72 h of culture inoculation. Use of fluorescence labeled monoclonal antibodies specific for chlamydial lipopolysaccharide (LPS) and major outer membrane proteins (MOMP) increase detec-

tion rates. Culture methods are dependent on viable organisms and have variable sensitivity from 60% to 80%. Their use is restricted to research laboratories [27].

3. *Antigen Detection*: Two types of antigen detection tests are available.
   (a) Direct immunofluorescent antibody test (DFA)—DFA assays are based on monoclonal antibodies directed against MOMP of chlamydial elementary bodies. Detection of 10 or more elementary bodies is considered a positive result. DFA assays have sensitivity of 80–90%, and specificity of 98–99% compared to culture methods, but have lower sensitivity as compared with NAATs. DFA is used as confirmatory test for positive results with other non-culture tests like enzyme immunoassays [28].
   (b) Enzyme Immunoassays (EIA)—EIAs use monoclonal or polyclonal antibodies for the detection of chlamydial LPS antigens in clinical specimens. EIAs have a sensitivity of 65–75% compared to NAATs, but have high false positive rates due to cross-reactivity with LPS of other gram-negative bacteria and chlamydial species [29]. Positive results need to be confirmed by repeating the test with more specific monoclonal antibodies to chlamydial LPS or by doing DFA test.
4. *Nucleic Acid Amplification Tests (NAATs)*: NAATs include polymerase chain reaction, transcription-based amplification, and strand amplification assays. These tests do not require viable organisms or any specific storage or transport medium and have a high sensitivity of 90–96% compared to culture and non-culture methods [30, 31]. NAATs can be performed on either endocervical or vaginal swabs or first void urine samples. Vaginal swabs have the highest sensitivity and can be self-collected. NAATs done on vaginal swabs are now considered the "gold standard" for diagnosis of CT infections.

   Rapid NAAT based tests have been developed, which include:
   (a) XPert C.*trachomatis/N.gonorrhoeae* (CT/NG) assay—This test is approved for use on endocervical or vaginal swabs and urine samples and can provide results within 90 min. The Xpert test uses a modular cartridge base for testing specimens by nucleic acid amplification. The use of cartridges minimizes processing steps and so results can be provided earlier as compared to other NAATs, which may take 1–2 days to process.
   (b) CT/NG NAAT assay (Binx io)—It is FDA approved for use on vaginal swabs and can provide results as early as 30 min. Rapid tests have a sensitivity of 96% and specificity of 99% [32].
5. *Serology Tests*: Testing for antibodies is not recommended for screening of genital chlamydial infections because a positive test cannot distinguish a current from past infection. However, serological tests can be used for diagnosing infections in the neonate, with the micro-immunofluorescence test (MIF) being the method of choice for serodiagnosis. An IgM titre of 1:32 or greater is considered diagnostic of neonatal CT pneumonia [27]. IgG antibodies are not useful as they may also represent passively transferred maternal antibodies.

19.1.4.4 Screening for Chlamydial Infection

NAATs done on endocervical swabs or self-taken vulvovaginal swabs and even on the first void urine sample are the screening tests of choice. All pregnant women should be screened for chlamydia to prevent maternal postnatal complications and chlamydial infection in infants. Antenatal screening, even in asymptomatic pregnant females, can be used as window of opportunity for the treatment of infected individuals. The US Preventive Services Task Force (USPSTF) recommends screening for chlamydia in all pregnant women who are under 25 years of age, and pregnant women 25 years or older with risk factors for chlamydial infection [33]. ACOG also recommends screening of all pregnant women

with increased risk. The screening recommendations of CDC, American Medical Association, and American Academy of Pediatrics are similar to the USPSTF. They recommend testing all pregnant women at their first antenatal visit and retesting in the third trimester in women with continued risk factors and in those who test positive at their first prenatal visit. Pregnant women at higher risk for chlamydial infection include those with HIV infection and those with a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has a sexually transmitted infection.

19.1.4.5 Management

Treatment of chlamydia during pregnancy is indicated to prevent adverse pregnancy outcomes and reduce the risk of perinatal transmission. Even women with untreated chlamydia infection who present in labor should be treated immediately, even though treatment at this stage does not reduce the risk of neonatal transmission.

Doxycycline and quinolones are avoided in pregnancy. Azithromycin 1gram orally given as a single dose is the recommended regimen for the treatment of chlamydial infection in pregnant women. Other effective and safe treatment options for the pregnant female include erythromycin, amoxycillin, and clindamycin, for a duration of 7 days. (Table 19.2) [34] *Neisseria gonorrhoeae* infection can coexist with chlamydia in a significant percentage of patients and requires additional treatment if detected.

As chlamydial infection does not provide long-term immunity and there are high chances of reinfection, these patients need to be followed up. Follow-up strategies include test of cure and retesting. Test of cure is done by NAAT 3–4 weeks after completion of therapy to document treatment success. Test of cure is not performed before 3 weeks as NAAT may be positive even in the presence of non-viable organisms. Retesting by NAAT 3 months after treatment of chlamydial infection is recommended to rule out recurrent or repeat infections. The first-line treatment with azithromycin remains effective for reinfection.

Table 19.2 Recommended treatment of maternal and neonatal chlamydia infection

	Recommended regime	Alternative regimes
Pregnant women with chlamydia infection	Azithromycin 1 gm orally, single dose	1. Amoxicillin 500 mg orally, thrice a day, for 7 days 2. Erythromycin base 250–500 mg orally, four times a day, for 7 days 3. Erythromycin succinate 400–800 mg orally, four times a day, for 7–14 days
Neonatal infection	Erythromycin 50 mg/kg/day, orally, four times a day, for 14 days	

Treatment of Sex Partner

Treatment of sexual partners is important to prevent reinfection of the patient. Treatment of sexual partners within the preceding 60 days from the onset of patient's symptoms or chlamydial diagnosis is particularly important. A pragmatic approach to partner treatment is by "Expedited partner therapy" (EPT), where the patient takes medication (single dose of 1gram azithromycin) or prescription to her partner without the healthcare provider first examining him. The patient and her partner are advised to maintain abstinence for at least 7 days after treatment or till they are free of symptoms.

***Treatment of infants*—**Antenatal screening and treatment of infected women remain the best methods to prevent transmission of infection to the newborn. Neonatal ocular prophylaxis is not indicated, and treatment of neonatal conjunctivitis is initiated only after a positive diagnostic test. Treatment for chlamydial pneumonia is based on clinical and radiological findings. Erythromycin in a dose of 50 mg/kg/day orally in four divided doses for 14 days is the treatment of choice for both conjunctivitis and neonatal pneumonia. Topical therapy for the treatment of neonatal conjunctivitis is not as effective as systemic therapy.

The efficacy of erythromycin treatment for neonatal conjunctivitis is approximately 90% and for pneumonia is 80%, and a second course of therapy might be required in infants with unresolved infections [35]. An alternative treatment regimen is azithromycin suspension for 3 days. An association between erythromycin, azithromycin and the development of pyloric stenosis in infants less than 6 weeks of age has been observed.

19.1.5 Gonorrhea

There has been a global increase in the incidence of *Neisseria gonorrhoeae* in the past few years. The estimated annual incidence of gonococcal infection globally is 86.9 million adults [36]. The highest disease burden is seen among women 20–24 years of age. The true global burden is difficult to establish due to under-reporting and asymptomatic infections.

19.1.5.1 Pathogenesis

N.gonorrhoeae are aerobic, encapsulated, nonspore forming, gram-negative diplococci. There are nine species of Neisseriae that infect humans, but only *N. gonorrhoeae* and *N. meningitis* are pathogenic. The important outer membrane proteins of gonococcus include pili, opacity-associated protein (Opa), and porins (previously designated protein I). Pili are important virulence factors mediating bacterial adherence and host mucosal penetration. Opa proteins bind to receptors on immune cells and mediate immune escape. Porins exhibit antigenic variations and form the basis for gonococcal serotyping. Two main serotypes have been identified. The PorB.1A strains are often associated with disseminated gonococcal infection (DGI), and PorB.1B strains usually cause local genital infections. Gonococcal lipo-oligosaccharide (LOS) is an endotoxin that provokes an immune response.

N. gonorrhoeae infects the columnar mucosal epithelium of urogenital tracts, rectum, pharynx, or conjunctiva. Women have higher chances of contracting the infection per exposure (60–90%), as compared to men [37]. Concurrent STDs like trichomonas vaginalis and chlamydial infection may be seen in 40–50% of cases [38]. Neonates can acquire infection during passage through the birth canal. Gonococcus has also been isolated from infants delivered by cesarean section of infected mothers, with prolonged rupture of membranes.

19.1.5.2 Clinical Manifestations

The incubation period of urogenital gonorrhea ranges from 2 to 8 days. Patients can be completely asymptomatic or have dysuria, vaginal discharge, pelvic pain, or fever (Fig. 19.3). Salpingitis and infertility may be the sequelae of untreated gonorrhea infection.

Acute gonococcal infection in pregnancy, is usually limited to vulvovaginal area. However, increased rate of pharyngeal infections is being reported in pregnancy, likely due to altered sexual practices. Gonococcal pharyngitis may present as mild sore throat but is often asymptomatic. Rectal infections usually have coexisting genital infections and present with symptoms of proctitis with mucopurulent discharge.

Disseminated gonococcal infection (DGI) is a rare condition in pregnancy with an incidence of 0.04–0.09% [39]. Patients in second and third trimester of pregnancy are more susceptible to

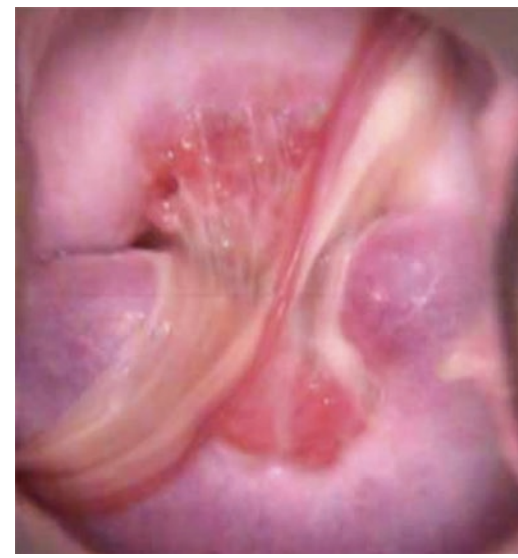

Fig. 19.3 Mucopurulent cervical discharge due to gonococcal infection

develop DGI. Disseminated infection occurs when gonococci invade bloodstream following initial pharyngeal, genital tract, or rectal mucosal infection. Patients usually present with fever, malaise, and anorexia. Small erythematous macules can be seen on skin of arms and legs, which can evolve into pustular lesions, finally becoming hemorrhagic necrotic lesions. The face and trunk are spared. Migratory polyarthralgia, tenosynovitis of the hands and feet, arthritis of large joints like knees can occur. Other less common consequences include meningitis, endocarditis, pharyngitis, hepatitis, pericarditis, pneumonia, and osteomyelitis. Often the diagnosis is based on high clinical suspicion, and appropriate cultures should be obtained.

Gonorrhea in pregnancy can have serious consequences. Gonococcal salpingitis and PID are more common in first trimester and are often associated with fetal loss. Premature rupture of membranes, chorioamnionitis, and sepsis in infant are common complications of maternal gonococcal infection in the third trimester. Preterm delivery rates as high as 12–40% have been reported, most likely due to maternal cytokine release and increased fetal corticotropin-releasing hormone in response to the gonococcal infection. Women with gonococcal infection who undergo medical or surgical termination of pregnancy are at increased risk of post-abortion endometritis [40].

19.1.5.3 Neonatal Manifestations

Neonates have 30–35% chance of acquiring infection during passage through the birth canal [41]. Ophthalmia neonatorum is the most common manifestation of *N. gonorrhoeae* in neonates. Signs of conjunctival infection usually develop 2–5 days after birth but can appear as early as few hours after delivery. Purulent conjunctivitis, eyelid edema, and in severe cases corneal ulcerations with permanent scarring, corneal perforations, and blindness can result. Conjunctival infection can be prevented by applying 1% topical silver nitrite (Crede's method). Early antibiotic treatment causes prompt healing and prevents systemic spread. Though rare, ophthalmia neonatorum can be associated with gonococcal meningitis.

In addition to conjunctivitis, other localized infections in neonates can involve pharynx, vagina, urethra, anus, or scalp. Disseminated gonococcal infection in the infant may present as sepsis, meningitis, or arthritis. Septicemia can develop after prolonged rupture of membranes. Gonococcal arthritis typically presents in 1–4 weeks after delivery. Symptoms are usually non-specific, including fever and feeding difficulties followed by erythematous swelling of the affected joints. Unlike adult arthritis, skin lesions are seldom seen, and usually multiple joints are involved.

19.1.5.4 Diagnosis

Pregnant women presenting with mucopurulent vaginal discharge, intrapartum and postpartum fever, and also mothers of infants with ophthalmia neonatorum should undergo testing for *N. gonorrhoeae.*

1. *Nucleic Acid Amplification Test (NAAT)*—These tests are US Food and Drug Administration approved for use on urine, endocervical, and vaginal swabs, but not cleared for use in rectal, oropharyngeal, or conjunctival specimens. Major disadvantage of NAATs is their inability to provide information on anti-microbial resistance, so in cases of treatment failure, relevant specimen should be obtained for culture.
2. *Culture*—Culture methods have sensitivity as high as 95–100% if specimens are collected and transported properly. CDC recommends selective (modified Thayer-Martin, Martin-Lewis, or modified New York City) and non-selective (e.g., chocolate agar) mediums for the growth and isolation of Neisseriae. Additional biochemical tests, NAATs or mass spectrometry must be performed to confirm the diagnosis of isolate as *N. gonorrhoeae*. Cultures have additional advantage of providing antibiotic sensitivity panel and genomic analysis if required.
3. *Microscopy*—The presence of gram-negative, intracellular diplococci on microscopic examination of smears from endocervical secretions can be used to make a diagnosis of *N.*

gonorrhoeae infection. However, because of lower sensitivity and specificity and requirement of technical expertise CDC does not recommend gram staining for detection of *N. gonorrhoeae* infection in endocervical, rectal, or pharyngeal specimens.

19.1.5.5 Screening for Gonorrhea Infection

USPSTF recommends screening of all pregnant women under 25 years of age and older women if at increased risk. CDC, ACOG, and FOGSI also recommend screening for gonorrhea in all sexually active women (including pregnant women) who are at increased risk for infection [42].

Risk factors for gonococcal infection include those with a new sex partner, having more than one sex partners, sex partner with concurrent partners or a sex partner who has an STD. Additional risk factors include inconsistent condom use among persons who are not in mutually monogamous relationships; previous or coexisting sexually transmitted infections; and exchanging sex for money or drugs.

Pregnant women should be offered a screening test at their first antenatal visit. Women who are at continued risk factor for gonorrhea should be retested in the third trimester.

19.1.5.6 Management

In view of increasing anti-microbial resistance, CDC has recently increased the recommended dose of ceftriaxone for the treatment of *N. gonorrhoeae*. The current recommendation is a single weight-based intramuscular injection (500 mg for all patients <150 kg weight) of ceftriaxone for treatment of uncomplicated gonococcal infection. A single oral dose of 800 mg cefixime is an alternative to parenteral ceftriaxone, albeit with lower efficacy. In cases where concurrent chlamydia infection is suspected, additionally azithromycin 1gm single oral dose is given. A single intramuscular injection of gentamycin (240 mg) plus a single oral dose of 2 g azithromycin is an alternative treatment option for penicillin-allergic patients [43].

Test of cure by either culture or NAAT is not necessary for uncomplicated gonococcal infections except for pharyngeal infections. Following treatment, CDC recommends retesting after 3 months due to increased risk of reinfection in these patients, regardless of whether their partners were treated or not. Patients should be retested in the third trimester if risk factors for reinfection persist. In cases of suspected treatment failure, clinical specimens for culture and sensitivity should be tested.

19.1.5.7 Treatment of Partners

Sexual partners of the infected patients should be evaluated and treated particularly with a preceding history of contact within last 60 days of onset of symptoms or diagnosis. Alternatively, expedited partner therapy can be done with a single 800 mg oral dose of cefixime. If chlamydial infection has not been excluded, then cefixime 800 mg single oral dose along with doxycycline 100 mg twice daily is given for 7 days. In case of resistant gonococcal infection, the sex partners should be treated with the same regimens as selected for the patient.

19.1.5.8 Treatment of Neonates

The best method to prevent gonococcal infection among infants is antenatal screening and treatment of pregnant women, and neonatal ophthalmic prophylaxis, with erythromycin (0.5%), 1% silver nitrate, or 1% tetracycline ointment. Neonatal gonococcal conjunctivitis and systemic gonococcal infections are treated with ceftriaxone.

19.1.6 Prevention of STDs

Prevention can be done at primary, secondary, and tertiary levels. Primary prevention involves health education and lifestyle modifications so as to prevent the infection. Young adults should be educated regarding safe sexual practices and hygiene. Pregnant females should use barrier methods like condoms, avoid contact with an infected partner, and be in long term mutually monogamous relationship to prevent sexually transmitted infections. Secondary prevention involves early detection and treat-

ment so as to prevent the complications associated with the infection. It is very important to take detailed history on the first antenatal visit regarding any genital lesions, both in the patient and her partner. Screening, especially in high-risk cases can detect infection even in asymptomatic females. Tertiary prevention involves appropriate treatment of acute and chronic infection.

Many prophylactic and therapeutic vaccines have been explored for chlamydia, gonorrhea, herpes, and HPV. However, till date, only prophylactic vaccines against HPV have been successful.

There are three prophylactic vaccines available against HPV, which are recombinant vaccines and contain virus-like particle without core DNA.

- Bivalent vaccine (Cervarix)—This vaccine is against types 16 and 18, with ASO4 as an adjunct.
- Quadrivalent vaccine (Gardasil)—It is against types 6, 11, 16, and 18, with an aluminum containing adjunct.
- Nonavalent vaccine (Gardasil 9)—This vaccine is against types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

Vaccination of adolescents and young girls by either bivalent or quadrivalent or nonavalent vaccines, 2 doses in 9–15 years of age, and 3 doses in 15–45 years of age in 6 months duration is 88% effective against HPV infection and its endpoint complications including pre-malignant and malignant lesions.

19.1.6.1 HPV Vaccination During Pregnancy

HPV vaccines trigger a more robust immune response than the natural infection. HPV vaccines are category B drugs and are not recommended during pregnancy. However, accidental vaccination of a pregnant woman does not need any intervention, and no congenital abnormalities have been reported in these cases. A pregnancy test is not routinely advised before vaccination.

19.1.7 Conclusion

Sexually transmitted infections pose a challenge in pregnant females due to their harmful effects on the mother and her fetus/neonate. Many of the infections can lead to adverse pregnancy outcomes like ectopic pregnancy, abortion, PROM, and low birth weight. Besides causing painful lesions, herpes simplex infection can lead to severe morbidity and mortality, if it is acquired in third trimester. The child usually gets infected intrapartum, but rarely may acquire infection transplacentally, and may have mild to severe illness. HPV-induced warts may become more florid during pregnancy, but usually regress postpartum. Intrapartum HPV infection can lead to anogenital warts in neonates or rarely laryngeal papillomas. Chlamydia and gonorrhea are common bacterial STDs where the neonate may get infected intrapartum. Adequate preventive and screening measures and appropriate treatment can prevent the maternal and fetal morbidity associated with these infections.

Key Points

1. Human simplex virus has two types, of which type-2 is responsible for causing maximum genital infections. Herpes infection may be asymptomatic or may present with painful vesicular lesions. Primary infection in pregnancy is the main cause of neonatal herpes.
2. Diagnosis of HSV infection should be confirmed by virus isolation or by detecting an antibody response against it.
3. Suppressive dose of acyclovir 400 mg three times a day, daily from 36 weeks of gestation till delivery, helps in reducing the herpes lesions at term, and need of cesarean section.
4. Cesarean section is recommended in cases of primary and non-primary genital herpes

especially if infection has been acquired within 6 weeks of delivery.

5. Human papilloma virus is responsible for causing many pre-malignant and malignant lesions of anogenital area. HPV infection in pregnancy may lead to spontaneous abortion, preeclampsia, preterm delivery, premature rupture of membranes, and low birth weight.
6. Juvenile laryngeal papillomatosis is a rare infection in neonates who are exposed to vaginal secretions of mothers with active HPV lesions for more than 10 hours.
7. HPV does not require active treatment in pregnancy, except treatment of large warts by excision.
8. Chlamydia trachomatis infection in pregnancy can be asymptomatic or may present with symptoms like mucopurulent vaginal discharge, lower abdominal pain, increased urinary frequency, or dysuria.
9. Chlamydial infections in pregnancy may lead to adverse pregnancy outcomes like spontaneous or recurrent abortions, premature rupture of membranes, preterm labor, stillbirth, or low birth weight. Neonates may acquire infection during passage through infected birth canal. Most common manifestation of neonatal chlamydia infection is ophthalmia neonatorum.
10. Chlamydial infection can be diagnosed by examination of tissue scrapings for intracytoplasmic inclusion bodies, isolation of organism by cell culture, or by antigen detection. Nucleic acid amplification tests are the gold standard for diagnosing chlamydia infections.
11. Single oral dose of 1 g azithromycin is recommended for the treatment of chlamydia infection in pregnancy.
12. Neisseria gonorrhea infection in pregnancy usually presents with vulvovaginal infection. It may present as pharyngitis, proctitis, or rarely as disseminated gonococcal infection, where mortality is high.
13. Maternal gonococcal infection can lead to premature rupture of membranes, chorioamnionitis, and preterm delivery. Neonates can acquire infection during passage through the birth canal, and can have neonatal conjunctivitis, or disseminated infection.
14. Nucleic acid amplification tests are considered to be gold standard for diagnosing gonococcal infection.
15. Due to high prevalence of anti-microbial resistance in gonococci, high dose ceftriaxone is recommended for treatment. Following treatment, retesting is advised after 3 months due to increased risk of reinfection.
16. There are no specific recommendations for screening of HSV and HPV during pregnancy. However, screening is advised for chlamydia, and gonorrhea infections in all pregnant women less than 25 years and others at risk.
17. Of all the sexually transmitted infections, prophylactic vaccine is available only for human papilloma virus.

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20 Syphilis, Lymphogranuloma Venereum, and Granuloma Inguinale Infection in Pregnancy

Mala Srivastava, Anshul Grover, and Ankita Srivastava

20.1 Introduction

Sexually transmitted diseases (STDs) are important global health indicators as they have a serious impact on the health of the women and also due to their associated inter-relationship with HIV. STDs and HIV occur in the same adult population and due to biological interactions, have been able to change epidemiological prevalence trends of the diseases globally. Infection during pregnancy affects both the mother and the fetus due to the relative immunosuppression, anatomic, physiological, and hormonal changes seen normally during pregnancy. Some STDs are transmitted transplacentally thus leading to congenital affection.

In this chapter, we will be discussing three STDs, which are known to cause ulcerative disease in the genitalia—syphilis, lymphogranuloma venereum, and granuloma inguinale (Donovanosis). Syphilis is a chronic systemic disease known to be transmitted transplacentally to the growing fetus. It is a significant cause of fetal affection, perinatal mortality, and childhood sequelae in contrast to LGV and Donovanosis which do not have any significant impact on fetal outcomes.

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20.2 Syphilis

Syphilis is chronic systemic infection caused by *Treponema pallidum* (*T. pallidum*), a spirochaete. It is a sexually transmitted disease that is an important cause of genital ulcer disease (GUD) in adults. *T. pallidum* has the ability to survive in the human host for several decades, thereby causing systemic manifestations even after 20 years post-inoculation. The clinical features of the disease are grouped into primary, secondary, latent, and tertiary according to duration from first infection and infectivity rate. Of epidemiological importance is the transplacental transmission of the *T. pallidum*, which results in perinatal morbidity and mortality. Congenital infection to the fetus can lead to abortions, stillbirth, prematurity, low birth weight, and even neonatal death. Infected infants may present with late sequelae and syphilitic stigmata later. *T. pallidum* is a Gram negative rod which cannot be cultured artificially, therefore making diagnosis and development of a vaccine difficult. The diagnostic evaluation of the disease is centered on direct visualization of the bacteria from lesions or using serological changes during the course of the disease. The treatment of choice is parenteral penicillin; resistance to penicillin has not been documented till date.

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20.2.1 Epidemiology

Syphilis accounts for about six million new cases in adults each year worldwide [1–3]. As per WHO 2016 report, congenital syphilis is responsible for more than 300,000 fetal and neonatal deaths [2]. In Sub-Saharan Africa, 20% of perinatal deaths are attributed to it [4]. Due to widespread use of antibiotics, the developed nations witnessed a fall in the prevalence of the disease in the 1980s and the 1990s. But due to rise in unsafe sexual practices among men who have sex with men, a resurgence of cases of syphilis has been reported in the USA, UK, Australia, and Europe from the year 2000 [5, 6]. A Sexually Transmitted Disease (STD) Surveillance conducted in 2016 by the Centers for Disease Control and Prevention reported that over 50% cases of syphilis in that year were attributed to men who have sex with men only. The highest prevalence of syphilis was found among black men in the USA. The mortality due to syphilis in untreated patients is 8%–58% with a higher death rate in males [7]. Prevalence of the maternal disease has stabilized in most parts of the world but increased in those where unsafe sexual practices have increased. The rate of maternal primary and secondary syphilis infection increased to 1.9 per 100,000 women and 15.7 cases of congenital syphilis (CS) per 100,000 live births in 2016 in comparison to 0.9 cases of maternal syphilis and 8.4 cases per 100,000 of CS in the United States of America in 2013 [8]. Brazil reported a rise in the prevalence of maternal syphilis from 3.1% in 2013 to 5% in 2014, while the annual incidence rate of CS escalated from 2.9 to 8.1 cases per 1000 live births from 2007 to 2014 [9, 10] . In Mongolia, the prevalence rates rose from 1.7% in 2000 to 3.0% in 2016 [11]. Canada witnessed a rise in the rate of congenital syphilis from 5.0 cases per 100,000 in 2010 to 9.3 cases per 100,000 live births in 2015 [12].

A new strategy to tackle the rising sexually transmitted infections (STIs) was formulated by the World Health Organization (WHO) for 2016–2021.The strategy focuses on elimination of congenital syphilis by promoting comprehensive syphilis screening and treatment among pregnant women. The strategy aims for a reduction of global incidence of syphilis by 90% by 2030 and achieving less than 50 cases of congenital syphilis per 100,000 live births in 80% of the countries [2].

20.2.2 Etiology and Transmission

Treponema pallidum *spp.* is a spiral shaped bacteria, belonging to the family Spirochaetaceae. It is a part of the family of morphologically and serologically similar treponemes—*T. endemicum*, *T. pertenue,* and *T. carateum* which cause non-venereal diseases such as bejel, yaws, and pinta, respectively [13]. The bacteria are small organisms that are invisible on light microscopy. They are classified as Gram negative bacteria but lack the typical lipopolysaccharide outer membrane [14]. They are actively motile but have a typical cork screw motility which is attributed to the presence of an endoflagella in the periplasmic space.

Humans are the exclusive host for this organism, and there are no known animal reservoirs. Syphilis is a sexually transmitted disease; vaginal, anal, and oral contact with actively infected individual transmits the bacteria. The spirochetes directly gain access into the mucus membranes or invade via breaks in the less heavily keratinized skin of the perigenital or perianal area. The infection can also be transmitted by nonsexual contact, such as skin-to-skin contact or via blood transfer (blood transfusion or needle sharing). An important route of transmission is transplacental vertical transmission which results in congenital syphilis. There is a 70% chance of acquiring fetal infection in the initial 4 years of disease from an infected untreated woman during pregnancy [15, 16]. The neonate also has chance of contracting the infection from ulcerative infected wounds of primary syphilis during passage from birth canal.

20.2.3 Clinical Manifestations

The clinical manifestations of acquired syphilis vary according to the stage of the disease.

Primary syphilis: It is the initial stage of the disease. The characteristic macular skin lesion (sore) develops in 3 weeks after contact with an infected person. The sore develops on the external genitalia, vagina, cervix, anus, or in the rectum. The macule develops into a painless papule which then breaks down to form the typical ulcer called the *chancre*. The chancre of primary syphilis is 1–2 cm in size, painless, with raised and indurated margins. The chancre may be genital or extra-genital, with involvement of regional lymphadenopathy which is generally bilateral and non-tender. This primary chancre heals spontaneously within 3–6 weeks and as this stage is asymptomatic, it usually goes unnoticed.

Secondary syphilis: In about 25% of untreated cases, the disease progresses to secondary syphilis which is the stage of dissemination. It is characterized by a widespread maculopapular skin rash which erupts on the palms, soles, and mucous membranes. Clinical features also include fever, pharyngitis, weight loss, and condylomata lata (highly infectious flat-topped papules and plaques at angles of mouth, nares, or anogenital area) together with enlargement of lymph nodes all over the body. This phase is extremely contagious and can persist for up to a year.

Latent Syphilis: Latent syphilis lacks clinical manifestation but can be diagnosed on serological testing. If it happens within 1 year of acquiring infection, it is called early latent syphilis and if beyond 1 year or of unknown duration, then it is called late latent syphilis. During this phase the person is infective and can infect their partners and the fetus.

Tertiary syphilis: It develops about 5–20 years after the active disease. 5–40% of untreated individuals may progress to tertiary syphilis. It manifests as skin or visceral lesions called *gummas*, destructive cardiac or neurological conditions, involvement of bones (tabes dorsalis) or general paresis and is not infective. The incidence of tertiary syphilis has declined with increase in the antibiotic usage.

Neurosyphilis: CSF infection can occur at any stage of the disease, but neurosyphilis is a rare event. Neurosyphilis can present either as early neurologic changes, within initial months of infection or as late sequelae after 10–30 years of infection. The early neurological infection presents as meningitis, stroke, acute altered mental status, cranial nerve dysfunction, and auditory or ophthalmic abnormalities. The late neurologic manifestations include general paresis and tabes dorsalis.

20.2.4 Diagnosis [17–20]

As humans are the only hosts of *T. pallidum*, it cannot be cultured. The tests available for its diagnosis include direct diagnostic methods and serological tests.

Direct Diagnostic Methods These tests aim to identify the spirochete *T. pallidum* by direct visualization under microscopic examination or by nucleic acid amplification methods such as polymerase chain reaction (PCR). The test can be performed on body fluid, smears prepared from the lesions, and histological specimens.

1. *Dark field microscopy*: It is one of the most reliable and simple test for the direct detection of *T. pallidum* and is based on the characteristic morphology and motility of the spirochete. It allows visualization of live treponemes obtained from a variety of cutaneous or mucous membrane lesions such as the active chancre in primary disease, the mucous patch or condyloma lata in secondary syphilis, moist discharge from the nose (snuffles), and vesiculobullous lesions of the skin in congenital syphilis. It is useful in patients with early syphilis and immunodeficiency when antibodies are not yet detectable. The test has the disadvantage of requiring experienced technicians. Care should be observed, not to take oral or rectal swabs as they may give false positive result due to presence of oral non-pathogenic treponemes in the oral cavity.
   The amount of specimen, thickness of smear, and use of antibiotics are factors which limit the specificity of the test. Failure to detect the spirochete does not rule out syphilis.

2. *Direct fluorescent antibody test for T. pallidum* (DFA-TP): This test is based on antigen detection and does not require to observe motility of the treponemes, thus is more specific and is easier to perform. It utilizes treponemes specific fluorescein isothiocyanate-labeled antibody to detect pathogenic bacteria only, therefore can differentiate between pathogenic and commensal treponemes. However, this test fails to distinguish between *T. pallidum* and other pathogenic treponemes which are responsible for endemic syphilis, yaws, and pinta.
3. *Nucleic acid amplification methods:* They are highly specific and sensitive tests which can detect up to one to ten organisms. Though these tests have not been approved by FDA, they have the potential to become important diagnostic tool for monitoring of treatment and to differentiate old from new infection.

Serological Tests In the absence of a lesion, serological tests are used for diagnosis. These tests work on the principle of antibody detection. They can be classified as treponemal (TTs) and non-treponemal (NTTs) tests. A reactive non-treponemal antibody test is followed by confirmation by a treponemal antibody test. A positive treponemal test confirms the presence of treponemal antibodies but does not indicate the stage of disease. The test cannot distinguish between current and past infection.

Non-treponemal tests: Centers for Disease Control and Prevention (CDC) approved standard tests include the following:

- VDRL slide test
- Rapid plasma reagin (RPR) card test
- Unheated serum reagin (USR) test
- Toluidine red unheated serum test (TRUST).

These tests become positive within 1–4 weeks of development of the chancre or 6 weeks after exposure. Each of these tests can be used as a qualitative and quantitative test. They are rapid, easy, and inexpensive tests which have been approved as screening modalities and for follow-up of patients after treatment. All of these are flocculation tests which use standardized amount of cardiolipin, cholesterol, and lecithin antigen to measure the antibody against lipid component of *T. pallidum* released following tissue injury. Venereal Disease Research Laboratory (VDRL) slide test and USR use micro-flocculation technique which requires assistance of a microscope for reporting. RPR card test and TRUST are macro-flocculation tests which require no microscope [19]. The tests most commonly used are VDRL and RPR. In 75% cases of primary syphilis and 100% of cases of secondary syphilis, these tests are positive. A fourfold rise in titer is suggestive of infection, re-infection, or failure of treatment. Fall in titer by four fold suggests success of treatment. In primary syphilis, the NTTs become negative within 1 year of receiving adequate treatment while in cases of secondary syphilis within 2 years. False positive results may be seen in pregnancy, autoimmune disorders, and infections [20]

Treponemal tests: These are confirmatory tests. They include the fluorescent treponemal antibody absorption (FTA-ABS) test, the treponemal-specific Microhemagglutination Treponema pallidum test (MHATP), and *Treponema pallidum* particle agglutination test (TP-PA). Recently Rapid automated treponemal tests-chemoluminescence immunoassays (CIA) and enzyme immunoassays (EIA) have been added to this list which are being used as screening tests. The principle behind these tests is to identify the surface antigens of *Treponema pallidum* by antigen–antibody complexes interaction. These tests have a sensitivity of 75–85% for TP-PA and FTA-ABS, respectively, in patients of primary syphilis. The detection rate of secondary syphilis is 100% with treponemal tests. False positive tests are seen in patients of Lyme disease, leptospirosis, and diseases caused by other pathogenic *Treponema* spp. TTs remain positive throughout life.

20.2.5 Syphilis in Pregnancy

Pregnancy has no known effect on the clinical course of syphilis.

Antenatal syphilis is known to cause detrimental effect on both the pregnancy and fetus especially if not adequately treated. The presentation of

the disease is no different during pregnancy. *T. pallidum* readily crosses the placenta during any stage of pregnancy and any stage of the disease [21]. The bacterial load in circulation at the time of transmission determines the risk of transmission. Vertical transmission of syphilis is more common in primary (nearly 100%) and secondary syphilis (appx. 50–60%), compared with early latent, late latent, and tertiary syphilis (rarely infectious) [18, 22]. Untreated mothers can pass the infection to about 70% of the fetuses [15, 16].

20.2.5.1 Maternal Outcomes

Pregnancies complicated by syphilis may result in spontaneous abortion, intrauterine growth restriction, nonimmune hydrops fetalis, preterm delivery, and stillbirth in more than half of pregnancies. Untreated primary or secondary syphilitic infection during pregnancy is reported to cause stillbirth in 25% and neonatal death in 14%. In about 41% the infant is born alive but is infected; only 20% infants are born healthy and uninfected. The incidence of these complications declines with late syphilis (early and late latent syphilis that occurs more than 1–2 years after infection). Untreated late syphilis can increase the risk of stillbirth by 12%, risk of neonatal death by 9%, and risk of giving birth to an infected infant by 2%. The probability of delivering an uninfected neonate is 77% in untreated mothers of late syphilis [23]. Jackson et al. reported 25–40% incidence of spontaneous abortion, intrauterine or perinatal death in untreated maternal syphilis [22].

20.2.5.2 Congenital Syphilis

Fetal infection can result from hematogenous spread through the placenta or by direct contact of the fetus with the infected genital lesions during delivery. The fetal affection is influenced by the stage of the maternal disease, gestational age during infection, maternal treatment, and immunological response of the fetus [24].

Stage of disease: The hematogenous spread depends on the degree of maternal spirochaetemia:

- Early syphilis—Nearly 100% hematogenous spread is seen due to maximum spirochaetemia during early stage of the disease [23].
- Secondary syphilis—50–60%probability of fetal affection [25].
- Late latent syphilis—Most infants born to these mothers are uninfected [26].

Gestational age: Earlier it was assumed the fetus could not acquire infection up to 20 weeks due to presence of the protective Langhans layer of the cytotrophoblasts, which provided a protective barrier. But later this theory was dropped when studies showed that the Langhans layer was found to be present throughout the pregnancy [27]. Spirochaetes have been demonstrated in abortuses of 9–10 weeks [28]. Nathan et al. demonstrated live spirochaetes in the amniotic fluid of untreated mothers suggesting crossing of spirochaetes across the placental barrier [29].

Fetal immune response: Fetal manifestations of the disease vary according to the immunological maturity of the fetus, which in turn is dependent on the gestational age. The fetus is not capable of generating an immune response until 22 weeks of gestation [30]. It has been documented that the levels of interleukins, interferons, tumor necrosis factor are lesser in premature than mature infants (fetal affection has been discussed later).

Maternal treatment: A woman who has not received treatment has a 70% chance of fetal affection within 4 years of the disease. The CDC/WHO regimen was evaluated by Alexander et al. and it was inferred that treatment with Benzathine Penicillin resulted in 100% effectiveness in cases of primary syphilis, 95% in secondary syphilis, 98% in early latent syphilis, and 100% in late latent syphilis [31]. Prestholt TF et al. documented that this treatment was not only effective but was inexpensive and safe [32].

Pathophysiology

Hematogenous spread causes *T. pallidum* to invade the placenta. Once the placenta gets infected the spirochaetes pass onto the fetal circulation and infect fetal liver and leads to its dysfunction. Later infection of the amniotic fluid, hematological system (causing anemia, thrombocytopenia), fetal ascites, and hydrops ensues. Syphilitic lesions in the fetus are characterized by perivascular infiltrates with plasma cells and

lymphocytes, endarteritis, and fibrosis [16]. The placenta shows endovascular and perivascular proliferation with placental thickening that increases with the severity of the disease. The liver shows hepatomegaly with inflammatory changes in the stroma (Table 20.1). Hollier et al. documented that rise in liver enzymes, gamma glutamyl transferase precedes the development of hepatomegaly and ascites [38].

Clinical Manifestations

Manifestations of CS range from fetal demise to clinically asymptomatic neonates. Untreated neonates develop clinical manifestations of the disease within 3 months of age. CS can be classified into early and late based on the time of its diagnosis since birth.

Early congenital syphilis—children presents between 0 and 2 years with syphilitic affection. These children present with:

- Rhinitis—The infected infant presents with copious, persistent white discharge, which contains spirochaetes that can be visualized under darkfield microscopy. This clinical manifestation presents within the first week of life.
- Rash—It is the second clinical presentation which presents in the second week of life. Small red or pink colored maculopapular lesions are seen on the back, buttocks, posterior thigh, and soles of the feet.
- Hepatomegaly and jaundice—It is the most common presentation. Liver function tests are abnormal. Ultrasonography shows an enlarged liver and associated splenomegaly. Liver biopsy specimen when evaluated on dark field microscopy reveals the spirochetes which can be diagnostic.
- Generalized non-tender lymphadenopathy.

Table 20.1 Pathological changes in congenital syphilis [33–37]

Placenta	Perivascular and endovascular inflammatory infiltrates, placental thickening
Liver	Stromal and perivascular inflammatory infiltrates, Hepatomegaly
Pancreas	Perivascular inflammatory infiltrates
Lungs	*Pneumonia alba*-characteristic lesion. The lung is enlarged, firm, yellowish-white due to increase in connective tissue
Kidney	Deposition of immune complexes similar to those seen in glomerulonephritis, causing secondary damage to the nephrons. Interstitial tissue shows evidence of perivascular infiltrates
Central Nervous System	Involvement of the meninges with thickening of the basilar meninges, and endarteritis

Late congenital syphilis: When congenital syphilis is detected after 2 years of age, it is called late congenital syphilis. The chronic inflammatory response leads to scarring and gumma formation.

The features of congenital syphilis are shown in Table 20.2.

Diagnosis

The transfer of maternal non-treponemal and treponemal IgG antibodies across the placenta makes the diagnosis of congenital syphilis complicated. The diagnosis is based on

- Identification of syphilis in the mother
- Adequacy of maternal treatment
- Presence of clinical, laboratory, or radiographic evidence of syphilis in the neonate
- Comparison of maternal (at delivery) and neonatal non-treponemal serologic titers using the same test, preferably conducted by the same laboratory.

20.2.5.3 Antenatal Surveillance of the Pregnant Woman

Serology—Routine prenatal screening has been proven to be the major prevention strategy to curb congenital syphilis. A policy of universal screening by serologic test is adopted so that timely diagnosis and management can prevent adverse neonatal and maternal outcomes [39–41].

All antenatal patients should be screened at first antenatal visit, preferably in the first trimester

- The screening test used is a non-treponemal test. If the test is positive in more than 1:16 dilution, then the patient is subjected to treponemal test for confirmation

Table 20.2 Stigmata of congenital syphilis

Barber-pole appearance of umbilical cord	Chalky white coloration on umbilical cord in spiral configuration as a result of necrotizing funisitis with alternate blue pink and blue areas
Battledore placenta	Marginal insertion of umbilical cord
Bulldog facies	Maxillary hypoplasia, saddle nose, and a prominent mandible together appear like a bulldog face
Café-au-lait tint	Yellow-brown discoloration of skin of the neonate due to anemia, jaundice, and hyperpigmentation. Seen in early congenital syphilis
Cluttons joints	Chronic, painless reactionary joint effusion of knees. Seen in late congenital syphilis
du Bois sign	Short incurved little finger
Skull	
• Natiform skull (hot cross bun skull) • Tower skull	Healed Gummatous osteoperiostitis presents as frontoparietal bossing and prominent suture lines of skull High cranium
Olympian brow (beetled brow)	Bony prominence of forehead
Eye signs	
• Ghost vessels • Ground-glass cornea • Salt and pepper fundus • Salmon patch	Empty blood vessels extending to deeper layers of cornea Hazy cornea due to cellular exudation Chorioretinitis—tiny light specks interspersed among dark specks. It can be seen in all stages Circumcorneal vascularization—a dull pink patch is seen at the periphery of cornea in late stages
Teeth	
• Mulberry molars (moon/Fournier molars) • Hutchison teeth	The biting surface of the first molars is dome shaped and has multiple underdeveloped and poorly enameled cusps (Screwdriver teeth) Abnormal permanent upper central incisors that are peg shaped and notched. The teeth are widely spaced and shorter than lateral incisors and the width of the biting surface is less than that of the gingival margin
Nose	
• Opera glass nose • Saddle nose (fleur de lis nose)	The lower nose appears to be pushed into the intact upper nose as a result of nasal chondritis Improper development of bony bridge of the nose—Stigmata of flattened nasal bridge
Virchow's sign	Smooth base of the tongue
Mouth	
• Krisovski sign • Rhagades (parrot's radial scars)	Cicatricial lines radiating from the mouth Seen in early congenital syphilis as radiating fissures at angles of mouth
Saber shin	Sharp anterior convexity of tibia which occurs due to thickening of middle third of shaft; seen in late syphilis
Wimberger sign (cat bite sign)	Localized bilateral metaphyseal destruction of medial proximal tibia in early congenital syphilis

Source: Shah I. Clinical Manifestations of Congenital Syphilis. Pediatr Oncall J. 2006;3:35

- Those who are at a greater risk for infection should be subjected to a repeat serological test at 28–32 weeks and again at delivery
- Partner should also be screened
- Those who have missed their antenatal screening or who delivered a still born after 20 weeks should be screened
- Women known to have syphilis should also be tested for HIV.

Once the screening test is positive, then a confirmatory test is required to rule out the false positive reports. A patient is considered to be suffering from the disease if both treponemal tests and non-treponemal tests are positive. The patients who were tested positive during pregnancy should have follow-up test at 4–6 weeks after delivery.

Reverse Algorithm Strategy for screening: In high prevalence areas, screening of syphilis with

initial rapid automated treponemal tests reflexed by non-treponemal tests has been found to be cost-effective. This reverse algorithm has been recommended by CDC for screening. If both tests are positive it suggests active infection or recently treated infection. If a positive treponemal test is followed by a negative non-treponemal test, the same sample should be processed again with a treponemal test of a different methodology. A positive second treponemal test suggests a past infection. If the woman has received complete treatment previously then no further treatment is required. If history of previous treatment is not available or incomplete treatment was taken, then the woman is a candidate for complete treatment this time. If the second test is also negative, then the test is labelled as false positive.

Ultrasonography and Doppler studies: After 20 weeks of pregnancy, USG may show features of congenital syphilis. Abnormalities include hepatomegaly (79%), placentomegaly (27%), polyhydramnios (12%), ascites (10%), and raised peak systolic Middle Cerebral Arterial (MCA) Doppler value. Once the diagnosis of congenital syphilis is made, then either weekly or biweekly surveillance is done by sonography to see the response to treatment. On favorable management, MCA Doppler abnormalities, ascites, and polyhydramnios resolve first, then placentomegaly, and finally there is resolution of hepatomegaly [42].

20.2.5.4 Treatment of Syphilis in Pregnancy

The standard recommended treatment by CDC and WHO for syphilis acquired during pregnancy is benzathine penicillin G given parenterally for all stages of the disease [43, 44]. Adequate treatment of the disease decreases IUD by 82%, growth restricted fetus and preterm labor by 65%, neonatal mortality by 80%, and congenital syphilis by 97% [31]. Success of maternal treatment is defined as a fourfold fall in the RPR titer from the time of diagnosis to the time of delivery and also resolution of symptoms, if any.

In cases of penicillin allergy, other alternatives like cephalosporins or macrolides have been used in non-pregnant individuals but in pregnancy, the only alternative is desensitization followed by benzathine penicillin treatment [43].

Penicillin Allergy and desensitization—Penicillin reported allergies have a prevalence of about 8–10% in the USA. Data regarding its prevalence in developing countries is not available [45, 46]. In about 10–15% persons who are allergic to penicillin, the response is IgE mediated. This can cause urticaria, angioedema, bronchospasm, or hypotension. For such individuals a second exposure in the form of re-administration may be fatal. Therefore, it is suggested that penicillin skin testing with major and minor determinants of penicillin should be carried out prior to giving the drug. Patients with positive penicillin skin test need to be desensitized.

Desensitization process should be carried out in the hospital as about one third of the patients might experience an allergic response which is mild but requires immediate care. The process of desensitization takes about 4–12 h after which the full therapeutic dose of penicillin can be administered. If in future, penicillin is required again, the process of desensitization has to be repeated as the tolerant state is lost after 24–36 h [47–50].

World Health Organization guidelines for treatment of syphilis classify the disease into early and late syphilis.

Early syphilis—Includes primary, secondary, and early latent syphilis with less than 2 years duration. The patients have a positive test for syphilis.

- Primary syphilis—positive syphilis test with genital ulcer (painless chancre) at the site of infection.
- Secondary syphilis—manifested by skin rash often seen on the palms and soles, condylomata lata, mucocutaneous lesions, and generalized lymphadenopathy.
- Early latent syphilis—manifested by no symptoms and known duration of untreated infection of not more than 2 years.

Late syphilis—defined as positive syphilis test without presence of any symptoms of more than 2 years duration (late latent syphilis) or of unknown duration of untreated infection (Table 20.3) [44].

Table 20.3 Treatment of syphilis in pregnancy

Stage of syphilis	Recommended	Alternative treatment	Remarks
Early Syphilis (Primary, Secondary, and Early Latent syphilis of not more than 2 years duration)	Inj Benzathine penicillin G 2.4 million units once intramuscularly	• Tab Erythromycin 500 mg orally 4 times daily for 14 days or • Inj Ceftriaxone 1 g intramuscularly once daily for 10–14 days or • Tab Azithromycin 2 g once orally	• Benzathine penicillin is preferred over Procaine penicillin 1.2 million units I/M for 10 days • Erythromycin and azithromycin do not cross the placental barrier completely, so the fetus does not receive treatment. It is, therefore, necessary to treat the newborn soon after delivery • Doxycycline should not be used in pregnant women
Late Syphilis	Inj Benzathine penicillin G 2.4 million units intramuscularly once weekly for 3 consecutive weeks	• Tab Erythromycin 500 mg orally 4 times daily for 30 days.	• Benzathine penicillin is preferred over Procaine penicillin 1.2 million units I/M for 20 days. • Erythromycin does not cross placental barrier completely, so fetus does not receive treatment. It is, therefore, necessary to treat the newborn soon after delivery • Doxycycline should not be used in pregnant women

Source: WHO guidelines for the treatment of *Treponema pallidum* (syphilis). Geneva: World Health Organization; 2016

Newer Alternatives to Penicillin

Amoxicillin—Structural similarity of amoxicillin to penicillin, safety in pregnancy, and high oral bioavailability prompted researchers to study its effectiveness in congenital syphilis. Amoxicillin when used along with probenecid is more easily available as compared to penicillin. It crosses the placental barrier and achieves high concentrations in the amniotic fluid. Katanami et al. published case reports of 2 patients treated with amoxicillin and probenecid. He reported significant fall in RPR titer and no evidence of congenital syphilis in both these patients [51]. This is a promising head way, which prompts further trials. Only disadvantage to amoxicillin usage is that it does not address the problem of penicillin allergies.

Cefixime—Although third-generation cephalosporins like ceftriaxone are being used as effective alternatives to penicillin, but use in treatment of pregnant women with syphilis is being evaluated. Cefixime is safe in pregnancy, and high levels of the drug are seen in the amniotic fluid. The drug is under phase trials.

Jarisch–Herxheimer reaction (JHR)—It is an acute, self-limiting febrile reaction characteristically seen in people infected with spirochaetes when treated with antibiotics. It is typically seen within 24 h of starting the antibiotic therapy. The reaction manifests as fever, headache, chills, rigors, nausea, and vomiting. The patients develop tachycardia, hypotension, and hyperventilate. JHR is seen in 55% of seronegative primary syphilis, 95% of seropositive primary syphilis, and 95% of secondary syphilis; it is rarely seen with latent and late syphilis. The exact pathophysiology behind the reaction is still not clear but is believed to be an acute inflammatory reaction following breakdown of spirochaetes and release of toxins after antibiotic usage. There is a surge of interleukin 6, interleukin 8, and tumor necrosis factor in the bloodstream. The patients should be informed regarding the reaction prior to giving antibiotic therapy. Mild reactions generally are self-limiting and subside within 24 h; supportive treatment with anti-pyretics, analgesics, intravenous fluid, and vasopressors maybe used.

JHR has an incidence of 40% in pregnant women treated for syphilis. Fetal monitoring is essential in these patients as it is seen to be associated with recurrent variable decelerations. The Jarisch–Herxheimer reaction may precipitate uterine contractions, preterm labor, and/or no reassuring fetal heart rate tracings especially when women are treated late in pregnancy [52].

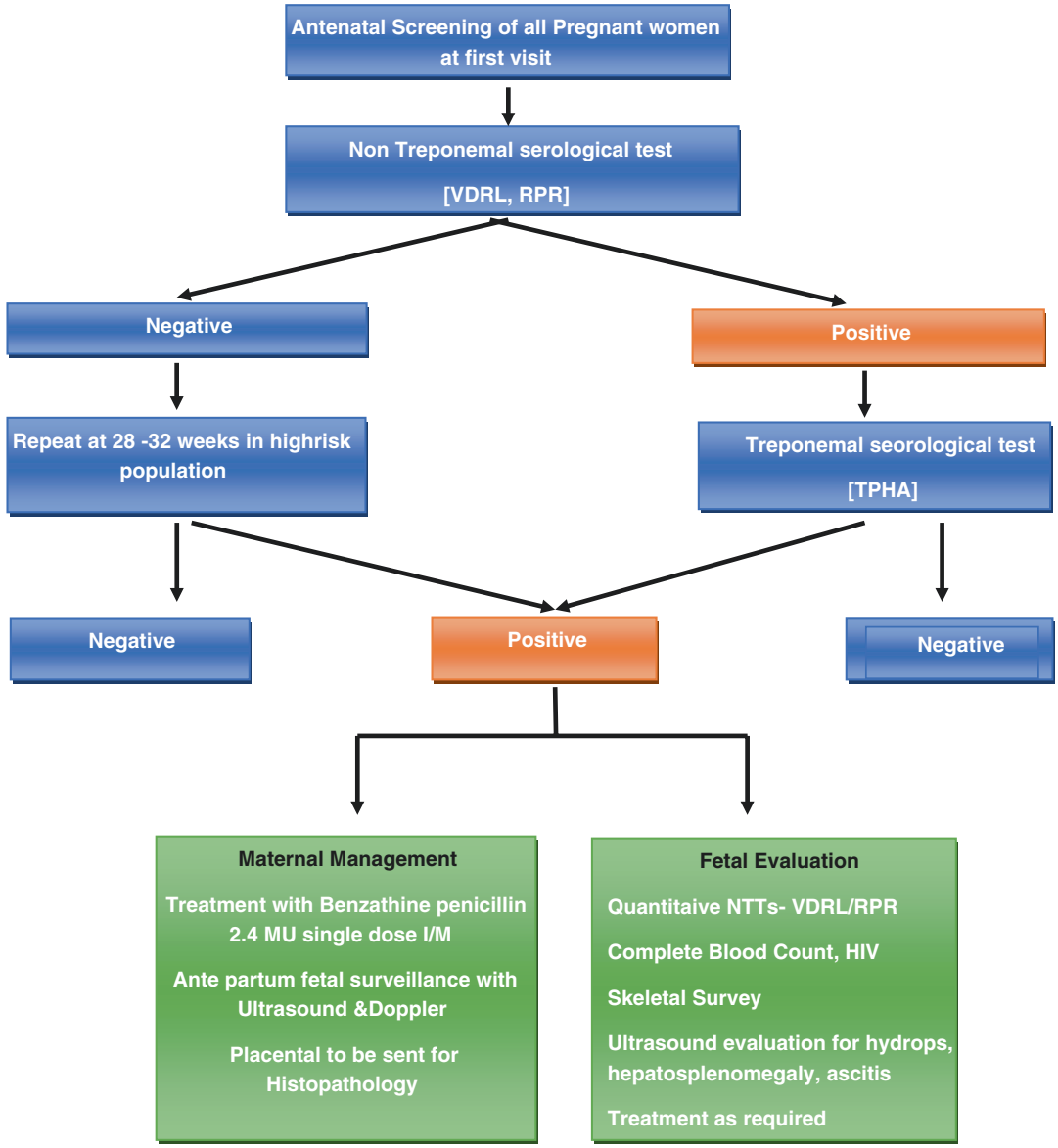

Fig. 20.1 Management of syphilis in pregnancy

20.2.5.5 Mode of Delivery

If appropriate treatment has been given, the mode of delivery is not affected by the disease except if active re-infection presents as genital lesions at the time of delivery. In such a case, cesarean delivery is preferred to avoid direct contact of the neonate with highly infective lesions in the perineum. At delivery the neonatologist should be informed about the maternal syphilis, her stage, management, and the sonographic features of the fetus [38, 53]. The placenta should be sent for histopathological examination [53] (Fig. 20.1).

All neonates of seropositive mother should be evaluated with

- Histopathologic evaluation along with specific staining (e.g., silver) or *T. pallidum* PCR test using a CLIA-validated test is done on the placenta or umbilical cord.

- Darkfield microscopic examination or PCR testing of suspicious lesions or body fluids (e.g., bullous rash and nasal discharge).
- Quantitative non-treponemal serologic test (RPR or VDRL) is performed on the serum of the neonate. The blood from the umbilical cord is not preferred as it can get contaminated with the maternal blood and also the presence of Whartons jelly can yield wrong results.
- Skeletal survey of all stillbirths should be done to demonstrate typical osseous changes.
- Evaluate all neonates for evidence of congenital syphilis—nonimmune hydrops, jaundice, hepatosplenomegaly, rhinitis, skin rash, and pseudoparalysis of an extremity.
- Complete evaluation and testing for HIV infection must be done for any neonate at risk for congenital syphilis.

20.2.5.6 Treatment of Congenital Syphilis

The treatment of CS varies according to the chances the neonate has of acquiring the infection.

Proven or highly probable CS—The neonate should be considered as a positive or highly probable case of CS if the neonate shows an abnormal physical examination that is consistent with congenital syphilis and/or the quantitative non-treponemal test shows a fourfold higher than maternal titer and/or a positive dark field microscopy of neonatal lesion or fluid. Such neonates are evaluated for other complications and sequel. They need to be treated and kept under follow-up as per protocol.

Recommended valuation includes

- CSF analysis for VDRL, cell count, and protein (interpretation of CSF varies according to gestational age of neonate and should be interpreted accordingly)
- Complete blood count (CBC) and differential and platelet count
- Other tests as clinically indicated (e.g., long-bone radiographs, chest radiograph, liver function tests, neuroimaging, ophthalmologic examination, and auditory brain stem response).

Suspected CS—CS is suspected if an infected mother has not received complete treatment or adequate treatment or received treatment less than 30 days prior to delivery or has not been treated with penicillin. The neonates of such mothers are considered as suspected CS and need to be treated and kept under follow-up as per protocol.

Recommended evaluation includes

- CSF analysis for VDRL, cell count, and protein
- Complete blood count (CBC) and differential and platelet count
- Long-bone radiographs.

Congenital Syphilis less likely-

Neonatal criteria

- Any neonate who has a normal physical examination.
- Serum quantitative non-treponemal serologic titer equal to or less than fourfold the maternal titer.

and both of the maternal criteria are true.

Maternal criteria

- Mother was adequately treated as per protocol for the infection stage and the treatment was initiated ≥30 days prior to delivery.
- the mother has no evidence of re-infection or relapse.

Such neonates do not require further evaluation but are treated with single dose of Procaine penicillin G 50,000 units/kg/dose IM in a single dose.

Congenital Syphilis unlikely—if the following criteria are met

Neonatal criteria

- The neonate has no positive findings on clinical examination.
- Serum quantitative non-treponemal serologic titer of the neonate is ≤ fourfold the maternal titer and both of the maternal criteria are true.

Table 20.4 Treatment of congenital syphilis

Syphilis in infants	Recommended	Alternate regimen	Remarks
Confirmed CS Asymptomatic infants of untreated and inadequately treated mothers Mothers treated with non-penicillin regimens	• Aqueous benzyl penicillin 100,000–150,000 U/kg/day is administered intravenously for 10–15 days.	• Procaine penicillin 50,000 U/kg/day as a single dose is administered intramuscularly for 10–15 days.	• Aqueous benzyl penicillin may be preferred over intramuscular injections of procaine penicillin, if an experienced venipuncturist is available. • Guidelines recommend close monitoring of infants who are clinically healthy and whose mothers had syphilis which was adequately treated with no signs of re-infection.

Source: WHO guidelines for the treatment of *Treponema pallidum* (syphilis). Geneva: World Health Organization; 2016

Maternal criteria

- The mother of the newborn was adequately treated before pregnancy.
- The mothers non-treponemal serologic titer remained low and stable (i.e., serofast) prior to, during pregnancy and at the time of delivery (VDRL <1:2; RPR <1:4).

In such cases no further evaluation or treatment of the neonate is required (Table 20.4).

20.2.6 Prevention

Syphilis is a sexually transmitted disease and its prevention is a part of public health policies formulated by each country for control of STDs. These policies go a long way in reducing the prevalence of the disease. These include:

- Modification of high-risk behavior
- Identification of infected individual and appropriate treatment
- Treatment of partner
- Identification of high-risk population
- Access to proper treatment.

20.2.6.1 Prenatal Care

Discussed in syphilis in pregnancy

20.2.6.2 Adequate Treatment

Identified cases should be counseled regarding the impact of the disease on the fetus, including the early and late affections and the importance of treatment and follow-up.

20.2.6.3 Treatment of Partner

Identification and treatment of the partner has a major role in prevention of re-infection of the pregnant woman. An individual who has had sexual contact with an untreated syphilis positive woman (irrespective of the stage of the disease) in the preceding 90 days needs to be serologically tested and treated. The treatment includes single dose of Benzathine penicillin 2.4 million units given intramuscularly. In case the serological test is negative, the test must be repeated at 3 weeks again.

20.2.6.4 Vaccine Development

Till date no vaccine has been developed or is in developmental stages for syphilis. In spite of having highly effective treatment for syphilis, the rise of epidemics of syphilis in industrialized nations has generated the need for a vaccine that limits both the disease and its transmission. Syphilitic infected individuals also pose an increased risk of transmission of HIV [54]. Thus, control of syphilis in turn would bring about a reduction in the new HIV infections. Only one study till date demonstrated development of complete immunity in rabbit model inoculated with multiple doses of gamma irradiated *T. pallidum*. The protocol was not tested in humans as it was found to be very cumbersome, impractical, and expensive. Vaccines using recombinant technology were found to provide only partial immunity [55–58]. The identification of multiple genetic variations in the surface proteins of syphilis—TprK, essential for its replication, has added to the

challenges of the vaccine developers. Researchers have still not given up and are hopeful of developing a vaccine against *T. pallidum* in the near future.

20.3 Lymphogranuloma Venereum

Lymphogranuloma venereum (LGV) is an ulcerative disease of the genital tract caused by Gram negative bacteria *C. trachomatis* serovars L1, L2, or L3 [59, 60]. The disease was first discovered by Wallace in 1833 and then by Durand, Nicolas, and Favre in 1913 [61]; thus was initially given the name—*Nicolas–-Favre disease*. It is transmitted via vaginal, anal, or oral sexual contact. It mainly affects the lymphatic system and is characterized by unilateral tender inguinal and/or femoral lymphadenopathy. In the recent past there have been increasing incidence of infections in men who have sex with men (MSM). No definite evidence exists regarding adverse effects of the disease on the fetus.

20.3.1 Epidemiology

LGV is primarily a disease of the tropics and subtropics. It is an endemic disease among heterosexuals populations of East and West Africa, parts of Southeast Asia, India, and the Caribbean [62]. In the last few years, rise in number of MSM has increased the cases of LGV in North America, United Kingdom, and Europe [63, 64]. The majority of women who have acquired LGV are also suffering from HIV infection. In New York City and UK outbreaks, 84% and 76% of patients with LGV were also found to have HIV coinfection, respectively [65]. The disease effects sexually active population between 20 and 40 years of age.

20.3.2 Pathophysiology

C. trachomatis has 15 known clinical serotypes, of which only three serotypes are known to be invasive and virulent and causative for LGV. The infection is transmitted through direct contact of breached skin or mucus membrane by infected partner through sexual contact. The disease mainly infects the lymphatics. The organism replicates in the macrophages and spreads through the lymphatics to cause systemic effects; proliferating in lymphatic tissues between the site of primary infection to the lymph nodes. When this infection spreads, it causes inflammation, necrotic areas within the nodes and then abscess formation. This process may take several weeks causing severe inflammation and fibrosis [66]. Nonsexual transmission through laboratory accidents and fomites has been reported.

20.3.3 Clinical Features

The LGV primarily affects lymphatic tissue. The clinical course of the disease can be classified into three stages:

Primary Stage—This is the inoculum stage. The incubation period of the disease is 3–30 days. It begins with the formation of a papule, pustule, or a vesicle in the balanopreputial groove of the penis or the internal face of the labia minora, which subsequently ulcerates. This is a painless stage in which the ulcer heals on its own. This stage may go unnoticed.

Second Stage—This is the stage of regional lymphatic dissemination and lymphadenopathy. It develops within 1–6 weeks after the initial lesion. It manifests as unilateral inguinal/femoral lymphadenopathy; the nodes may form abscesses which may rupture through multiple sites simulating "rose water can." In females, the lymphatic drainage of the vaginal mucosa and uterine wall is into the deep or perirectal iliac ganglia; therefore, they may present with nonspecific backache and/or abdominal pain. Inguinal lymphadenopathy occurs only in 20–30%. The patients may have constitutional symptoms like fever, chills, myalgias, and malaise.

Third Stage—This is the stage of sequels. It is more frequently encountered in MSM and women who practice anal sex. The common presentations include esthiomene (chronic lymphatic obstruction) in women; rectal, vesical, and anal fistulas and even rectal stenosis. There may be symptoms of procto-

colitis and rectal discharge (79%), anal pain (69%), constipation (25%), fever, and/or tenesmus (29%). There may be bleeding per rectum and involvement of intestinal and perirectal lymphatic tissue [59, 65]. Late sequelae also include fibrosis and strictures in the anogenital region causing elephantiasis of vulva and anal fistulas [59].

20.3.4 Differential Diagnosis

The disease needs to be differentiated from:

- Soft chancre/chancroid—is a shallow ulcer of the genital area caused by *Haemophilus ducreyi*
- Syphilis—discussed above
- Scrofuloderma—It is a rare cutaneous manifestation of tuberculosis caused by direct extension from underlying tubercular lymphadenitis
- Cat-scratch disease—is a bacterial infection affecting lymph nodes which drain the inoculation site of the Gram negative bacteria *Bartonella henselae*. This infection usually follows a cat bite or scratch. 40% of cats are carrier of this bacteria at some time during their lifestyle. It is a common cause of chronic lymphadenitis in children and adolescents.
- Hodgkin's disease—group of tumors of the lymphatic system. Role of Epstein–Barr virus in its etiogenesis is still controversial. It affects individuals in the age group of 15–40 years. The nodular sclerosing variant simulates LGV.

20.3.5 Diagnosis

Diagnosis in STDs is generally clinical followed by syndromic management and laboratory testing is not required.

Tissue culture—Culture is definite but technically difficult and expensive and yields only in 30% of the cases. The tissue culture identifies the inclusion corpuscles in the monolayers of McCoy or HeLa-229 cells [67]. Fine needle aspiration is used to obtain tissue from the enlarged buboes.

Serological testing—The disease generates a strong immunological response which is measured by tests to identify the disease. There are four serologic tests available which tests gene specific assay of Chlamydia. These include:

- Complement fixation test
- Enzyme linked immunosorbent assay (ELISA)
- Micro-immunofluorescence test
- Anti-major outer membrane protein (MOMP) immunoglobulin A (IgA) assay.

Compliment fixation test and ELISA become positive after fourth week of infection. Titers more than 1:64 are suggestive but pairing after 2 weeks with four fold rise is diagnostic [68]. Cross-reactivity between various chlamydial infections can occur but chlamydial urethritis, cervicitis, or conjunctivitis rarely produce titers greater than 1:16.

Micro-immunofluorescence test (MIF) detects the presence of specific antibodies directed against *Chlamydia trachomatis* present in serum and other secretions. Detection of IgM indicates new infection [47].

Nucleic Acid Amplification Test (NAAT)—It has been used to identify Chlamydia in urine, cervical swabs, and male urethral swabs with sensitivity of 96–100% and specificity of 99.1–100%. This test is US FDA approved for the above samples [47].

Histological evaluation—Typical stellate abscesses are seen on lymph node biopsies performed in the second and third stage of the disease. Histopathological evaluation is not required for confirmation of diagnosis.

20.3.6 Treatment

The treatment requires antibiotic therapy along with drainage of the infected lymph nodes.

The recommended treatment for all stages of the disease is [47, 69, 70]

- Doxycycline 100 mg orally twice a day for 21 days

or

- Erythromycin base 500 mg per oral, 6 hourly for 21 days.

20.3.7 LGV Infection in Pregnancy

Pregnancy being an immunosuppressed state has been shown to increase susceptibility to sexually transmitted diseases. Coinfection in HIV positive cases has increased especially in industrialized countries where initially the disease was uncommon. The diagnosis and appropriate treatment during pregnancy is important to prevent development of perineal and rectal strictures and rectal stenosis. The disease is not known to cause any effect on the fetus [71].

20.3.7.1 Treatment During Pregnancy

As Doxycycline is contra-indicated in pregnancy, erythromycin (stearate or ethyl succinate) 500 mg is given orally every 6 h for 21 days. Azithromycin use is being considered but research regarding its safety and efficacy is still incomplete.

Surgical incision and drainage of buboes are not recommended except in cases of intense pressure symptoms. In such a condition, a thick bevel needle is used for decompression for patient's relief. Presence of lesions with fibrosis and stenosis obstructing the birth canal may be a reason for a cesarean section [71].

It is recommended to treat sexual partners with history of contact 30 days before the development of clinical manifestations.

20.3.8 Prevention

To reduce transmission to others, the patients should avoid sexual contact till the treatment is completed.

In case there is sexual exposure the partner should be treated with azithromycin 1 g orally for a single dose or doxycycline 100 mg orally twice per day for 7 days.

20.4 Granuloma Inguinale (Donovanosis)

Donovanosis is also known as granuloma inguinale or granuloma venereum. It is one of the causes of Genital ulcer disease (GUD). It is a chronic, indolent, sexually transmitted disease of low infectivity, affecting the skin and mucous membranes of the genital and perigenital area. *Klebsiella granulomatis* (earlier also called *Calymmatobacterium granulomatis*), an intracellular Gram negative bacterium is the causative organism for Granuloma Inguinale (GI). It is characterized by occurrence of slow growing, painless ulcers in the genitalia and perineum without any regional lymphadenopathy. The infection can be extra-genital or spread to intra-abdominal organs, bones, or the mouth. The disease is aggravated in pregnancy, thus leading to an increase in the number of lesions [68].

20.4.1 Background

The bacteria was first described by Mc Leod, in Kolkata in India in 1882 [72]. Mason, in 1898 found similar lesions in individuals from East India (pre-independence days). Thus, initially it was thought to be a disease of tropical countries. The disease got its name Donovanosis in 1905 after Donovan described intracellular inclusion bodies present in the macrophages on histological examination of the tissue obtained from the ulcers [73]. Donovan proposed the causative organism to be a protozoan. The intracellular inclusions were termed as donovanosis. Further research by Monbreun and Goodpasture and Walker established the microorganism to be a Gram negative bacillus [74, 75].

20.4.2 Epidemiology

Donovanosis is commonly seen in tropical and sub-tropical countries and in areas of unhygienic standards of living. Papua New Guinea, India, Indonesia, South Africa, Australia, Argentina, the Caribbean, French Guiana, and Brazil have been endemic areas for Donovanosis. The disease is rarely seen in developed non-tropical countries like the United States of America [76, 77]. The largest epidemic of donovanosis was in Papua New Guinea between the years 1922 and 1952, when 10,000 cases were identified from a

population of 15,000 [78]. Another epidemic struck Durban in the late 1980s and the 1990s when 3153 cases of donovanosis were reported from the sexually transmitted disease (STDs) clinic [79]. There has been a decline in the prevalence with improvement in health facilities. Australia has been able to eradicate the disease among its aborigines by an intense surveillance and treatment project [78]. Exact incidence of the disease is difficult to establish these days as many countries have adopted syndromic approach towards treatment of STDs and need for diagnosis is no longer required for administration of antibiotic. In developed countries, the health workers find it difficult to identify the cases due to lack of exposure to tropical diseases [80]. The disease has no gender predilection. It affects adults between 20 and 40 years of age. Nonsexual spread through autoinoculation and contamination from fecal route in children has been documented. The exact incubation period of the disease is not known but varies from 1 to 100 days with an average of 50 days. The disease like other STDs has been found to be co-existing with HIV, therefore HIV testing should be recommended for all cases [81].

20.4.3 Clinical Features

The common sites of infection in men are prepuce, coronal sulcus, frenum and glans penis. While in women the labia minora and the fourchette are commonly affected. The infection usually begins with the development of a firm papule or subcutaneous nodule that breaks down and ulcerates. The ulcerative lesions are beefy red in color with rolled up edges. The lesions are very vascular and can bleed easily. They can be classified into four types [81]:

1. *Ulcerogranulomatous*—This is the most common type of presentation. Single or multiple ulcers which are non-tender, fleshy, beefy red are characteristic of this type. The ulcers generally bleed on touch.
2. *Hypertrophic or verrucous type*—The ulcer or growth is characterized by the presence of a raised irregular edge. This appearance is likened to the description of a walnut.
3. *Necrotic*—The ulcer is deep due to tissue destruction and is associated with foul smell.
4. *Sclerotic*—The ulcer is usually associated with extensive fibrosis and scar tissue.

In 90% of the cases the genitals are affected while extra-genital site involvement is seen in 10% cases. Of these, the inguinal area is most commonly affected. In about 6% cases lips, gums, cheek, palate, and pharynx may be involved. Atypical cases affecting the facial region are usually reported in children. Lymphadenitis is uncommon. Donovanosis can also cause granulomas in the subcutaneous tissue called pseudobuboes. Lesions generally grow more rapidly during pregnancy.

20.4.4 Diagnosis

Demonstration of Donovan *bodies on cytological examination is pathognomic for the infection* [82, 83]. The bacillus is visualized within the cytoplasm of histiocytes. The organism exhibits a bipolar staining due to the presence of chromatin densities, which gives it a closed safety-pin appearance. These are referred to as Donovan bodies (Fig. 20.2).

Direct microscopy—It is the most reliable and economical method which gives results immedi-

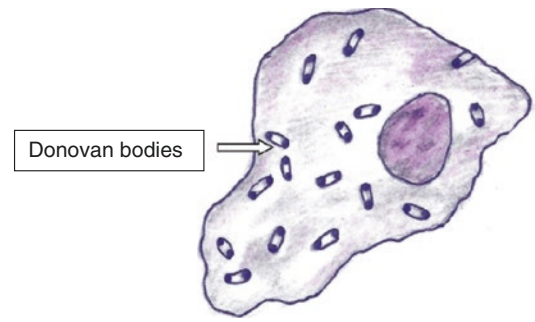

Fig. 20.2 Donovan bodies

ately. The material obtained from the lesions with active granulation tissue is pressed against a glass slide. The slides are then air dried and heat fixed before staining with Giemsa, Leishman, or Wrights stain.

Biopsy—It is performed on active lesions. The epidermis shows acanthosis and the dermis shows inflammatory infiltrate with lymphocytes, plasma cells, and histiocytes. Small neutrophilic abscesses are seen in the upper epidermis. Inclusion bodies are seen on staining with Warthin–Starry, Wright–Geimsa, or Leishman stain [76, 84]. Electron microscopy may be required to visualize the etiological agent.

Culture—The bacteria is very difficult to culture in the yolk sac of chicken embryo. The technique is associated with high failure rates and is economically not feasible and so is not used routinely. Monolayer cell culture has been described using human monocytes, Hep-2 cells, and mouse peritoneal macrophages [82, 83].

Serology—Polymerase chain reaction is used for gene detection, but due to its cost, it is used only in research programs. Immunofluorescence tests are used in chronic lesions but show low sensitivity in early disease. At present no serological tests are available for diagnosis. Donovan bodies may be seen on Papanicolaou smears on routine cervical screening.

20.4.5 Treatment

Aragon and Vianna in 1913 introduced intravenous emetic tartar as the first effective treatment for this ulcerative disease. The advent of antibiotics changed the treatment. At present Azithromycin is the drug of choice. Patients with intense tissue destruction and scarring may require tissue reconstruction surgery along with antibiotics.

The drug regimens are

- Azithromycin 1 g orally once a week for 3 weeks or until complete healing has occurred

or

- Azithromycin 500 mg daily for 3 weeks or until complete healing has occurred.

Other treatment options are:

- Three weeks of Doxycycline 100 mg orally twice a day or until complete healing has occurred.
- Three weeks of Ciprofloxacin 750 mg orally twice a day or till complete healing.
- Three weeks of Erythromycin base 500 mg orally four times a day or till complete healing.
- Three weeks of Trimethoprim-sulfamethoxazole one double-strength (160 mg/800 mg) tablet orally twice a day or until complete healing.

Sometimes aminoglycosides have to be added, e.g. gentamicin 1 mg/kg IV every 8 h to improve the symptoms.

20.4.6 Donovanosis and Pregnancy

Immunosuppression during pregnancy raises the possibility of a more aggressive course of the disease. Atypical lesions are more common during pregnancy, with more predilection for extragenital sites [76, 85]. Procedures like abortion and surgical reconstruction of lesions may lead to dissemination of the bacteria to liver and bones [86]. There are no reports of histotoxic effects of this bacterium on fetal development [86–88]. The preferred drug during pregnancy is erythromycin or azithromycin [71]. Doxycycline is avoided during pregnancy and lactation due to known side effect of discoloration of teeth and bones if given in the second and third trimester. Sulfonamides may cause kernicterus in babies with G6PD deficiency, so should not be given in third trimester and during lactation. Management of chronic injuries by surgical reconstruction is postponed till after pregnancy. Tab Erythromycin stearate 500 mg is prescribed four times a day for 3 weeks. In the presence of a perineal lesion, cesarean delivery is preferred over vaginal delivery to avoid fetal affection [86, 88]. Cap Azithromycin (20 mg/kg/day for 3 consecutive days) should be considered

as prophylactic treatment in neonates of mothers with genital lesions of donovanosis [89].

20.5 Conclusion

STD's are important global health indicators. The three STDs discussed in this chapter, syphilis, lymphogranuloma venereum, and granuloma inguinale (Donovanosis) are known to cause ulcerative disease in the female genitalia. The importance of these diseases lies not only in the fact that they are aggravated during the immunocompromised pregnant state but also due to their inter-relationship with HIV. Syphilis is a chronic systemic disease known to be transmitted transplacentally to the growing fetus. It is a significant cause of fetal affection, perinatal mortality, and childhood sequelae in contrast to LGV and Donovanosis which do not have any significant impact on fetal outcomes. Penicillin is the gold standard for the management of syphilis in pregnancy while oral Erythromycin is the drug of choice for treatment of LGV and Donovanosis. The new policy for controlling STD's by WHO focuses on elimination of congenital syphilis by promoting comprehensive syphilis screening and treatment among pregnant women and appropriate treatment of partners.

Key Points

- Syphilis is a chronic infectious disease caused by *Treponema pallidum*, a spirochete.
- Pregnancies complicated by syphilis may cause up to 50% affection in the form of spontaneous abortion, intrauterine growth restriction, preterm delivery, hydrops fetalis, and stillbirth.
- Universal screening for syphilis is recommended for all pregnant women at first antenatal visit.
- Penicillin is the gold standard for the management of syphilis in pregnancy.
- Lymphogranuloma venereum (LGV) is an ulcerative infection of the genital region seen in tropical and sub-tropical countries. *Chlamydia trachomatis strains* L1, L2, and L3 are the causative organisms.
- LGV is characterized by unilateral tender inguinal or femoral lymphadenopathy; It has not been reported to have any direct toxic effect on the fetus.
- Donovanosis is a chronic, indolent, sexually transmitted ulcerative disease of low infectivity, affecting skin and mucous membranes of the genital and perigenital area. The causative organism is a Gram negative, intracellular bacterium—Klebsiella granulomatis.
- Donovanosis has not been reported to have any adverse effects on the fetal development.
- The preferred drug for Donovanosis during pregnancy is erythromycin or azithromycin.
- All pregnant women with any sexually transmitted diseases should be evaluated for HIV.

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HIV in Pregnancy: A Comprehensive Update

21

Nalini Mittal

21.1 Introduction

HIV is a public health issue of paramount importance worldwide, having claimed approximately 33 million lives till date. Due to increased availability of effective preventive measures, diagnostic methods, effective treatment and care, HIV has become a manageable chronic health condition, enabling HIV-infected individuals to lead long and healthy life. Apart from other routes of transmission, mother-to-child transmission of HIV still is a major route of infection especially in children. The transmission occurs during pregnancy, labor, and breastfeeding in 25–30% women in the absence of treatment. Global strategies of antiretroviral therapies and appropriate care have helped to reduce the incidence to 1% or less in people who have undetectable viral load. The role of various organizations like WHO and United Nations in creating a global communion has helped destigmatize HIV/AIDS to some extent. In this chapter, we will be discussing the HIV infection with emphasis on strategies to reduce mother-to-child transmission.

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21.2 Global Burden of the Disease

As per statistical data of 2019, approximately 38.0 million people are infected with HIV, of which 36.2 million people are adults and 1.8 million are children less than 14 years of age. The majority of people living with HIV belong to developing nations, of which about 68% burden is borne by the Sub-Saharan Africa. In the year 2019, around 6,90,000 people had died of AIDS related illness. This number has declined by 60% since the peak of 1.7 million in 2004 and 1.1 million in 2010 (Table 21.1). Global prevalence of the infection is 0.8%. In 2019, it is estimated that females (women and girls) accounted for 48% of all new HIV infection.

As a result of a global communion working together to control HIV and AIDS, provision for

Table 21.1 Number of people living with HIV/AIDS (2019)

Country	No. of people living with HIV/AIDS	No. of annual deaths due to HIV/AIDS
South Africa (2019)	7,500,000	72,000
Zimbabwe (2019)	1,400,000	20,000
Mozambique (2019)	2,200,000	51,000
Nigeria (2019)	1,800,000	45,000
Brazil (2019)	920,000	14,000
Indonesia (2019)	640,443	38,000
United States (2018)	1,040,352	
India (2017)	2,100,000	69,000

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lifelong antiretroviral therapy (ART) has been made available to 68% of adults and 53% of children living with HIV. About 85% of pregnant and breastfeeding HIV-infected women are receiving ART, thus ensuring prevention of infection to their newborn. In the past decade, remarkable progress has been made in the prevention of mother-to-child transmission of HIV (PMTCT) in resource poor countries. In 2018, 82% of HIV positive pregnant females had access to ART, an increase of more than 90% from 2010.

The JOINT UNAIDS (United Nation Programme on HIV/AIDS) updated its global targets for HIV people. According to it, by 2020, 90% of HIV positive people should be aware of their HIV status, 90% of which should be put on ART, and 90% of which should achieve viral suppression. In pursuit of these targets, by 2019, among all the people living with HIV globally, 81% knew their HIV status, of these 82% had access to treatment, of which 88% were virally suppressed.

21.3 HIV Virus

The two human immunodeficiency viruses, HIV1 and HIV2, belong to the family of retrovirus and the subfamily of lentivirus. Worldwide, HIV 1 is implicated as the commonest cause of HIV disease. HIV 2 has limited geographical distribution and was originally restricted to West Africa. However, currently, cases initially restricted to West Africa are being found throughout the world.

21.3.1 Structure of the Virus

HIV virus (HIV 1 and HIV 2), the etiological agent of AIDS, is a member of the family of Retroviridae and the subfamily of lentivirus. It is an RNA virus having enzyme reverse transcriptase which permits reverse transcription of its genomic RNA to DNA.

HIV virus is an icosahedral enveloped virus approximately 90–100 nm in diameter. The envelope is composed of two phospholipid layers having numerous external spikes formed by trimeric transmembrane glycoprotein gp41 and attached surface glycoprotein gp120. Glycoprotein gp120 contains sites that attach to receptors on the host cell surfaces, CD4 molecules. The CD4 molecules are predominately found on the surface of helper T lymphocytes, dendritic cells, macrophages, and microglial cells. After binding to CD4 receptors, conformational changes occur in the gp120 protein which enables binding to one of the two major co-receptors, i.e. CxCR4 and CCR5 receptors (Fig. 21.1).

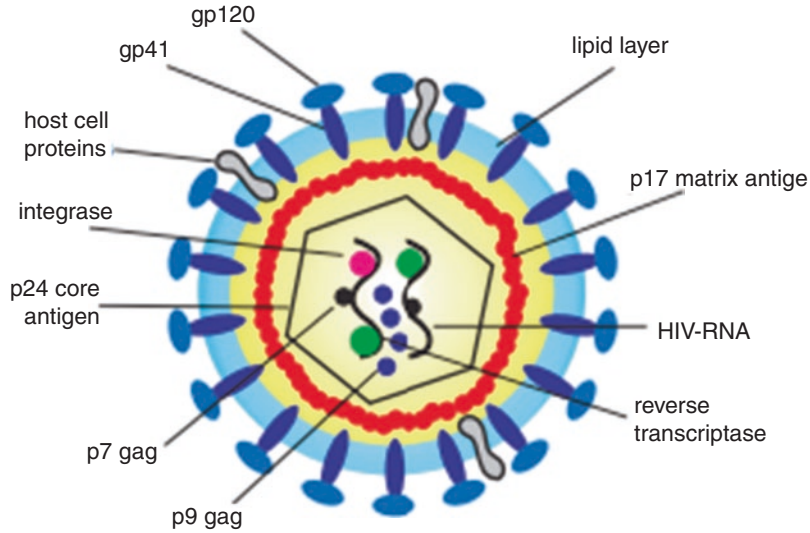

Fig. 21.1 Structure of HIV virus (Source: National AIDS Control Organization, Ministry of H&FW, India)

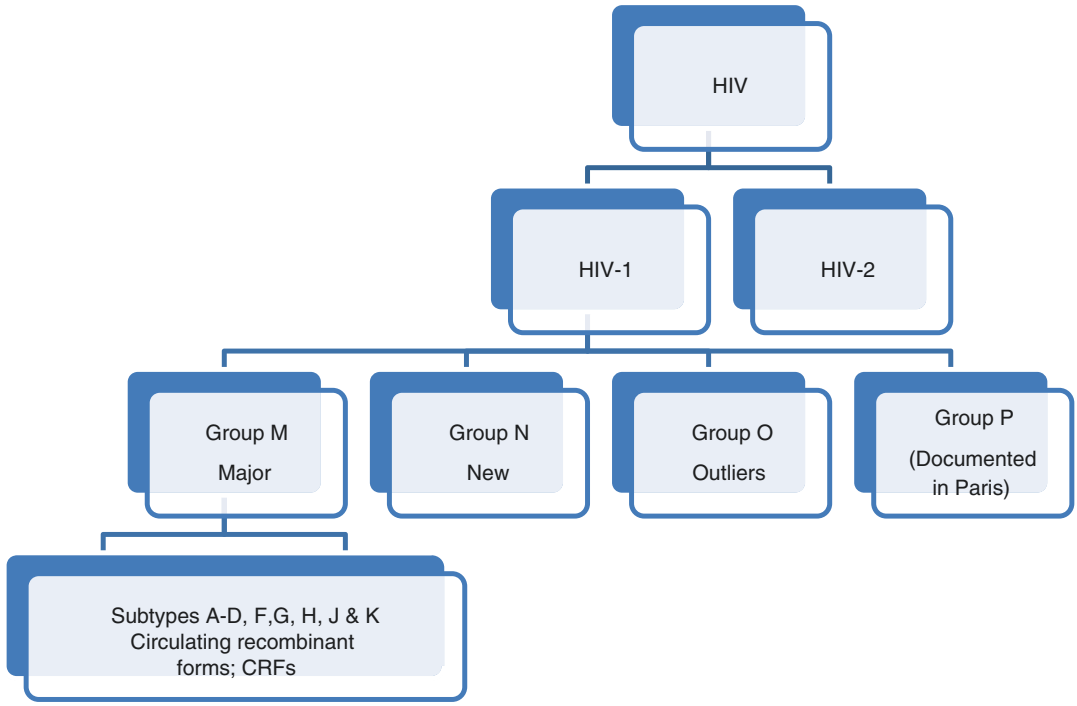

Fig. 21.2 Classification of HIV

21.3.2 Genetic Diversity of the Virus

Numerous divergence is observed in HIV virus because of high mutation rate, high replication rate, limited fidelity of the enzyme reverse transcriptase, i.e. tendency towards copying errors of the enzyme and recombination of different types of virus present. HIV has been divided into various groups and subtypes based on the phylogenetic analysis of numerous isolates from various geographical regions.

HIV 1 and HIV 2 are two distinct viruses. More than 55% of genetic variability is seen between the two viruses. The strains of HIV 1 are classified into four groups M, N, O, and P. Majority of the global epidemics are attributed to group "M." Group O is responsible for 5% of infections in various Central and West African countries. Infection with groups N and P is rare with few cases reported from Cameroon. All the antibody detection kits of HIV 1 are able to detect all groups.

Group M can be further subdivided into nine genetically distinct subtypes, i.e. A, B, C, D, F, G, H, J, and K as well as 90 different circulating recombinant forms (CRF) and numerous unique recombinant forms (Fig. 21.2). Intersubtype recombinants are generated by presence of two subtypes in the same individual. They recombine and create a new virus subtype.

HIV 1M subtype C is assumed to be more transmissible than other subtypes and has been responsible for the global pandemic. Subtype B is the dominant subtype in North America, certain South American countries, Western Europe, and Australia. HIV 2 is not as diverse. However, existence of A–H subtypes has been suggested in HIV 2. The extraordinary diversity of HIV virus has implications on development of resistance to antiretroviral drugs and development of vaccine against HIV.

21.3.3 Life Cycle of HIV Virus

Life cycle of the HIV virus has the following steps:

1. Binding and fusion—The viral surface protein gp120 binds to CD4 receptors and CCR5/CXCR4 co-receptors. This is followed by the merging of the virus envelope and the host cell membrane. Thereafter, the genetic material of the virus (RNA) is released in the protoplasm of the host cell.
2. Reverse transcription—The single stranded viral RNA is transcribed into a double stranded cDNA by the enzyme reverse transcriptase. This action is completed in the protoplasm of the host cell, and thereafter the newly formed cDNA enters the host cell nucleus.
3. Integration—The viral enzyme integrase causes integration of resultant HIV DNA into the host DNA resulting in the formation of "provirus." The provirus may remain inactive (latent) for several years showing varying levels of transcription depending on the metabolic state of the infection.
4. Transcription—On activation of the host cell, the host RNA polymerase transcribes the integrated provirus to make copies of HIV RNA and HIV mRNA. These are transported from host nucleus to host protoplasm.
5. Protein synthesis and assembly—The HIV enzyme protease cuts the viral polyproteins formed into smaller individual proteins. This occurs in the protoplasm. The smaller HIV proteins formed with HIV RNA forms a new virus.
6. Budding—The newly formed HIV virus is released from the host cell by budding. During budding, the virus envelope is obtained from the host membrane protein and lipid bilayer.

The different antiretroviral drugs target the steps of HIV life cycle like reverse transcription, integration, protease action, and binding of virus to CD4 receptors to halt its replication (Fig. 21.3).

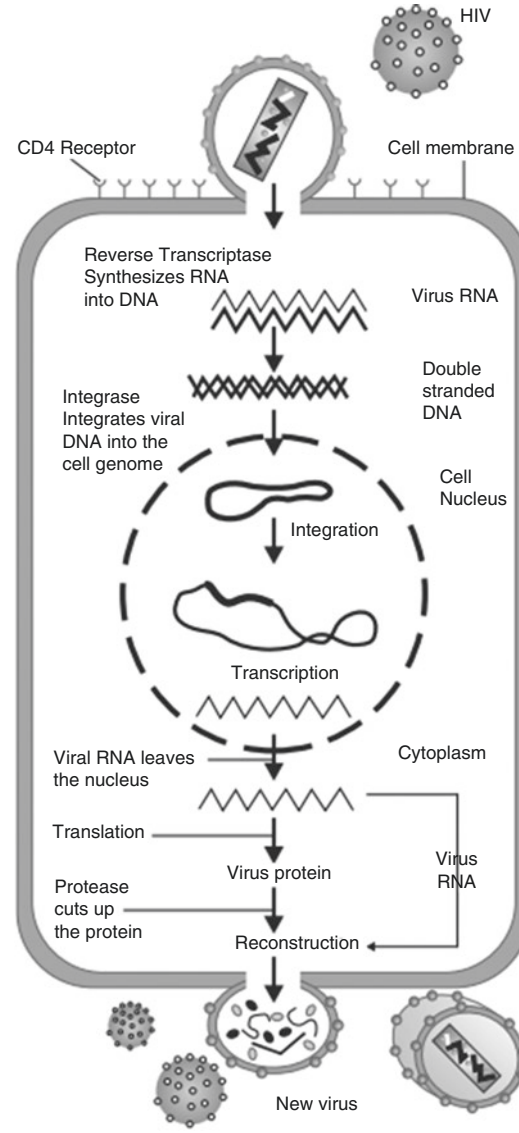

Fig. 21.3 Life cycle of HIV virus (Source: National AIDS Control Organization, Ministry of H&FW, GOI)

21.4 Transmission and Pathogens

21.4.1 Transmission of HIV

The mode of transmission of HIV is by sexual contact, by exposure to infected blood and other body fluids, and from an infected mother to the

infant either intrapartum, perinatally, or via breast milk. In developing countries the most common route of transmission is by heterosexual route. Male to male mode of transmission dominates many western developed countries. Actions such as kissing, hugging, shaking hand or sharing food, etc., do not transmit disease.

People with HIV who are on ART and are virally suppressed do not transmit HIV to their partners sexually. Viral suppression is defined as viral copies <200/ml. Therefore, early access to ART and continuous ART therapy is critical for improving health of the people and also to prevent HIV transmission.

21.4.1.1 Sexual Transmission

The predominant mode of HIV transmission all over the world is the sexual route. Heterosexual transmission is the most common mode, particularly in developing countries. In most western countries male to male sexual transmission predominates. The virus has been demonstrated in seminal fluid, vaginal fluids, and cervical smears.

Based on epidemiological studies various factors have been observed to effect HIV transmission. Male to female sexual transmission is generally more than female to male transmission. Also, transmission by anal sex is more efficient than vaginal sex. Oral sex is a less effective route of transmission of HIV compared to anal or vaginal intercourse. Transmission of HIV infection is affected by factors like viral load and presence of ulcerative genital disease. Bacterial vaginosis also may be linked with increased rate of HIV transmission.

Transmission by heterosexual route is not very high with transmission rate from male to female being 0.04% and from female to male 0.08% per act, in the absence of ART and condom use. Reduction in viral load as a result of antiviral therapy is associated with a dramatic fall in rate of transmission. This has been widely referred to "*treatment as prevention*." With reduction of viral load below detectable levels by ART, there is essentially no chance of sexual transmission to the uninfected partner.

Male circumcision is known to reduce the risk of acquisition of HIV infection. Also, it reduces HPV and genital ulcer disease in men and among female sexual partners. Thus, indirectly it benefits female sexual partners of circumcised men in reducing their risk of acquiring HIV. Oral contraceptive use is indirectly related to an increase in HIV acquisition, which may be due to reduced use of condom for contraception and changes in cervical mucosa making it susceptible to HIV infection.

21.4.1.2 Transmission Through Infected Blood and Blood Products

HIV can be transmitted through contaminated blood and blood products and transplantation of infected organs. Transfusion of whole blood, packed red blood cell, platelets, leukocytes, and plasma can transmit HIV infection. However, hyperimmune gammaglobulin, hepatitis B immunoglobulin, and Rh immunoglobulin are not associated with HIV transmission. This may be because of inactivation or removal of virus while processing these products.

Blood is an efficient means of transmission of HIV infection. Over 90% seroconversion is observed after infected blood transfusion. The chances of such transmission has been virtually eliminated in developed nations by introduction of universal screening of blood for HIV antibodies prior to transfusion, introduction of tests which further reduce window period like p24 antigen detection and nucleic acid detection tests (NAT), appropriate selection of donor and judicious use of blood. In few developing countries transmission of HIV infection by blood and blood products is still an ongoing threat wherein screening of blood is not universally practiced due to lack of financial resources.

In spite of universal screening of blood a very low but theoretically possible risk of HIV transmission persists in the following situations-

- the donor is in the window period of HIV infection
- a false negative HIV negative report
- human and operational error

21.4.1.3 Transmission of HIV by Other Body Fluids

HIV has been isolated from saliva in low titers in a small percentage of HIV-infected individuals. But in spite of these, there is no conclusive evidence that kissing or other occupational exposures to health care workers can transmit the infection. There is no evidence to support HIV transmission by tears, sweat, or urine also.

21.4.1.4 Mother-to-Child Transmission

Mother-to-child transmission is defined as the transmission of HIV from a HIV positive mother to her child during pregnancy, delivery, or breastfeeding. The transmission rates are 15–45%, in the absence of any intervention. Interventions such as antiretroviral treatment for the mother and newborn are effective in lowering this rate of transmission to 1% or less in virally suppressed individuals. High maternal viral load, measured at the time of delivery, has been described as the strongest risk factor for both in utero and intrapartum transmission. Other factors such as maternal viral load in the genitalia (presence of genital ulcers), CD4+ T cell count, and clinical stage of infection are independent factors affecting transmission.

21.4.2 Pathogenesis

Profound immunodeficiency is the hallmark of HIV infection resulting primarily from a progressive quantitative and qualitative depletion of a subset of T lymphocyte referred to as helper T lymphocyte or CD4+ T cell. The entry of the virus into the human body is followed by rapid viral replication. This is followed by a rapid fall in the CD4+ T cell count and a rise in the CD8+ T cells. The CD8+ T cells generate an antibody response by destroying the HIV-infected cells. A good CD8+ T cell response has been associated with a protracted disease progression and a better prognosis, though it is not known to eliminate the virus. The target cells for HIV are the CD4+ T cells and depletion of these cells results in AIDS as well as the weakened immune system allows opportunistic infections. During the chronic phase, there is a gradual loss of ability of the immune system to generate new T cells which is reflected as reduced CD4+ T cells. The T cell loss is first manifested in the mucosal cells, evident within the first week of infection. Tropism for mucosal cells is explained by the fact that most of the mucosal CD4+ T cells express the CCR5 protein which is used by HIV as a co-receptor to enter into the cells, whereas only a small proportion of CD4+ T cells in the bloodstream do so.

21.5 Clinical Manifestations and Disease Progression

In natural course, the HIV infection goes through three stages, i.e. acute infection phase, chronic asymptomatic phase, or latent phase and AIDS (acquired immune deficiency syndrome). Primary illness maybe followed by an asymptomatic period which can last for a median period of 10 yrs in untreatd patients. The infected individuals appear healthy and feel well until progression of the disease with subsequent damage to the immune system. Pregnant women also present with similar symptoms.

Acute Infection Phase—It is estimated that 50 to 70% of individuals after HIV infection experience acute clinical syndrome with varying degree of severity. This syndrome is associated with the presence of high level of viraemia that lasts for several weeks. It may be associated with acute mononucleosis like syndrome having features like fever, pharyngitis, lymphadenopathy, headache etc., which is largely self limiting. The period usually lasts 3 to 6 weeks and ends with the appearance of an adaptive immune response to HIV. This high level of viraemia is associated with higher likelihood of transmission of virus to others during this phase.

The initial level of viremia in primary HIV infection does not determine the rate of progress. However, a set point of the level of steady plasma viremia is attained approximately one year post infection which seems to correlate with the rate of disease progression in untreated patients. Due to the non-specific nature of the symptoms, they may go unnoticed.

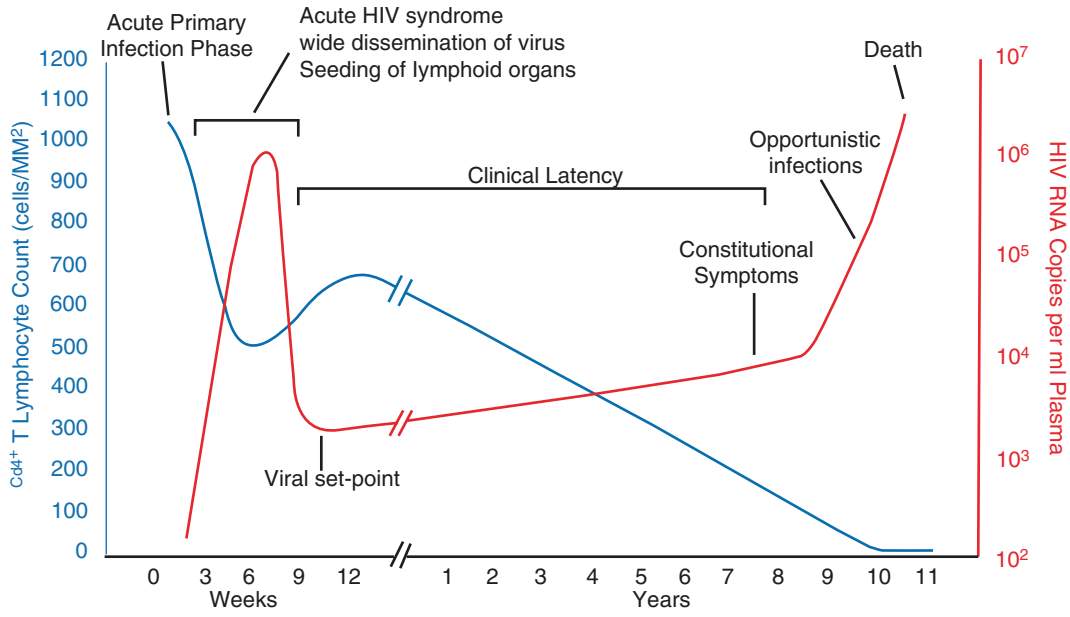

Fig. 21.4 Stages of HIV infection

Phase of Clinical Latency—Chronic asymptomatic phase also known as phase of clinical latency

Acquired Immunodeficiency Syndrome—If untreated, 50% of the HIV-infected individuals progress to AIDS in 10 years. By definition, AIDS is HIV infection with CD4+ T cell count less than 200 cells per μL or the presence of HIV associated conditions. These include diarrhea (90%), pneumocystis carinii pneumonia (40%), cachexia (20%), esophageal candidiasis, recurrent respiratory tract infections, opportunistic infections, and viral induced cancers—like Kaposi's sarcoma, Burkitt's lymphoma, primary central nervous system lymphoma, and cancer of the cervix (Fig. 21.4).

21.5.1 Pattern of Disease Progression

Depending on various viral, host, and environmental factors, the progress of HIV disease in an individual shows different patterns.

Typical Progressor: 85–90% of people infected with HIV infection show typical pattern of progress with median survival period after infection being 10 years. The typical course of progress consists of primary infection, clinical latency, and development of AIDS.

Rapid Progressors: They constitute 5–10% of individuals who develop end stage of disease or AIDS within 2–3 years of HIV infection.

Long-Term Non-Progressor: In few rare cases of HIV-infected individuals, the infection does not progress to AIDS for extended period of time; these are called long survivors. It is seen in 5% of individuals infected with HIV. In a high percentage of such individuals, inherited mutation of the co-receptor CCR5 is seen.

Elite controllers: They are the subset of long-term non-progressors whose immune system has the ability to contain the virus to an undetectable level, i.e. HIV RNA below 50 copies/ml for many years even in the absence of ART (Fig. 21.3).

Factors which affect the disease progression include:

- Viral factors including rate of mutation, latency, and co-receptor usage.
- Host factors consisting of genetic factors such as HLA polymorphism, chemokines receptor gene polymorphism, HLA types, and mutation of co-receptors.
- Environmental factors such as nutrition, co-infection with TB or hepatitis B, and Vit A deficiency.

21.6 HIV Diagnosis

HIV testing is not only a laboratory test but a complete package with a full range of services including pre and post-test counseling, the linkage to treatment and other supportive care services. CDC recommends that screening of HIV infection should be performed as a matter of routine healthcare services. Testing is required for:

- For the purpose of surveillance
- To avoid contaminated blood transfusion and organ donation
- To identify people with high-risk behavior
- Antenatal screening of pregnant women to prevent transmission from an infected mother to her child
- To diagnose patients presenting with opportunistic infections.

The diagnosis of HIV infection is made by detection of antibodies specific to HIV, by initial screening tests followed by confirmation by supplemental tests. ELISA is the most widely used screening test as it is economical for a large number of specimens on a daily basis. The fourth-generation ELISA assays detect both HIV antibody and antigen (p24), thereby leading to earlier detection of HIV seroconversion. With advancement in technology visually read, easy to perform, instrument-free, initial tests are also available. These are called simple/rapid (S/R) assays. Their results are available in 30 minutes or less, and are appropriate for use in testing centers and laboratories which have limited facilities. Previously the most common confirmatory test was the Western blot (WB). But due to the large number of indeterminate results and high cost, other suitable tests like Line immuno-assays (LIAs) are replacing it. Various studies have reported that by combining ELISAs and S/R assays a similar specificity to WB can be achieved but at a lower cost. The same has been recommended by WHO and UNAIDS also.

UNAIDS and WHO recommend three testing strategies based on prevalence of the disease in that area and requirement for testing, to maximize accuracy while minimizing cost. In the selection of HIV antibody tests for use in strategies II and III, the first test should be such that it has the highest sensitivity, whereas the second and third tests should have a similar or higher specificity than the first.

Strategy 1—This is used by laboratories for transfusion/transplant donors irrespective of prevelance, for surveillance in areas where prevalence is more than 10% and for diagnosis of the disease in the presence of clinical features in areas where the prevalence is more than 30%. Each serum/plasma specimen is tested with one ELISA or simple/rapid assay and the test is reported as positive and negative.

For transfusion and transplant purpose, the main objective is to protect against transmission. Therefore, all units with positive or indeterminate results are to be discarded. The donor who is found to be positive based on his/her prior consent is to be reffered for testing referred for testing after proper counselling. For diagnosis, strategy I can be used to confirm for individuals meeting the WHO criteria of stage III or IV of HIV infection and when the HIV prevalence in the sample population is above 30% (e.g., a sample of patients from a tuberculosis ward).

Strategy 2—It is used for surveillance in areas where the disease prevalence is less than 10%, for diagnosis in the presence of clinical features of HIV in areas where prevalence is less than 30% and for diagnosis in asymptomatic population in areas with prevalence more than 10%. The serum/plasma is first tested with one ELISA or simple/rapid assay. The serum which is reactive on the first assay is subjected to a retest with a second ELISA or simple/rapid assay based on a different antigen preparation and/or different test principle for confirmation of diagnosis. Any serum that is reactive on the first test but nonreactive on the second test should be retested with a third test for making a diagnosis; if the third test is reactive, then it is reported as indeterminate and follow-up reporting is done after 2–4 weeks.

Strategy 3—It is used for diagnosis in asymptomatic patients. This is the strategy used for universal screening of all pregnant women. Strategy 3 of HIV testing is similar to strategy 2 with the addition of a third test to confirm a positive result. The test utilized for the first screening should be

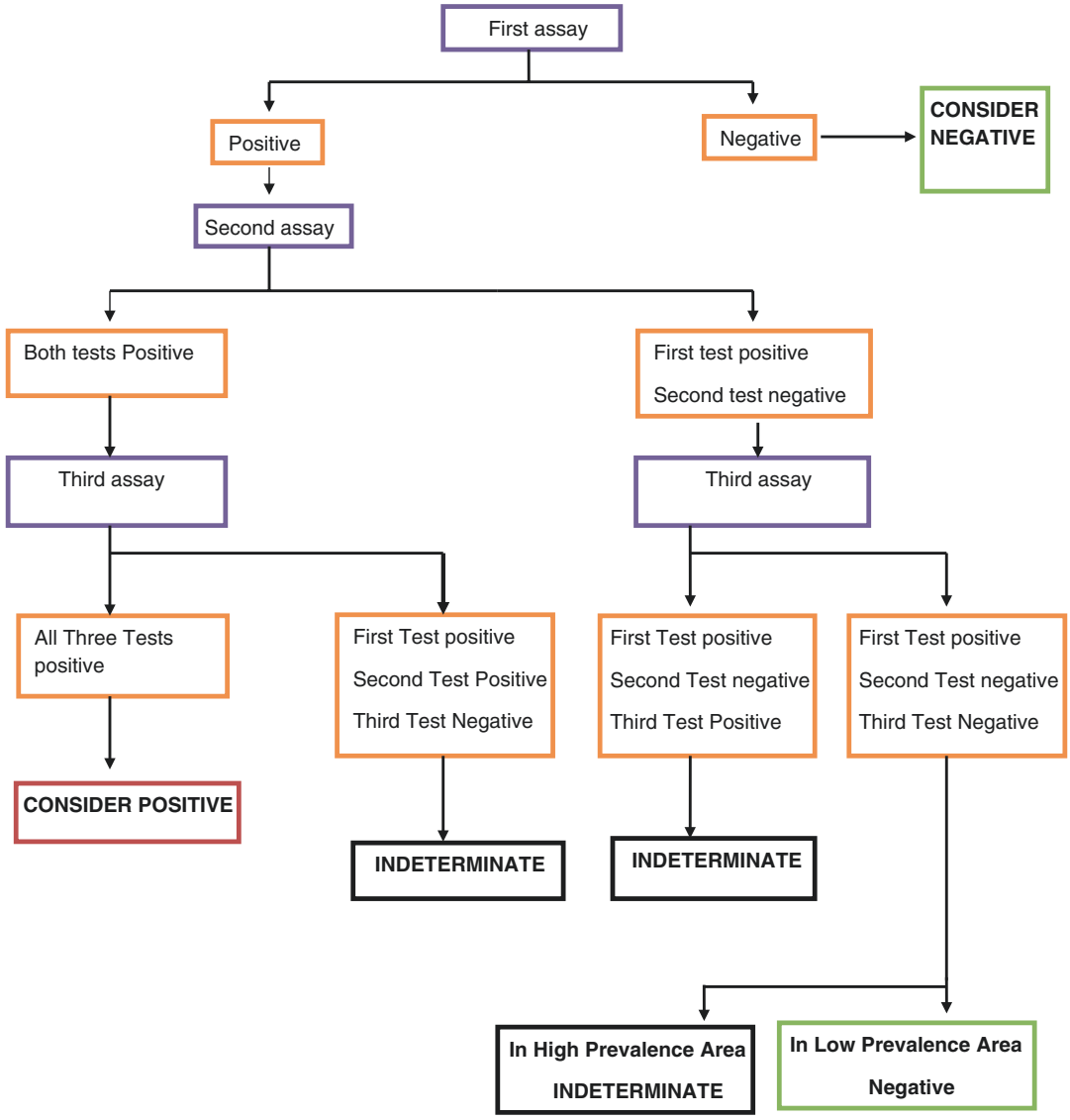

Fig. 21.5 Interpretation of strategy 3. Assays A1, A2 & A3 are three diffrent assays having either diffrent principal or diffrent antigenic composition. A2 & A3 should be able to diffrentiate between HIV1 & HIV 2

the one with the highest sensitivity and those used for the second and third tests are those with the highest specificity (to minimize false positive reactions (Fig. 21.5)).

21.6.1 Tests for HIV

HIV testing is a part of the composite health care package which is provided to the person under the WHO guidelines. These services go a long way in gaining confidence of the patient and create a social acceptance. HIV testing services are voluntary and involve pre- and post-test counseling.

The earliest viral marker to appear in the blood is p24 antigen. Antigen p24 maybe detected in blood about 2 weeks following infection coinciding with viraemia. IgM antibodies appear in about 4–6 weeks to be followed by IgG antibodies. The antibody tests are the most important tests for screening. They are dependent on the seroconversion—development of antibodies. The

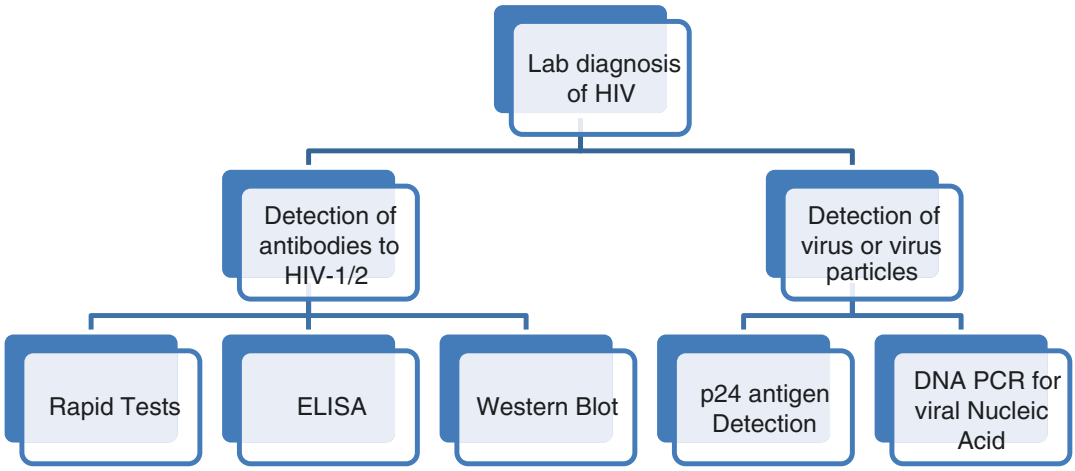

Fig. 21.6 Tests used for HIV diagnosis in adults and children above 18 months of age

antibody based tests are unable to diagnose the infection till detectable antibodies develop. This time duration is called the window period.

Window period—It is defined as the period after the entry of HIV into the body and the appearance of detectable levels of antibodies with the available tests. The patient is highly infectious but the antibody test is negative in the window period. The window period can vary from 3 weeks to 3 months. 99% people develope detectable antibodies by 3 months. For a variable period of time ranging from few days to several days virus cannot be detected by any means in the plasma. This period is called *eclipse* phase of infection the earliest marker to be detected is HIV viral load (usually by 1 to 6 wks of exposure). p24 is the first HIV antigen to be detected (1 to 8 wks of exposure). in 99.9 % of people HIV antibody can be detected by 12 weeks. though approx 94% if infected individul have detectable antibodies by 4 weeks.

Specific tests (Fig. 21.6)

- Antigen detection: p24 antigen
- Virus isolation
- Detection of viral nucleic acid
- Antibody detection

Non-Specific Tests

- Total and differential leucocyte count
- T-lymphocyte subset assays
- Platelet count
- IgG and IgA levels
- Skin Tests for CMI (Cell Mediated Immunity)

21.6.1.1 Specific Tests

p24 antigen detection: This antigen is the earliest to appear and is detected in the blood by 2 weeks coinciding with the viremia. The p24 antigen capture ELISA uses anti-p24 antibodies as the solid phase and the test is positive in about 30% cases. The disease can be diagnosed by documenting p24 antigen even in the window period. The test may be negative if the infecting dose is small.

Virus isolation: Virus titers generally correspond to the p24 titers, being high soon after infection, low and antibody-bound in the asymptomatic period. The titers rise again when the patient is terminally ill. The virus can be isolated from the peripheral lymphocytes by the cocultivation of the patient's lymphocytes with uninfected lymphocytes in the presence of interleukin-2. As this test involves risk of infection, it is to be performed only in laboratories with appropriate precautions. It is not used for screening.

Detection of viral nucleic acid: NAAT—It is a most sensitive and specific test for diagnosis of HIV infection. Polymerase chain reaction (PCR) is used for detecting structural genes (usually gag, pol, and env) of HIV. It is the preferred

method to diagnose the disease in the window period and in infants less than 18 months (antibody assays cannot be used due to circulating maternal antibodies).

Antibody detection: This is the simplest and most frequently used diagnostic technique. IgM antibodies appear by 2 weeks and disappear in 8–10 weeks while IgG appear by 4 weeks and persist for life. Antibody testing should be done after 2–6 months to ascertain whether infection has occurred or not. This test is negative in the window period. These can be divided into two types of tests—

- Screening (E/R/S) tests
- Confirmatory tests

A. Screening (E/R/S) Tests—(ELISA/Rapid/Simple ELISA based)
   (i) ELISA (enzyme linked immunosorbent assay) is recommended as a first-line test. The test is simple with a high sensitivity and specificity. The assay requires an ELISA reader; therefore, WHO has recommended this test to be used in laboratories where more than 30 samples are tested at a time (WHO, 2003). Most commercially available ELISA kits can detect both HIV-1 and HIV-2 (Fig. 21.7). ELISA can be performed on whole blood, saliva, urine, and dried blood spot (WHO, 2003). The use of saliva is beneficial in intravenous drug abusers as blood sample is difficult to obtain in such people. The test has economic advantage over rapid test as it can be automated for testing a large number of samples and the reagents have a shelf life of 6–12 months. It has the disadvantage that they take yield results and requires expertise.

   False positive ELISA test can be seen in conditions like blood malignancies, multiple myeloma, autoimmune disorders, primary biliary cirrhosis, alcohol-induced hepatitis, chronic renal failure, positive RPR test for syphilis, any infection due to DNA-virus, vaccination against influenza and hepatitis B, and if the test is performed during the window period.

   (ii) Rapid assays—Rapid tests include dot-blot assays, particle agglutination (gelatin, erythrocyte, latex, and microbeads), HIV-spot test, and fluorometric microparticle technologies. These tests allow differentiation of HIV-1 and HIV-2 infection by using HIV-1 or HIV-2 recombinant or synthetic peptide antigens separately. Rapid tests are visual tests and do not require an ELISA reader. These tests are suitable for a laboratory processing of smaller number of samples (WHO, 2003) (Fig. 21.8). The presence of a built-in immunological

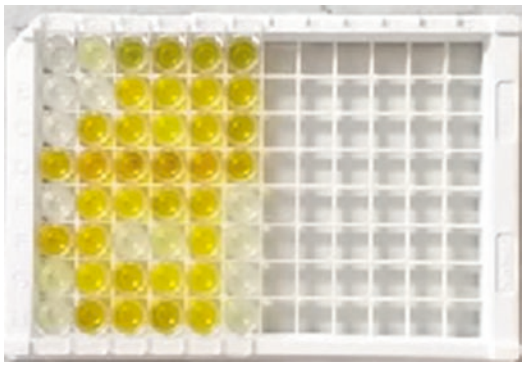

Fig. 21.7 ELISA test

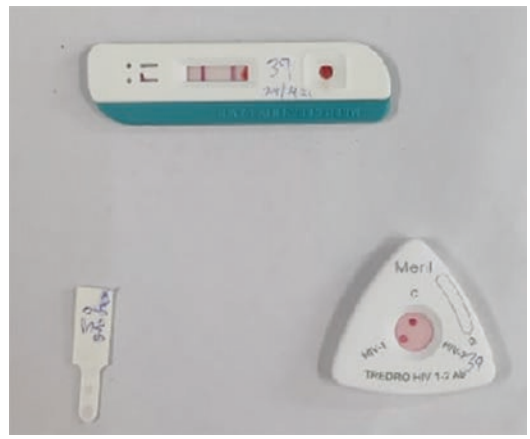

Fig. 21.8 Rapid/simple assay for HIV infection

control "dot" system in the rapid assay is advantageous in confirming the accuracy of the test. The tests have sensitivity and specificity comparable to that of ELISA and can be performed in less than 10 min. They do not require any specific equipment for identifying positive reaction. The main disadvantages of the tests include high cost, subjective end-point and faulty results with stored and contaminated samples.

(iii) Simple tests based on ELISA principle—These tests take a little more time to perform—30 min as compared to the rapid tests. They are also based on the same principal as ELISA. As per WHO recommendations, reconfirmation of a positive sample tested by ELISA/rapid test is to be performed by another ELISA/rapid test, based on a different principle, and using a different antigen preparation.

B. Confirmatory (or Supplementary) Tests

(i) Western blot (WB)—It is the standard confirmatory assay, which is recommended to confirm indeterminate results or diagnose HIV-2 infection (WHO, 2003). The western blot (WB) detects antibodies to p24 (gag gene, core protein) and gp 120, gp 41, gp 160 (env gene, envelope protein). As the assay does not contain any cellular components, the chances of indeterminate results and false positives are reduced. The testing kits available commercially can be for isolated HIV-1 and HIV-2 antibodies or both.

(ii) Line immunoassay (LIA): It is a modification of the Western Blot single—a strip line immunoassay. Synthetic peptides and recombinant antigens for HIV-1 and HIV-2 are coated as separate lines on a nylon strip. Both individual and combination kits for detection of HIV-1 and HIV-2 antibodies are available.

(iii) Immunofluorescence assay (IFA)—The test uses fluorescein-conjugated anti-human gamma globulin for reaction with HIV-infected cells. The fluorescent immune complexes are identified under fluorescent microscope. Immunofluorescence assay is less time consuming as compared with the WB technique, but more expensive.

(iv) Radioimmunoassay (RIA) and Radioimmuno precipitation assay (RIPA) are other modifications of WB.

21.6.2 Non-specific Tests

These tests are suggestive of the disease during advanced stage. Total leukocyte counts suggest leucopenia and the lymphocyte count is less than 2000/mm^3. Reduced platelet count and absolute CD4+T cell count—usually less than 200/mm^3 is noted.

21.6.3 Laboratory Tests Used for Monitoring Patients on Antiretroviral Therapy (ART) and Progress of HIV Infection

- CD4 cell count
- HIV RNA load assays

21.6.3.1 CD4 Count

CD4 cells are the T-helper cells which have the CD4 receptor molecule on their surface and coordinate the cell-mediated immune response. A healthy adult has a CD4 cell count of 600–1200 cells/mm^3 normally. Variation of CD4 cell counts is seen with circadian rhythm, fatigue, stress, vaccinations, infections such the flu, and at the time of menstrual cycle.

HIV primarily targets CD4 cells; therefore, the CD4 cell count is an important investigation for monitoring HIV disease progression. Both CD4 count and viral load provide information regarding effectiveness of ART. CD4 cell count below 200 cells/mm^3 subjects the person to risk of infections such as *Pneumocystis carinii* pneumonia (PCP). A fall in the CD4 count below 100 cells/mm^3 makes the person prone to opportunistic infections such as cryptosporidiosis and toxoplasmosis while counts lower than 50–75 cells/mm^3 for *Mycobacterium avium complex* and CMV. CD4 count is measured every 3–6 months. ART in preg-

nancy as per WHO recommendations does not require CD4 count for initiation or monitoring.

21.6.4 HIV Viral (RNA) Load Assays

It measures the amount of genetic material (HIV RNA) in the blood. It is a reflection of the actively multiplying virus in the circulation. The viral load and CD4 cell count together are the most important measures for predicting HIV disease progression and assessing effectiveness of the treatment. Viral load is stated as copies of HIV virus in one milliliter of blood. The viral load of copy number below 20 per ml usually goes undetected and is considered best. But it is to be noted that undetectable viral load in blood does not rule out its presence in other body fluid such as CSF, genital secretions, semen, and tissues like lymph nodes. This means that the chances of transmission are still present though low. According to the current HIV treatment guidelines in the USA, it is recommend that people should consider starting treatment if their viral load is above 55,000 copies/ml. Monitoring HIV1 viral load has become a standard protocol of care for monitoring and managing the response to ART in people living with HIV and their progress towards AIDS. The first test should be repeated at 4 weeks of starting the therapy or after change of therapy and thereafter at 3–6 months. However, the test is costly and technically cumbersome. Thus, it is generally used in resource poor countries to identify first-line ART failure cases.

Currently available techniques for HIV RNA load estimation are:

- Target Amplification Assays
- Quantitative Reverse Transcriptase PCR
- Real Time PCR
- Nucleic Acid Sequence Based Amplification Assays (NASBA)
- Signal Amplification Branched DNA Assay

21.6.5 Newer Tests

Rapid test kits like OraQuick HIV test (saliva based) and the Home access HIV 1 test (urine based) test systems which help people to test themselves are being introduced. Many countries are introducing self-testing as an additional option to encourage HIV testing. A positive result from these has to be confirmed by healthcare facilities (Fig. 21.9).

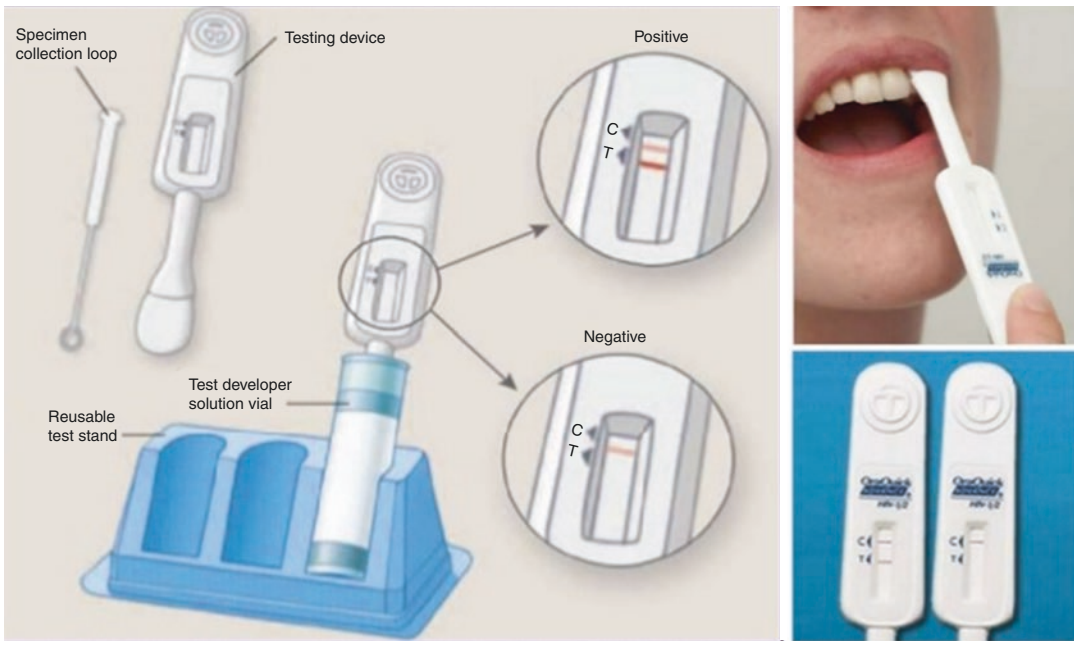

Fig. 21.9 OraQuick HIV rapid test

21.7 Effect of HIV on Pregnancy

Pregnancy does not have any adverse effect on the course of the disease, but infection during pregnancy is an important means of transmission to the neonate.

HIV is associated with increased incidence of sexually transmitted diseases and also increases the risk of malaria and tuberculosis. All these diseases affect the pregnancy outcomes as discussed in concerned chapters. No increase in congenital anomalies is noted though few studies have documented an increase in the incidence of prematurity, low birth weight, and stillbirths.

Combination Antiretroviral Therapy (ART) was evaluated for its role in increasing the pregnancy related adverse effects in a large multicentric randomized trial on 3490 women; the PROMISE (Promoting Maternal and Infant Survival Everywhere) trial. The trial concluded that the probability of delivering infants weighing less than 2500 g or preterm infants was more with women who received ART in pregnancy than those who received non-suppressive monotherapy with zidovudine. Gestational diabetes, pre-eclampsia, and low birth weight infants are known side effects of protease inhibitors. In a more recent retrospective study (2004–2012) conducted in the United States, infants born to perinatally HIV-infected (PHIV) women were evaluated for growth patterns during their first year of life and compared to non-perinatally HIV-infected (NPHIV) mothers who received care. It was found that infants of PHIV mothers had lower mean length-for-age z-scores (LAZ) that were associated with birth length. Other small-for-gestational age anthropometric parameter associations included those of birth weight and weight-for-age *z*-scores (WAZ) and those of both birth length and weight with weight-for-length z-scores (WLZ). The investigators also reported increased WAZ and WLZ if the delivery HIV RNA level was below 400 copies/mL.

21.7.1 HIV 2 Infection in Pregnancy

HIV 2 infection is endemic in West Africa but cases have been reported from other parts of the world also. HIV 2 infection is mainly transmitted via heterosexual route. Compare to HIV1, it is less infectious, has longer asymptomatic phase, and slower progression to AIDS. Sexual transmission is five times less and vertical transmission rate is 20–30 times less than HIV 1 infection. This may be due to lower plasma viral load and reduced cervical shedding in females with HIV 2 than with HIV 1 infection. Guidelines regarding treatment of HIV 2 infection in pregnancy are same as HIV 1 infection. However, antiretroviral agents that are active against HIV2 virus should be used. Non-nucleoside reverse transcriptase inhibitors and enfuvirtide are inactive against HIV 2, therefore should not be used in its management.

21.7.2 Maternal to Child Transmission (MTCT)

Transmission of HIV infection from infected mother to infant can occur intrapartum, perinatally, or through breast feeding. The vertical transmission if no antiretroviral therapy is initiated ranges between 23–30% before birth, 50–65% during birth, and 12–20% by breast feeding. The overall risk of transmission is between 15 and 35% (Table 21.2). However, with antiretroviral therapy for HIV, the rate if maternal to child transmission of HIV has fallen to less than 1% in virally suppressed individual.

21.7.2.1 Perinatal Transmission

Risk factors for perinatal transmission include

- High maternal level of viremia
- Closer human leukocyte antigen (HLA) match between mother and child

Table 21.2 Risk of mother-to-child transmission (MTCT) without intervention

Timing	Transmission rate (%)
During pregnancy	20–25
During labor and delivery	60–70
During breastfeeding	15–20
Without breastfeeding	15–25
With breastfeeding for 6 months	20–25
With breastfeeding for 18–24 months	30–45

- Prolonged rupture of membranes prior to delivery
- Preterm delivery
- Chorioamnionitis
- Active sexually transmitted diseases such as genital ulcers
- Assisted instrumental delivery, e.g., vacuum or forceps delivery
- Cigarette smoking
- Procedures like amniocentesis, amnioscopy, and episiotomy.

21.7.2.2 Transmission During Breastfeeding

HIV is also transmitted from mother to child during breast feeding. The risk of HIV transmission through breastfeeding is maximum in the early months of breast feeding and more when mixed feeding is followed or there is mastitis, maternal vitamin A deficiency and low CD4 count. In developed countries breast feeding is contraindicated in babies of HIV-infected mother. However, in developing countries breast feeding may be necessary for the comprehensive health of the newborn. Continuation of antiretroviral therapy during the period of breast feeding markedly reduces the risk of transmission to the infant.

21.8 Screening for HIV in Pregnancy

21.8.1 Antenatal Screening for HIV

All antenatal women must be offered screening for HIV after counseling. HIV testing and counseling should be voluntary, and follow the five C's of *consent, confidentiality, counseling, correct test results and connections to care, treatment and prevention services.*

The American College of Obstetricians and Gynecologists (ACOG) recommends two types of screening—routine HIV screening for all women in the age group of 19–64 years and targeted screening for at-risk women outside of this age reference. All pregnant women should have their HIV serostatus evaluated when they first present for prenatal care. WHO also recommends universal screening of all antenatal women at the first visit and additional testing of all HIV negative women in the third trimester residing in high-risk areas (Box 21.1). Guidelines from other important organizations all recommend the following:

- Linking care with voluntary counseling
- Provide screening and treatment as a complete package
- Maintain confidentiality
- Test for sexually transmitted diseases
- Encourage partner testing as transmission through sexual route during pregnancy increases the incidence of HIV in pregnancy and during the postpartum period.
- The sexual partners and drug injecting partners of people living with HIV are at a greater risk of developing HIV. Therefore, WHO recommends that voluntary assisted HIV partners notification services are simple and practical way to reach these people.

Box 21.1 WHO Guidelines for Provider Initiated Testing and Counseling (PITC)
(Source: World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection)

WHO GUIDELINES (2016)
In high-prevalence settings

- Provide PITC for women as a component of the complete package for care in antenatal, intrapartum, postpartum, and newborn care
- Retest all HIV negative pregnant women in the third trimester, postpartum, and/or during labor, because of the high risk of acquiring HIV during pregnancy
- Periodic retesting of all lactating mothers who are HIV negative throughout the period of breastfeeding.

In low-prevalence settings

- Consider PITC for pregnant women as a part of antenatal care and integrate it with testing for screening of syphillis and Hepatitis B infection

To retest HIV negative pregnant women who are in a serodiscordant couple, from a key population group or have known ongoing HIV risk.

Women who present directly in labor with an unknown HIV status should be offered bedside counseling and HIV screening test by nursing staff and if the woman consents, *whole blood finger prick test* is done. If she is detected HIV positive, the medical officer in-charge should initiate ART-TDF + 3TC + EFV and ensure immediate linkage to ART center counselor. Further tests for confirmation of HIV are then subsequently done as per guidelines (Fig. 21.10).

21.9 Management of HIV in Pregnancy

21.9.1 Antenatal Care

Three different categories of HIV-infected patients are encountered in pregnancy. One group is those which are already on ART, second group comprises women who are diagnosed through universal screening during pregnancy and then there are pregnant women who present directly in labor with unknown HIV status (Fig. 21.10). The antenatal and intrapartum care required for all these groups is the same.

All women are enrolled for routine antenatal care. Need for lifelong ARV is explained to them. The care-giver should ensure involvement of

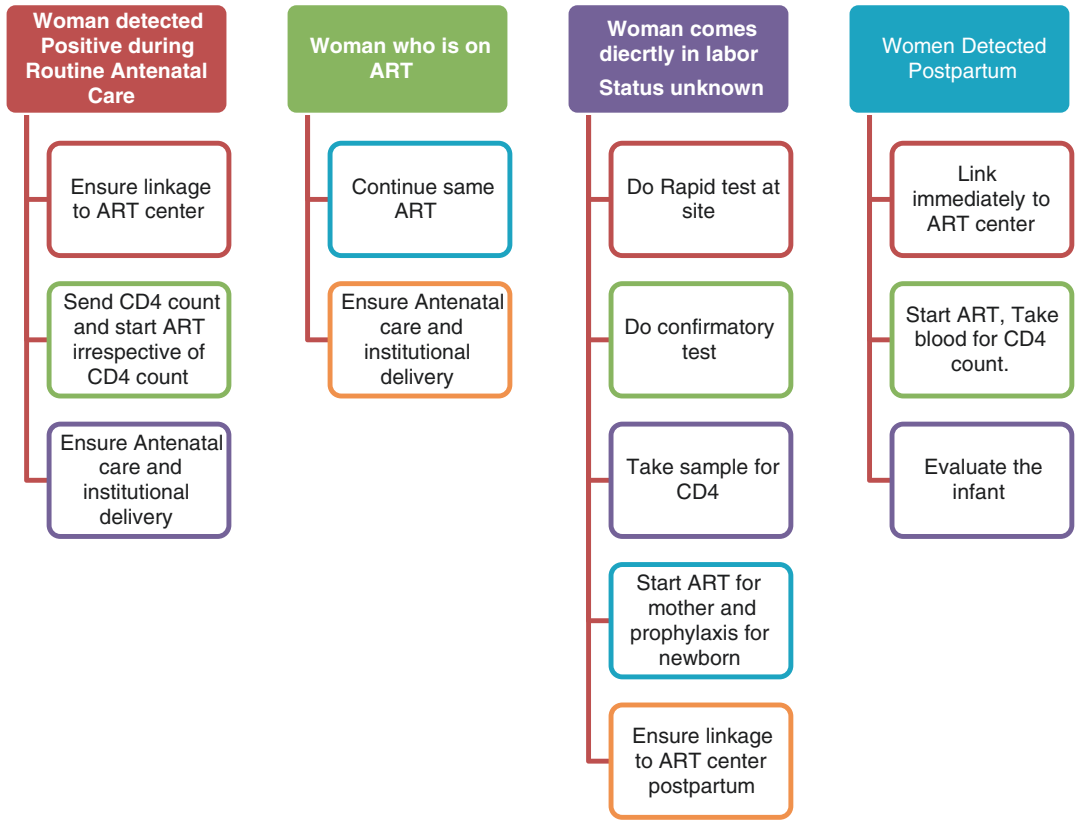

Fig. 21.10 WHO guidelines for antiretroviral treatment

spouse and other family members, give nutritional counseling and psychosocial support to HIV-infected pregnant women. Institutional delivery must be promoted. The couple should be counseled regarding initiation of exclusive breastfeeds within the first hour delivery, explaining its benefits for the neonate. Important points to be incorporated in ANC care

- Look for development of anemia especially between 28 and 32 weeks.
- Weight loss may be an indicator of clinical deterioration of the disease
- Due to hemodilution, the CD4 count may show a decline in comparison with the pre pregnancy level/first documented level. This may not necessarily indicate an immunological decline.
- About 50% of the HIV positive women develop depressive changes and suicidal tendencies during pregnancy. Identification of these symptoms and psychological counseling is required. Family involvement and social support provided by the health care worker are also very important part of management.
- In patients with active tuberculosis, concurrent anti-tubercular and antiretroviral has been recommended with certain precautions. If tuberculosis is diagnosed during screening, the anti-tubercular treatment is started prior and after 2 weeks ART can be started. Nevirapine is replaced by Efavirenz due to drug interaction between Rifampcin and nevirapine.
- If patient is diagnosed with hepatitis B or C co-infection, it does not defer starting ART. Patient should be under simultaneous care of medical specialist.

21.9.2 Intrapartum Care

HIV positive woman in labor is to be managed as per labor and delivery protocols of the institute for other routine pregnant woman but certain precautions need to be taken to decrease the chances of intrapartum transmission and to protect the healthcare worker.

21.9.2.1 To Prevent MTCT

- The number of vaginal examinations to be reduced to reduce the microabrasions in the vagina.
- Artificial rupture of membranes is to be avoided unless obstetrically indicated like in case of fetal distress and delay in progress of labor.
- Invasive procedures like fetal scalp electrodes and fetal blood sampling are to be avoided.
- Instrumental delivery is to be avoided unless indicated for obstetrical reasons. If indicated a low outlet forceps is preferred over ventouse as the former is associated with less fetal trauma.
- Routine episiotomy is to be avoided.
- Milking of the cord is discouraged.
- Early cord clamping is practiced but in preterm delivery, delayed cord clamping is acceptable.
- The cord should be cut using precaution to cover it with a surgical cotton pad to avoid spurt of blood during cutting.
- Suction in newborn with nasogastric tube is to be avoided unless indicated as in meconium staining of liquor to prevent meconium aspiration.
- Postpartum hemorrhage is best managed with oxytocin and prostaglandins as methergine or other ergotamine interact with protease inhibitors and reverse transcriptase to cause severe vasoconstriction.

21.9.2.2 Role of Cesarean Section

ACOG Recommendation (2017)—Laboratory evaluation of viral load between 34 and 36 weeks of gestation is the single most important factor that determines the optimal mode of delivery. It is recommended that if HIV RNA viral load at term is >1000 copies/ml, cesarean delivery at 38 wks should be performed after counseling. An elective procedure is recommended to prevent onset of spontaneous labor. Vaginal delivery should be recommended and discussed with the patient at term (37 wks to 39 wks) if the HIV RNA viral load at the time of delivery is <1000 copies/mL as various cohort studies have documented only

1–2% risk of perinatal transmission with viral load of 50 copies/mL to 999 copies/mL at term. Intrapartum, women with a viral load >1000 copies/mL should receive intravenous zidovudine (2 mg/kg loading dose over 1 h, then 1 mg/kg/h continuous infusion) over 2 h prior to vaginal or cesarean delivery.

WHO (2016)—It is recommended that, in countries with limited resources, the indications for cesarean section should be guided by obstetric or medical conditions and not the HIV status. This is even though cesarean birth has been shown to protect against HIV transmission, especially in the absence of ARV drugs or in the case of high viral load. Instead, WHO recommends that all pregnant women infected with HIV should be on ART.

21.9.2.3 Safe Surgical Practices

1. Wear appropriate size gloves, mark, eye shield, shoe cover, and impervious gown
2. Avoid spillage of body fluids and incase of spillage follow spill management criteria
3. In case episiotomy is given, use of round tipped needles is preferred
4. During Cesarean—*DRY* hemostatic technique should be followed to minimize bleeding
   (a) Follow surgical planes during dissection to minimize bleeding
   (b) Judicious use of cautery
   (c) Blunt round tip needles should be used
   (d) Use forceps to hold and receive needle
   (e) Good practices should be practiced while transferring sharps like holding containers for the sharp
   (f) Whenever possible during cesarean section the membrane should be left intact till the delivery of the head and clamp the cord as soon as possible after delivery
   (g) Appropriate disposal of placenta, and soiled linen as per protocol.

21.9.3 Postpartum Care

21.9.3.1 Breastfeeding

In 2010, WHO recommended that policy makers in each country should decide and promote infant feeding practice which is practically feasible for their population to follow—avoidance of all breastfeeding with replacement feeds or breastfeeding with an ARV intervention to reduce transmission. WHO recommends that replacement feeding should only be recommended if it is acceptable, feasible, affordable, sustainable, and safe (AFASS). Breastfeeding also has the benefit of developing a mother and child bond which helps combat postpartum depression. Researchers have documented that unhygienic feeding practices with commercial feeds or mixed feeding are associated with development of infections and increased infant mortality.

21.9.3.2 Care of the Infants

- Immediately after birth the infant born to HIV positive mother must be given Nevirapine syrup at a dose of 1 mg per kilogram weight within 1 h of delivery. This should continue for at least 6 weeks. It can be extended to 12 weeks if ART was initiated late in the mother.
- Early infant diagnosis (EID) by dried blood spot or DBS at 6 weeks for all babies is recommended (Fig. 21.11). If positive, a whole blood sample (WBS) is tested. Infants who test negative are reevaluated when the HIV exposure (usually through breastfeeding) ends. The CHER (Children with HIV Early Antiretroviral Therapy) Trial, conducted in South Africa in 2008 was a landmark study in management approach. It observed a 75% reduction in early mortality and HIV progression in asymptomatic perinatally infected children with normal CD4 percentage (i.e., CD4 more than >25%), in whom early HIV diagnosis was made and triple-drug ART was initiated before 12 weeks when compared with children in whom treatment was delayed till clinical or immune criteria were met. It was observed that, more than 95% of infants infected in utero and intrapartum could be identified by virological testing at 4–6 weeks of age. Therefore, early diagnosis and treatment is recommended by WHO 2014. All infant born to HIV positive mothers are subjected to testing at 4–6 weeks of age, or at the earliest opportunity thereafter by HIV DNA

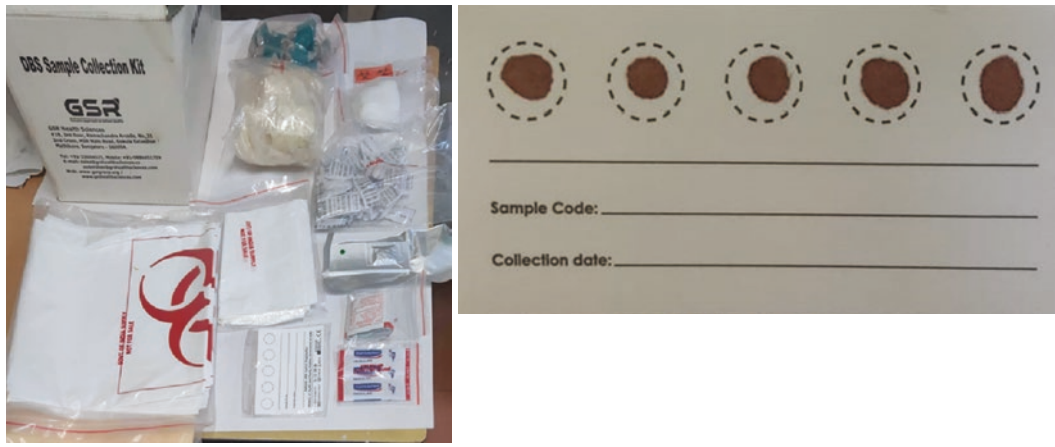

Fig. 21.11 Dried blood spot collection kit and card

PCR, RNA PCR, or ultrasensitive p24 (Up24) antigen test. The increased cost factor and requirement of specialized equipment for P24 antigen has made testing with HIV DNA PCR, RNA PCR more acceptable. It is suggested that those infants who test positive should undergo a confirmatory test on a new sample, but initiation of ART should not be delayed while the reports of the tests are awaited. Therefore, a Dried Blood spot (DBS) is performed on the infant at 4–6 weeks using Nucleic Acid Amplification test (NAAT).

- Start CPT (Cotrimazole) prophylaxis from 6 wks for all HIV exposed infants. Continue upto 18 moths of age irrispective of EID status and thareafter if confirms HIV positive.
- Immunization as per schedule.
- HIV exposed infants should be followed up every month in the first year of life and thereafter every 3 months till 18 months of age.
- Symptomatic infant should be screened for HIV regardless to age.

21.9.4 Family Planning Counseling

One of the main strategies to reduce HIV transmission is to prevent unwanted pregnancies by providing effective contraception.

- Barrier contraceptives—Provides dual protection (i.e., protection against unplanned pregnancy and STI). It is important in preventing HIV cross-infection of partner. It can be safely used by those with asymptomatic infection and those who are on ART. Consistent usage is important for best results.
- Hormonal Contraceptives—Oral contraceptive or depot medroxyprogesterone acetate is safe in HIV positive women on ART. No Interaction is seen between ARV drugs like NVP, EFV and Nelfinavir and hormonal contraceptive drugs. Antiviral drug Ritonavir is known to decrease effect of oral contraceptive and is usually not used together.
- Intrauterine Contraceptive Device—is also a good method of contraception in HIV-infected women following delivery.
- Male sterilization should be motivated.

21.9.5 Antiretroviral Therapy (ART)

Antiretroviral Therapy (ART) consists of a combination of at least three antiretroviral drugs from different classes which suppress the replication of HIV and reduce viremia to undetectable levels. The various drugs do not eliminate the virus but help to transform the disease to a chronic illness where an individual can lead a near normal life.

Continued suppression of viral replication brings about an increase in the CD4 count, reinstates the immune response, slows down the disease progression, reduces the frequency of

Table 21.3 Recommended doses of drugs used in antiretroviral therapy (WHO 2016)

Generic name	Dose
Nucleoside reverse—transcriptase inhibitor (NRTIs)	
Abacavir (ABC)	300 mg twice daily or 600 mg daily
Emtricitabine (FTC)	200 mg daily
Lamivudine (3TC)	150 mg twice daily or 300 mg daily
Zidovudine (AZT)	250–300 mg twice daily
Nucleotide reverse transcriptase inhibitors (NtRTIs)	
Tenofovir (TDF)	300 mg once daily
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	
Efavirenz (EFV)	600 mg daily
Etravirine (ETV)	200 mg daily
Nevirapine (NVP)	200 mg daily for 14 days followed by 200 mg daily
Protease inhibitors (PI)	
Atazanavir (ATV) + Ritonavir (RTX) (ATV/r)	300 mg +100 mg once daily
Darunavir (DRV) + Ritonavir (DRV/r)	800 mg +100 mg once daily (For individuals with no previous use of PI) Or 600 mg + 100 mg once daily (for individuals with previous use of PI)
Lopinavir (LPV)/ Ritonavir (LPV/r)	400 mg +100 mg twice daily
Integrase strand transfer inhibitors (INSTIs)	
Dolutegravir (DTG)	50 mg daily
Raltegravir (RAL)	400 mg twice daily
Elvitegravir (EVG)	Used as combination drug

Source: World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, 2016

opportunistic infections and thereby brings about an improvement in the quality of life and increases the life span.

The ARV drugs target different site of the life cycle of the virus. Fusion inhibitors and CCR 5 co-receptor blockers block the attachment of HIV to the target cell while reverse transcriptase inhibitors block the viral RNA cleavage and inhibit the enzyme reverse transcriptase, integrase inhibitors (INSTIs) block the enzyme integrase, which helps in incorporation of the proviral DNA into the host cell chromosome, and the protease inhibitors (PI) block the enzyme protease (Table 21.3).

21.9.5.1 Investigations Before Initiating ART

The investigations which should be done before starting ART include a complete blood count, fasting blood sugar, blood urea, liver enzymes, VDRL, and HbsAg; anti-HCV test should be done in intravenous drug users. If there is significant history of tuberculosis, then sputum examination for AFB is required. A preliminary CD4 count is done to evaluate the viral load and risk of transmission to the fetus, but it does not alter the initiation of ART.

21.9.5.2 Recommended ART

WHO recommends lifelong ART for HIV-infected pregnant and breastfeeding women which should be initiated irrespective of their CD4 count or WHO clinical stage of the disease.

The recommended ART for pregnant and breastfeeding women with HIV includes:

- Pregnant women who are ART Naive/Not-already receiving ART—Tenofovir 300 mg + Lamivudine 300 mg + Efavirenz 600 mg
- Women who are already on ART—Continue the same regimen
- Pregnant women having prior exposure to NNRTI for PPTCT—Tenofovir 300 mg + Lamivudine 300 mg once a day and Lopinavir 200 mg and Ritonavir 50 mg twice a day.
- In patients with toxicity to Tenofovir or renal disease, replacement with Abacavir should be done in the drug combination, i.e. Abacavir + Lamivudine +Efavirenz
- As per PPTCT guidelines, Lopinavir/ritonavir (LPV/r) instead of Efavirenz (EFV) is initiated in all infected pregnant women who have been exposed to NVP/EFV in past.
- *Role of Integrase Inhibitors*—Dolutegravir (DTG) is an Integrase Strand inhibitor (INSTI) and has been accepted in 2018 by WHO as a potentially safe ART after published studies from Botswana and Quebec have disapproved its association with neural tube defects. Other INSTI like Elvitegravir and Raltegravir have also been found to be safe for use. United

States is already considering to include them in first-line ART though they have not been included in the WHO regimen.
- Patients on Tenofovir based regimen should be monitored with serum creatinine, Nevirapine containing regimen with SGPT, Efavirenz containing regimen with lipid profile, and Ritonavir containing regimen with both lipid profile and blood sugar.
- Clotrimazole prophylaxis is to be started if CD4 count is less than 250 cells/cu mm. It prevents opportunistic infections like Pneumocystis carinii pneumonia (PCP), toxoplasma, diarrhea as well as other bacterial infections. It should be continued throughout the pregnancy, delivery, and breastfeeding.

Pre-exposure Prophylaxis (PrEP) This is offered to women who are trying to conceive or are pregnant, postpartum or breastfeeding, and are at risk of acquiring HIV infection such as unprotected sex with a partner with HIV, recent STI, or injection drug use. Oral combination tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) is recommended

21.9.6 Guidelines for Couples with HIV Planning Conception

Patients on ART should plan conception according to the couples infection status. There is a risk of sexual transmission to the partner with every act even though the viral load is undetectable.

21.9.6.1 Natural Conception Vs Artificial Reproductive Technology

HIV-Infected Female with Non-Infected Male—Assisted insemination is the safest method for conception with partner semen once ovulation is initiated by Artificial reproductive technology and patients viral suppression has been achieved.

HIV-Infected male with non-infected female—As the uninfected partner is at risk of transmission during natural conception, the couple is given the following options:

- Adoption
- Donor Semen
- Pre-exposure prophylaxis to the infected to reduce viral load in blood to undetectable level. The semen is then analyzed for any viral concentration in the semen. If detected, the semen is washed and then reanalyzed before using it for Intrauterine insemination or IVF.

Concordant couples (both partners are HIV-infected)—It is recommended that both the partners should be treated for genital tract infections, achieve maximum viral load suppression, and be screened before planning conception.

As per WHO guidelines, the woman should continue on the Antiretroviral Therapy she has been on throughout the pregnancy.

Pre-exposure Prophylaxis—non-infected partner of discordant couple if not willing for artificial routes for conception can be offered pre-exposure prophylaxis with antiretroviral drugs.

21.10 Prevention

Key approaches by which individuals can bring down the risk of acquiring HIV are:

1. Condom usage by both males and females—Correct and consistent use of condoms (both male and female) can prevent spread of STIs, including HIV. Consistent use of male latex condoms has an 85% or greater protective effective against HIV and STIs.
2. Needle and syringe program for HIV prevention—encouraging people to use sterile injecting equipment for every injection and to avoid sharing of drug delivery systems and drug solution.
3. Voluntary Medical Male Circumcision (VMMC)—It reduces chances of heterosexually acquired HIV infection by approximately 50%. In 2020, WHO recommended VMMC in males above 15 years of age as an additional intervention.
4. Secondary benefits of ARV in HIV prevention—Studies confirm that people living with

HIV infection taking ARV therapy are virally suppressed and do not transmit HIV to their partners. Thus, ART contributes to reducing HIV transmission. Early initiation of ART to both mother in pregnancy and child and during breast feeding can eliminate the risk of MTCT.

5. Pre-exposure prophylaxis (PrEP) for HIV negative partner to reduce transmission risk to the fetus.
6. Post exposure prophylaxis (PEP) for HIV—28 days PEP should be started within 72 h of exposure for both occupational and non-occupational exposures as recommended by WHO.

21.11 Conclusion

HIV is a global public health issue. Years of research and understanding have highlighted that destigmatization, prevention, protection, and timely intervention should be the key strategies to control the disease. MTCT can be effectively reduced to 1% or less by effective screening, initiation of lifelong ART and intrapartum interventions. Education, counseling, and support by care-giver have helped us to reach out to the people and ensure healthy and safe motherhood to the women.

Key Points

- Worldwide, HIV is a public health issue of paramount importance.
- HIV virus (HIV 1 and HIV 2), the etiological agent of AIDS, belongs to the family of Retroviridae and the subfamily of lentivirus. It is an RNA virus having enzyme reverse transcriptase which permits reverse transcription of its genomic RNA to DNA.
- The mode of transmission of HIV is by sexual contact, by exposure to infected blood and other body fluids, and by infected mother to the infant either intrapartum, perinatally, or via breast milk. In developing countries the most common route of transmission is by heterosexual route.
- Mother-to-Child Transmission (MTCT) rates range from 15% to 45% in the absence of any intervention but with effective interventions can be reduced to below 1%.
- UNAIDS and WHO recommend three testing strategies, based on prevalence of the disease in that area and requirement for testing, to maximize accuracy while minimizing cost.
- WHO recommends universal screening of all antenatal women at the first visit and additional testing of all HIV negative women residing in high-risk areas in the third trimester.
- Provider Initiated Testing and Counseling (PITC) is provided for women as a part of the comprehensive maternal and newborn care.
- Lifelong ART for HIV-infected pregnant and breastfeeding women should be initiated irrespective of their CD4 count or WHO clinical stage of the disease.
- A minimum of 6 weeks prophylaxis with Nevirapine is recommended for every infants born to HIV-infected mothers. This prophylaxis can be extended to till 12 weeks.
- First-line ART, for ART naïve women is Tenofovir 300 mg + Lamivudine 300 mg + Efavirenz 600 mg daily.
- Every infants born to HIV-infected mothers should be evaluated at 6 weeks with NAAT for diagnosis. Early initiation of ART in HIV positive infants helps to reduce mortality.
- Condoms, hormonal contraception, and intrauterine devices are all acceptable methods of temporary contraception in HIV-infected couples.

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Vulvovaginitis in Pregnancy

22

Veena Rahatgaonkar-Joshi

22.1 Introduction

Reproductive tract infection is a significant health problem globally. Vaginal infections are common reproductive tract infections seen in hospital as well as in community acquired setting. Though commonly occurring, vulvovaginitis is often underestimated as a health problem. Vaginitis is a broad term and encompasses various differential diagnoses. Successful treatment of vaginitis rests on accurate diagnosis.

Vaginitis is defined as inflammation of vagina which is associated with spectrum of symptoms like burning, irritation, vulovaginal itching, abnormal vaginal discharge, and dyspareunia. Pregnancy itself increases the risk of developing vaginal infections due to the physiological changes associated with it. Vaginal infections during pregnancy have negative impact on pregnancy outcome and are associated with increased incidence of perinatal and neonatal morbidity.

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22.2 Normal Defense Mechanism of Vulva and Vagina

22.2.1 Vulvar Microflora

The vulva is the protective barrier of the genital tract from infection. Normal vulvar flora includes vaginal, urethral, colonic, and microbes characteristic of intertriginous skin. The vulvar microbiota is diverse and different in all women. Maintenance of the microbiota ratio plays a key role in vulvovaginal health. Various microbes seen in vulva are staphylococci, micrococci, streptococci, lactobacilli, diphtheroids, Gram-negative rods, and yeasts.

22.2.2 Normal Vaginal Flora

In the reproductive age, the vaginal flora remain heterogeneous. Commonly found organisms in the vaginal flora include Gardnerella vaginalis, group B streptococci (GBS), *Escherichia coli*, genital mycoplasmatales, and Candida albicans. The vaginal flora also contains protective microbes like Lactobacillus. It is a Gram-positive, non-sporing bacillus which converts glycogen of the mature squamous epithelial cells of vagina into lactic acid and makes the vaginal pH acidic. Vaginal pH is regulated by the amount of lactic acid produced by the vaginal mucosa and the

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microbial flora. Most of the pathogenic organisms except Candida cannot grow in acidic environment. These commensal microbes are protective and compete with exogenous pathogens to adhere to the vaginal mucosa. They also produce antimicrobial compounds such as bacteriocin to fight the pathogens.

22.2.3 Vaginal Secretions

The vaginal secretions are normally composed of vaginal epithelial cells and lactobacilli suspended in secretions from the vagina walls and cervix. The secretions have a pH of 3.5–4.6. They are odorless and are not responsible for any itching or irritation. Grossly the secretions appear clumpy and generally remain in the vagina. These physiological vaginal secretions help to clear the infecting organisms. Vaginal fluids have documented in-vitro anti-bacterial activity against non-resident bacterial species, including Group B Streptococcus and *Escherichia coli*.

22.2.4 Other Factors

- Vaginal epithelial cells produce lysozyme and lactoferrin compounds having antimicrobial activity.
- Various factors like Toll-like receptors, surfactant protein A, complement system, β-defensins, and nitric oxide present in the vaginal epithelium are important components of innate and adaptive immunity of the female genital tract.
- There is rapid turnover of the vaginal epithelium which also serves as a protective mechanism.

In spite of natural defense mechanisms, increased prevalence of vulvovaginitis is seen during pregnancy.

Contributing factors for increased prevalence of vulvovaginal infections during pregnancy are as follows:

- *Low immunity status*—The high estrogen levels in pregnancy result in loss of maternal cellular immunity. Consequently, the chances of acquiring the infection, clinical presentation, and course of diseases are altered in pregnant women.
- *Hormonal changes*—High levels of estrogen and progesterone make pregnant women more susceptible for infections.
- *Alteration of vaginal microbiome*—Disturbance of natural balance of bacterial flora leads to increased incidence of vaginal infections. Stress, vaginal douching, or use of soap to clean the vagina may change the protective environment of vagina.
- *Increase in glycogen storage in vaginal cells*—Glycogen favors growth of infective organisms and causes alteration in vaginal PH.
- *Excess moisture*—There is increase in vaginal discharge during pregnancy due to elevated hormone levels. The vulva is susceptible to infections as the vulvar skin ceases to act as a barrier due to excessive moisture due to urine or increased vaginal discharge, enzymes, stool residue, friction, and heat. Excess moisture may overgrow the yeasts and cause imbalance between protective and nonprotective vaginal flora and lead to favorable environment for fungal growth.

Important and tricky part for early detection of vaginitis during pregnancy is to differentiate between normal and pathological discharge.

22.3 Types of Vaginitis

Following types of vaginitis are seen during pregnancy which can have adverse outcome if left untreated.

- *Bacterial vaginitis*
  - Bacterial vaginosis.
  - Chronic purulent vaginitis caused by Gram-positive cocci.
  - Vaginitis due to mycoplasma.
- *Fungal vulvovaginitis.*
  - Candidal vulvovaginitis.
- *Parasitic vulvovaginitis.*
  - Trichomoniasis.

The three most common causes of vaginitis are bacterial vaginosis, vulvovaginal candidiasis, and trichomoniasis. Bacterial vaginosis is responsible for 40–50% cases of vaginitis, vuvlovaginal candidiasis is implicated in 20–25% cases and trichomoniasis is causative in about 15–20% cases. Only 5–10% of cases of vaginitis are attributed to non-infectious causes like inflammatory vaginitis due to allergy or irritants.

22.4 Bacterial Vaginosis

Bacterial vaginosis (BV) was earlier classified as non-specific vaginitis as no one specific organism could be implicated. The vaginitis was seen to arise and remit spontaneously. It is characterized by a shift from the normal aerobic flora to anaerobic flora.

22.4.1 Pathophysiology

Bacterial vaginosis infections are generally polymicrobial with presence of both aerobic and anaerobic bacteria. It is a polybacterial dysbiosis, i.e. microbial imbalance as a result of an overgrowth of mainly anaerobic bacteria found in normal flora like Gardnerella vaginalis, Prevotella spp., Mycoplasma hominis, and Mobiluncus spp. with a decline in the normal protective lactobacilli. The organisms become adherent to vaginal epithelial cells. These cells studded with bacilli are called as "Clue cells" (Fig. 22.1).

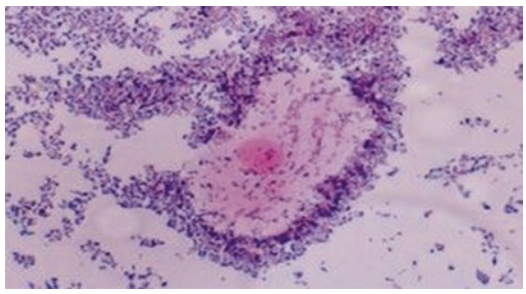

Fig. 22.1 Clue cells—vaginal epithelial cells with adherent coccobacilli

If the dysbiosis which occurs in bacterial vaginosis persists for longer duration, then it can be associated with increased risk of developing human immunodeficiency virus (HIV), human papillomavirus, herpes simplex virus-type 2 (HSV-2), and trichomonas vaginalis infection.

Risk factors for BV during pregnancy

- History of unprotected coitus.
- History of multiple sexual partners.
- History of use of intrauterine device for contraception.
- Vitamin D deficiency.

22.4.2 Clinical Features

More than 50% of the women with bacterial vaginosis are asymptomatic. Common symptoms associated with it are vaginal discharge which is described as malodorous. On clinical examination there is a homogenous, greenish vaginal discharge with fishy odor which can be easily wiped off the vaginal wall. Clinical criteria referred to as Amsel's criteria require presence of any three of the following signs or symptoms for diagnosis of bacterial vaginosis.

22.4.2.1 Amsel's Diagnostic Criteria

- Homogeneous, thin, greenish white discharge that coats the vaginal walls smoothly
- Positive Whiff test— addition of 10% KOH to the vaginal discharge produces a fishy odor
- Presence of clue cells (vaginal epithelial cells studded with adherent coccobacilli) on microscopic examination
- pH of vaginal fluid >4.5—The swab for pH evaluations is obtained from the mid-portion of the vaginal side wall. This is done to avoid false elevations in pH results due to cervical mucus, blood, or semen.

22.4.3 Laboratory Diagnosis

- Positive Whiff test: (described above).
- Saline wet mount microscopic examination: Presence of clue cells is pathognomonic of

Table 22.1 Nugent's criteria

Score	Lactobacillus morphotypes	Gardnerella and Bacteroides	Mobiluncus
0	>30 /HPF	0/HPF	0/HPF
1	5-30/HFP	>1/HFP	1–4/HPF
2	1–4/HPF	1–4/HPF	≥5/HPF
3	>1/HFP	5–30/HFP	
4	0/HPF	>30/HPF	

Score of 0–3: Normal; 4–6: Intermediate; 7–10: Bacterial vaginosis
Source: Nugent, R P; Krohn, M A; Hillier, S L. "Reliability of diagnosing bacterial vaginosis is improved by a standardized method of gram stain interpretation" Journal of Clinical Microbiology 1991; 29 (2): 297–301

BV infection. Clue cells are vaginal epithelial cells which are studded with adherent coccobacilli. These cells are covered with a heavy coating of bacteria such that their peripheral borders are obscured.

- pH of vaginal fluid >4.5: The swab for pH evaluation is obtained from the mid-portion of the vaginal side wall to prevent false elevations in pH values as a result of cervical mucus, blood, or semen.
- Gram stain: The gold standard for laboratory diagnosis of BV is the Gram stain. It determines the relative concentration of lactobacilli (long Gram-positive rods), Gram-negative and Gram-variable rods and cocci (*G. vaginalis*, *Prevotella*, *Porphyromonas*, peptostreptococci) and curved Gram-negative rods (Mobiluncus) *in vaginal discharge.* For diagnosis of BV, Nugent's criteria is used which is based on Gram stain assessment (Table 22.1).
- Nugent scoring system was proposed by Robert Nugent in 1991, while evaluating vaginal smears from pregnant women. The scoring system is based on the quantification of three types of bacteria on Gram stain: Lactobacillus, Gardnerella/Bacteroides, and Mobiluncus. The scoring system quantifies a decline in Lactobacillus (score 0–4), a presence of Gardnerella/Bacteroides, (score 0–4), and presence of mobiluncus (score 0–2). A score of 0–10 is calculated after combining the three scores. A score between 0–3 is considered negative for BV, 4–6 is considered indeterminate for bacterial vaginosis, and 7+ is indicative of BV. Nugent's score is rarely used now as it is time consuming and requires a trained microbiologist.
- Culture of *G. vaginalis: Due to lack of specificity, i*t is not recommended as a diagnostic tool.
- Cervical Pap test: This test has low sensitivity and specificity. Thus, it does not have clinical utility for the diagnosis of BV.
- Affirm VP III (Becton Dickinson, Sparks, MD): It is a DNA hybridization probe test to detect high concentrations of *G. vaginalis and Candida species. It has a sensitivity of 90–100% but is not species specific.*
- OSOM BV Blue test (Sekisui Diagnostics, Framingham, MA) detects vaginal fluid sialidase activity, an enzyme produced by Gardnerella, Bacteroides, Prevotella, and Mobiluncus. It has a sensitivity of 92.8% and a specificity of 98% compared with Gram stain.
- Proline aminopeptidase card test: It detects elevated pH and trimethylamine. It has low sensitivity and specificity and therefore is not recommended.
- Polymerase Chain Reaction (PCR) test: It is used in research settings for the detection of a variety of organisms associated with BV, but evaluation of its clinical utility is still under research.

22.4.4 Obstetric Consequences of BV Infection

Polymicrobial BV infection causes vaginitis or cervicitis leading to ascending infection. Infection of the fetal membranes leads to chorio-

amnionitis. There is substantial increased risk for serious complications like:

- Preterm labor—There is a twofold increased risk of preterm labor with associated BV infection. The bacteria lead to release of phospholipase A2 enzymes once fetal membranes are infected. This causes liberation of arachadonic acid from the amnion for conversion to the oxytocic agent prostaglandin E2.
- Spontaneous abortion—Ascending infection leads to inflammatory reactions infection which subsequently leads to miscarriage.
- Premature rupture of membranes.
- Low-birth-weight infants.
- Chorioamnionitis.
- Postpartum endometritis—There may be fever during and after delivery. Sometimes wound infections are seen in pregnant women suffering from BV.
- Bacterial vaginosis is a risk factor for ascending infection and tubal damage. It is associated with increased risk of implantation failure in IVF pregnancies.

22.4.5 Treatment of Bacterial Vaginosis in Pregnancy

22.4.5.1 Rationale for Treatment

Rationale of treatment of BV is to provide relief of symptoms, to avoid recurrence and to prevent adverse pregnancy outcomes. Bacterial vaginosis is polymicrobial nature, therefore treatment and control of recurrence is a more complex processes than those related to diseases caused by a single infectious agent. Therefore it is imperative that all symptomatic pregnant women with bacterial vaginosis should be treated. Benefit of treating asymptomatic pregnant women is still under consideration and needs more research.

22.4.5.2 Antimicrobial Therapy

Recent guidelines from the Centers for Disease Control and Prevention (CDC) recommend that asymptomatic high-risk pregnant women with bacterial vaginosis and symptomatic low-risk pregnant women with bacterial vaginosis should be treated to eliminate their symptoms.

Table 22.2 Treatment for bacterial vaginosis

Oral therapy	Local therapy
Metronidazole 500 mg orally twice a day for 7 days	**Metronidazole** gel 0.75%; 5 g intravaginally once a day for 5 days
Clindamycin 300 mg orally twice daily for 7 days	**Clindamycin** cream 2%; 5 g intravaginally at bedtime for 7 days
	Clindamycin ovules 100 mg intravaginally once at bedtime for 3 days
	Recurrent BV–0.75% metronidazole gel; twice weekly for 4–6 months

Regimens recommended for treatment of symptomatic pregnant women are the same as for non-pregnant women (Table 22.2). They can be treated with either oral or vaginal antibiotic. Oral BV therapy reduces the risk for late miscarriage and decreases the incidence of adverse outcomes in the neonate. Topical antibiotics usually eradicate local bacterial vaginosis infection but do not reduce preterm birth due to lack of access to the upper genital tract. Therefore, systemic antibiotics are preferred to reduce the risk of pregnancy-related complications.

Oral metronidazole and metronidazole combined with erythromycin have been shown to reduce pregnancy complications associated with bacterial vaginosis. Metronidazole is preferably given from mid to late pregnancy. Recurrences can be treated with 0.75% metronidazole gel twice weekly for 4–6 months after completion of treatment. This may be continued post delivery (Table 22.2). Alcohol consumption should be avoided during treatment with nitroimidazoles, to prevent disulfiram-like reaction.

Adverse effect of drugs—Metronidazole crosses the placenta but various cross-sectional and cohort studies in pregnant women have failed to document evidence of teratogenicity or mutagenic effects in infants. Lactobacilli and bifidobacteriae are safe in pregnant women as they are components of the normal vaginal flora and they have been used for a long time in food industry and in douches without harmful effect.

22.4.5.3 Supportive Treatment

Probiotics: Adjunctive use of specific probiotics along with antimicrobial therapy for treatment of BV and other forms of vaginitis has potential benefits to improve treatment outcomes, prevent recurrence, and reestablish healthy vaginal flora. Probiotics have immunomodulating effects and they lead to increase in immunologic activity as well as anti-inflammatory activity.

Probiotics protect vaginal flora by various mechanisms.

- Produce lactic acid and maintain acidic pH of vagina so that the growth of pathogenic organisms is prevented.
- Produce biosurfactants which cover the surface of the vaginal wall thus inhibiting adhesion of pathogens to the vaginal epithelium.
- Produce hydrogen peroxide (H_2O_2) which releases oxygen and has a disinfecting effect.
- Co-aggregation molecules are produced which block the spread of pathogens.

Douching: data does not support the use of douching for treatment or relief of symptoms.

22.4.5.4 Syndromic Approach

World Health Organization has developed guidelines for syndromic management of symptomatic patients of sexually transmitted infections for countries with poor infrastructure and without laboratory support. Based on risk assessment and clinical signs, the women are provided with two or more antibiotic regimens for trichomoniasis, BV, chlamydia, gonorrhea, and candidiasis. World Health Organization does not recommend any syndromic management of asymptomatic pregnant women.

22.4.5.5 Test of Cure

Relief from symptoms is important for assessment of cure. According to US FDA, cure is defined as the absence of all four Amsel's signs and a Nugent score of less than 4 as a test-of-cure at visit 21–30 days after the first day of treatment.

22.4.6 Screening for BV in Pregnancy

Routine screening for BV in asymptomatic pregnant women is not recommended.

The US Preventive Services Task Force 2008 does not recommend routine screening for BV in pregnancy due to lack of sufficient evidence. It states that etiology of preterm labor is multifactorial.

The American College of Obstetricians and Gynecologists (2012) suggests that testing for bacterial vaginosis in asymptomatic women does not reflect any improved perinatal outcomes. Therefore, routine testing is not recommended.

The American Academy of Family Physicians endorses the 2008 USPSTF recommendation on screening for bacterial vaginosis.

NICE guidelines 2016 also support no routine screening for BV in asymptomatic pregnant women (Table 22.3).

22.5 Trichomoniasis

Trichomonas vaginalis (TV) infection is of public health concern due to its high prevalence and association with other sexually transmitted infections (STI). It is associated with an increased risk of infection with gonorrhea, human papillomavirus (HPV), herpes simplex virus (HSV), and HIV.

Table 22.3 Recommendations for BV screening in pregnancy

Organization	Recommendations for Screening of BV in Pregnancy
US Preventive Services Task Force 2008	Not Recommended
ACOG (2012)	Not Recommended
AAFP	Not Recommended
NICE (2016)	Not Recommended
CDC (2015)	Screening in asymptomatic pregnant women irrespective of their risk status not recommended; Evaluate and treat symptomatic pregnant women

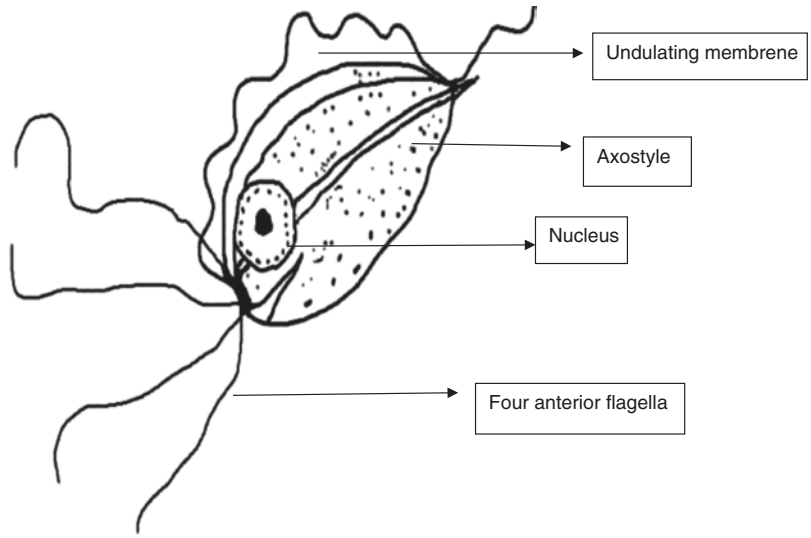

Fig. 22.2 Diagrammatic representation of *T. vaginalis*

22.5.1 Pathophysiology

T. vaginalis is an anaerobic, parasitic protozoan. It is a flagellated organism which adheres to epithelial cells of the urogenital tract. Humans are the only natural host of *T. vaginalis and infection with T. vaginilis* is known as trichomoniasis.

T. vaginalis are pyriform or amoeboid shaped and are 9 by 7 μm in size. They are nondividing organisms and have four anterior flagella (Fig. 22.2). *T. vaginalis* trophozoite is transmitted through coitus and no cyst form is known. The trophozoite divides by binary fission and reproduces in the lumen and on the mucosal surfaces of the urogenital tract. Although survival on fomites is documented, the organism is thought to be transmitted almost exclusively by sexual activity. The incubation period of this infection is 4–28 days. These organisms can be found in the vagina, cervix, bladder, and Bartholin, Skene, or periurethral glands.

22.5.2 Clinical Manifestations

Approximately 50% women with *T. vaginalis* are asymptomatic. Various symptoms seen are as follows:

- Vaginal discharge
- Genital pruritus and irritation
- Dysuria
- Pain in the lower abdomen
- Postcoital bleeding as a result of cervicitis caused by *T. vaginalis* or other associated pathogens.

On clinical examination:

- Vaginal discharge with malodor—The discharge is typically described as frothy, but only in 10% of the cases it is actually frothy (Fig. 22.3). The discharge does not have any specific color.
- Erythema of the vagina which appears red and inflamed.
- Strawberry spots on vagina and cervix—Colpitis macularis (strawberry cervix) is a specific clinical sign for this infection (Fig. 22.4).
- A small number of patients with trichomoniasis may be present with regional lymphadenopathy.

The relative concentration of *T. vaginalis* organisms present in the vagina, the hormonal levels, and the severity of the symptoms are

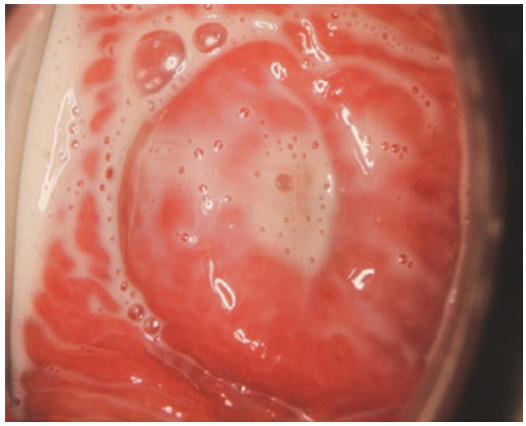

Fig. 22.3 Vaginal frothy discharge typical of TV infection *T. vaginalis*

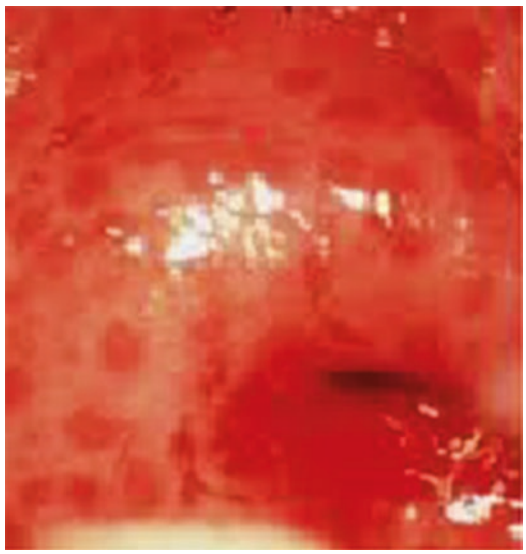

Fig. 22.4 Strawberry spots on the cervix on cervix

important in deciding the extent of the inflammatory response.

22.5.3 Laboratory Diagnosis

Wet mount examination of vaginal discharge—Microscopic visualization of the motile parasite in vaginal discharge is seen on wet mount examination. It has a sensitivity of up to 65%. For accurate diagnosis, samples should be examined within 10 min of collection.

Culture of vaginal discharge: It has high specificity (almost 100%) but low sensitivity (75%) for diagnosis. Culture of *T. vaginalis* has a higher sensitivity compared with microscopy; however, 5 days are required for the result.

Culture examination should be advised and performed in the following circumstances:

- Patients with a negative wet mount test
- History of trichomoniasis with persistent symptoms even after treatment
- High vaginal pH and presence of leukocytes on microscopy
- Pap test showing presence of trichomonas
- Patient's desire for trichomonas screening because of a possible exposure

Papanicolaou screening test: Organisms can be detected by Pap test but this has low sensitivity.

Immunoassay dipstick testing: It is a rapid antigen test and results are available in 10 min. The test has a high sensitivity (82–95%) and specificity (97–100%).

NAAT (Nucleic acid Amplification test): NAAT is the most sensitive test to diagnose *T. vaginalis*. The test has a sensitivity and specificity of 95–100%. The nucleic acid amplification tests like PCR or transcription-mediated amplification (TMA) are more sensitive than nonamplified tests. Earlier culture was the "gold standard," but due to its high sensitivity, NAAT is considered as the test of choice for the diagnosis of TV. The test can detect TV using vaginal/cervical/urine sample. Vaginal swabs are taken from posterior vaginal fornix at the time of speculum examination. Both self-sampling and clinician-taken samples produce similar results. New FDA-approved TMA assay (APTIMA, GenProbe, San Diego) are available commercially.

22.5.4 Obstetric Consequences of *T. vaginalis* Infection

1. Preterm delivery*:* TV infection is involved in the pathogenesis of preterm labor though the precise mechanism remains unknown.

2. Premature rupture of membranes: It is proposed that the *T. vaginalis* infection and the host inflammatory response may reduce chorioamnionic membrane strength. This can cause premature rupture of membranes leading to preterm birth.
3. Low-birth-weight infants: The association of TV with low-birth-weight (LBW) infants is based on the study conducted by the National Institute of Health in 1980. This landmark study evaluated more than 13,000 racially and ethnically diverse pregnant women to find out the role of TV, an inhabitant of the vagina and its role in adverse pregnancy outcomes. The study documented a 30% increase in low-birth-weight (LBW) infants and 30% increase in preterm birth with *T. vaginalis* infection
4. Postpartum endometritis: Approximately 16% cases of postpartum endometritis are associated with *T. vaginalis*.
5. Neonatal vaginal infections: 2–17% of female infants born to infected mothers have evidence of vaginal infection. These infections are usually asymptomatic but some cases may present with vaginal discharge.

22.5.5 Neonatal *T. vaginalis* Infection

The first case of newborn TV infection was reported by Trussell et al. in 1942. Transmission can occur by direct vulvovaginal contamination during vaginal delivery or by ingestion of maternal secretions during birth. The neonatal vaginal epithelium undergoes maturation under the influence of maternal estrogen and is susceptible to *T. vaginalis* infection. Maternal estrogen transferred to the newborn circulation gets metabolized by 3–4 weeks of age, and the vaginal epithelium returns to a prepubescent state that is relatively resistant to *T. vaginalis*. The exact prevalence of infection in the newborn is unknown. The infection is usually asymptomatic but a few newborns may develop vaginal discharge. The newborn may present with irritability, cloudy-white vaginal discharge, fever, urinary tract infection, and even respiratory distress.

22.5.6 Treatment

It is recommended that symptomatic pregnant women should be tested and treated irrespective of the duration of pregnancy. Treatment is necessary not only in symptomatic patients but in all cases where testing reveals infection. Treatment of symptomatic trichomoniasis with oral metronidazole is essential for the prevention of preterm births (Grade I-A recommendation). Appropriate and timely treatment not only reduces the symptoms of vaginal discharge in pregnant women but also reduces sexual transmission to partners and respiratory/genital colonization of the newborn.

22.5.6.1 Antimicrobial Therapy

Metronidazole is the treatment of choice. The recommended dose of metronidazole in pregnancy is the same as for non-pregnant women. Cure rates of approximately 88% are documented with these regimens. Simultaneous treatment of sexual partners results in even higher cure rates.

During the first trimester of pregnancy, symptomatic women are treated with local vaginal administration of clotrimazole twice a day for 1 week. In the second and third trimester, oral metronidazole either 2 g as a single dose or 500 mg twice daily for 7 days is recommended.

Test of cure following treatment is not recommended (Grade I-D recommendation). Metronidazole gel has a lower efficacy as compared to oral metronidazole because it does not reach therapeutic levels in the urethra and perivaginal glands. Side effects of metronidazole after oral dosage include nausea, vomiting, headache, insomnia, dizziness, drowsiness, rash, dry mouth, and metallic taste (Table 22.4).

Table 22.4 Treatment for *Trichomonas vaginalis* in pregnancy

	Recommended treatment
First trimester	Vaginal application of Clotrimazole cream 2% or Clotrimazole vaginal pessary 1 HS for 6 days
Second and Third trimester	Oral metronidazole 2 g as a single dose or Oral metronidazole 500 mg twice daily for 7 days

22.5.6.2 Douching

It is not advocated as it exacerbates symptoms.

22.5.6.3 Syndromic Treatment

World Health Organization developed syndromic management guidelines for symptomatic patients of sexually transmitted infections for countries with poor infrastructure and without laboratory support. Syndromic management of *T. vaginalis* infection is the same as discussed for bacterial vaginosis.

22.5.6.4 Treatment of Partner

The PHAC 2010 guidelines on STI do not recommend screening of partner but do recommend treatment for all partners. Both the patient and her partner should be given the same type of treatment regimen. The 2010 Centers for Disease Control STI Guidelines suggest abstaining from intercourse until complete treatment of both partners.

22.5.6.5 Treatment in Breastfeeding Women

The recommended treatment of breastfeeding mother is metronidazole 400 mg three times daily for 7 days. Metronidazole crosses the placenta but data suggests that only a small concentration of the drug has been found in the breast milk. Therefore, it can be given safely for longer durations. No evidence of adverse effects in infants exposed to metronidazole has been reported in the various case series reported till date. Metronidazole may affect the taste of breast milk. The manufacturers recommend avoiding high doses in breastfeeding women, and if using a single dose of metronidazole, breastfeeding should be discontinued for 12–24 h to reduce infant exposure.

Though tinidazole has many advantages over metronidazole it should be avoided in pregnant women and breastfeeding should be deferred for 72 h as data regarding its use is limited. However animal data suggest this drug has moderate risk to the fetus.

22.5.7 Follow-Up

Follow-up after treatment is done by assessment of relief of symptoms. Repeat testing is advised only if the patient remains symptomatic after treatment. In case of recurrence, clinician should confirm whether the woman and her partner have taken treatment completely.

22.5.8 Screening and Prevention

Routine screening for *T. vaginalis* in asymptomatic pregnant women or in women with history of PROM and preterm labor is not recommended due to lack of any proven benefit.

Screening and prompt treatment is recommended in pregnant women with HIV infection at first antenatal visit because *T. vaginalis* infection is an important risk factor for vertical transmission of HIV.

22.6 Vulvovaginal Candidiasis

Vulvovaginal candidiasis (VVC) is the second most common cause of vaginitis worldwide, after bacterial vaginosis. VVC affects approximately 30–50% of women at least once during their lifetime. Candidal infection occurs more frequently during pregnancy. Management of VVC includes prevention, early diagnosis, and prompt treatment, especially among risk groups to prevent complications.

22.6.1 Risk Factors

22.6.1.1 Host Related Factors

- Pregnancy—candidal vulvovaginitis affects at least 50% of pregnant women. The risk for developing candida vulvovaginitis increases with period of gestation and gravidity of the woman.
- Antibiotic or corticosteroid therapy—Due to repeated antibiotic treatment, there is a

reduction in protective bacterial vaginal flora and increase in opportunistic organisms.
- Diabetes
- Hormone replacement therapy—Impairs host immune response and increase in candidal adhesion to vaginal mucosa
- Obesity
- HIV infection
- Genetic predispositions

22.6.1.2 Behavioral Risk Factors
- Use of oral contraceptives
- Intrauterine contraceptive device
- Spermicides and condoms: They lead to disturbances in vaginal microbiota
- Habits of hygiene: An increase in blastopore load in vaginal environment in poor hygiene has been seen
- Clothing and sexual practices: Moisture triggers candida invasion in epithelial tissue.

22.6.2 Classification of Vulvovaginal Candidiasis

VVC is classified on the basis of severity as uncomplicated, complicated VVC, and recurrent VVC.

22.6.2.1 Uncomplicated VVC
Features of uncomplicated VVC are as follows:

- Episodes on infection are infrequent and sporadic
- Mild to moderate symptoms or findings
- Suspected *Candida albicans* infection
- Nonpregnant woman without medical complications

22.6.2.2 Complicated VVC
- Recurrent episodes
- Presence of severe symptoms or findings
- Suspected or proved non-albicans Candida infection
- Women with diabetes, severe medical illness, immunosuppression
- Pregnancy

22.6.2.3 Recurrent VVC (RVCC)
RVVC is defined as four or more episodes of complicated VVC infections per year. RVVC has been seen to first present during pregnancy in a large proportion of women. Pregnancy is an important risk factor for the development of VVC and many studies have documented an increased incidence ranging between 0% and 76.0% of acquiring VVC during pregnancy. Contributing factors for increased prevalence of VVC during pregnancy are as follows:

- High progesterone and estrogen levels—The increased levels of sex hormone secretions in pregnancy is responsible for high incidence of VVC in pregnancy is attributed to. The prevalence of VVC is maximum in the last trimester, when the level of hormones is at its peak. Estrogen and progesterone levels are increased up to 30 times that of non-pregnant values. Of the two hormones, in-vitro studies have shown no role of progesterone in induction and persistence of vaginal infection. Estrogen is the dominant reproductive hormone that has been seen to sustain experimental *C. albicans* infection in the vagina. *C. albicans*, *C. guilliermondii*, *C. krusei*, *C. parapsilosis,* and *C. tropicalis* have a corticosteroid-binding protein (CBP) which has high affinity for corticosterone and progesterone, but low affinity for estrogens.
- The production of glycogen by hormone stimulated epithelium possibly contributes to the proliferation of candida species and increased adhesion and hyphae formation. Increased glycogen content also provides an excellent nutritional source of carbon for candidal growth.
- The acidic environment of the vagina with a pH value of <5 enhances adherence of yeast cells to the vaginal mucosa.
- Immunosuppression during pregnancy results in suppression of the protective resident bacteria. The decreased vaginal immune response enhances the growth of fungi and decreases.
- Eating habits of sugar-rich food during pregnancy and emotional stress contribute to the development of VVC.

22.6.3 Pathophysiology

Candida is found in two states.

1. Blastopores: They are resistant form of fungus and associated with symptomless colonization.
2. Mycelia: These are the germinative forms which can invade tissue and cause symptoms.

Candida albicans is responsible for at least 80% of candida vulvovaginitis cases. Non-albicans candida infections like Candida tropicalis, Candida glabrata, and Candida parapsilosis are now becoming more common causes of vulvovaginal infection. The development of VVC is usually as a result of disturbance in the balance between candida vaginal colonization and host environment by physiological or nonphysiological changes (Fig. 22.5).

22.6.4 Clinical Manifestations

Symptoms of candidiasis may be more severe during late gestation. Women are often asymptomatic early in pregnancy and if the infection is caused by non-albicans candida.

In VVC, following symptoms are seen:

- Discharge per vaginum—The discharge is specifically thick, cotton cheese like, curdy white
- Burning and soreness of vagina
- External dysuria (33%)
- Vulvar pruritus (27%)
- Dyspareunia

22.6.5 Diagnosis

22.6.5.1 Clinical Diagnosis

Evaluation of a woman with vaginitis should include a detailed history regarding the site of

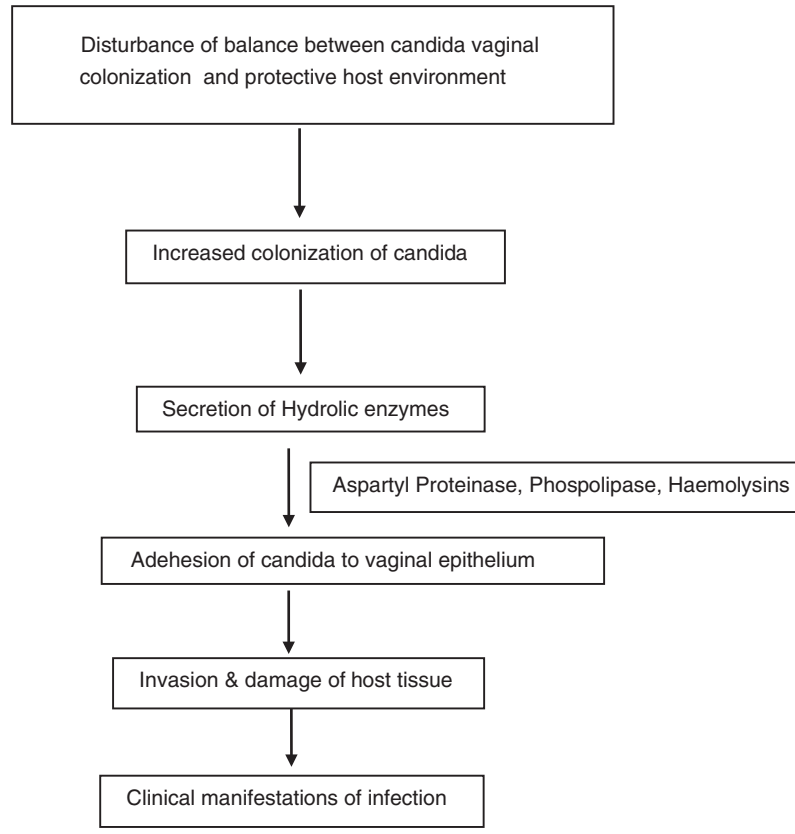

Fig. 22.5 Pathogenesis of Candida infection

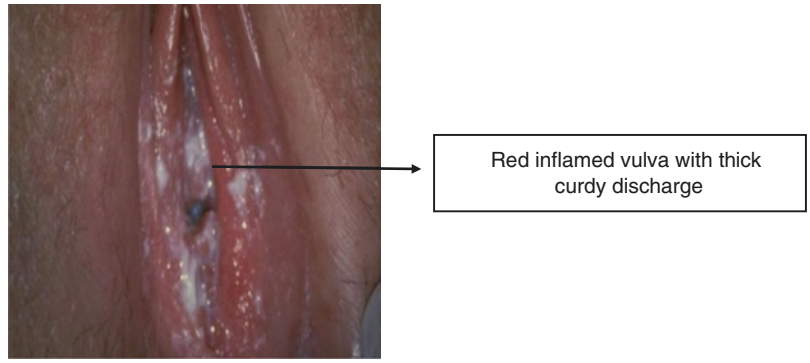

Fig. 22.6 Vulvitis with candidal discharge

symptoms (vulva, vagina, anus), duration, history of self treatment, douching, and sexual history.

The clinical examination should begin with a thorough examination of the vulva and any erythema or discharge should be noted. This is followed by a per speculum examination and a red inflamed vagina with thick, curdy white discharge can be seen (Fig. 22.6).

22.6.5.2 Laboratory Diagnosis

- Vaginal secretions pH < 4.5.
- Whiff test is negative.
- Wet mount examination or 10% KOH microscopy: Budding yeast, blastospore, and pseudohyphae are seen in vaginal secretions (Fig. 22.7). Microscopy is used commonly in clinical practice and its sensitivity to detect yeast is around 50%.
- Gram stain: It reveals polymorphonuclear cells, budding yeast, and pseudohyphae.
- Culture examination is positive—Culture is advised in the presence of complicated VVC (as there is an increased likelihood of non-albicans strains), symptomatic women with negative microscopy and in high-risk groups.

As culture examination for yeast can pick up small number of organisms, it is considered the gold standard for diagnosis.

22.6.6 Obstetric Consequences of VVC

Usually symptomatic vulvovaginal candidiasis (VVC) occurs during the second and third trimester of pregnancy. Candidiasis in pregnancy is associated with increased risk of pregnancy complications including

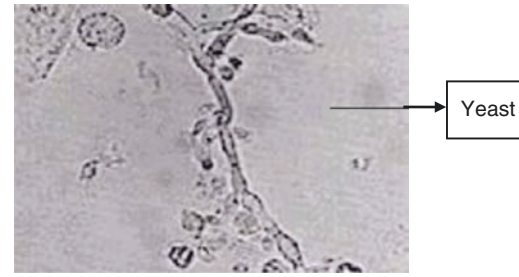

Fig. 22.7 Microscopy of candidal infection

- Premature rupture of membranes.
- Preterm labor.
- Chorioamnionitis.

22.6.7 Neonatal Complications

- Congenital cutaneous candidiasis.
- Low birth weight (LBW) and prematurity.
- Neonatal septicemia: Most commonly produced by *C. dubliniensis infection* in premature infants with LBW and is associated with increased mortality.
- Oral thrush: If the disease is not treated completely in pregnancy, oral thrush is seen in neonates delivered vaginally. It is a serious health problem in premature babies. Infants with oral thrush can give rise to nipple candidiasis in breastfeeding mothers.

22.6.8 Treatment

Prompt diagnosis and early institution of treatment in pregnant patients is essential to avoid complications in the mother and neonate. While prescribing antifungal therapy in pregnancy, consideration should be given to the benefit for the mother versus the risk to the fetus.

The topical formulations of Azole antifungals (imidazole and triazole) are therapy of choice during pregnancy.

22.6.8.1 Principles of Treatment

1. Avoid oral antifungals

   Oral fluconazole may increase the risk of tetralogy of Fallot in the fetus and therefore should be avoided in pregnancy. Oral Flucanazole in single dose of 150 mg is not known to cause serious side effects and can be used as a second line of therapy in late trimester in women not responding to topical therapy. The safety profile of oral fluconazole in the second and third trimester of pregnancy has not been investigated. Case reports suggest that increasing the dose of fluconazole from 400 mg to 800 mg/day has been associated with major malformations. Fluconazole is considered safe in breastfeeding women.
2. Use of topical antifungals is preferred in any trimester of pregnancy

   The systemic absorption of topical antifungals is very minimal, therefore there is very little risk of transfer to the fetus.
3. Longer course of therapy is advocated in pregnancy

   Affection during pregnancy is associated with more severe symptoms and also results in a prolonged course of the disease. Thus, a longer course of treatment is required for resolution of symptoms. A 7-day course of intravaginal therapy is advised to improve success rate. Cases of severe symptoms and long-lasting infection may require external imidazole creams and intravaginal ovules for up to 14 days. Those affected with complicated vulvovaginal candidiasis should receive a more aggressive treatment in pregnancy.
4. Safe and effective azole is used for VVC treatment in pregnancy

Due to the uncertainities regarding fetal toxicity and altered maternal pharmacokinetic parameters which may affect efficacy, the choice of antifungal agent remains a challenge in pregnant women.

During pregnancy, imidazoles are considered safe as topical therapy. Nystatin is minimally absorbed and is effective for vaginal therapy. Azoles and Nystatin are fungistatic drugs. The most experienced systemic antifungal drug in pregnancy is Amphotericin B. It does not have any teratogenic effects. Ketoconazole, flucytosine, and griseofulvin have been shown to be teratogenic and embryotoxic and are not to be used.

22.6.8.2 Antifungal Therapy

Various regimens have been discussed in detail in Chap. 25. The Syndromic Approach to management of BV, Trichomoniasis, and VVC in Pregnancy is shown in Fig. 22.8.

The common recommended regimes include:

- Clotrimazole
  - 1% cream 5 g daily for 7 days
  - 100 mg vaginal suppository 100 mg daily for 7 days
  - 200 mg vaginal suppository 200 mg daily for 3 days
- Miconazole
  - Miconazole ointment 5 g daily for 7 days
  - Miconazole nitrate 2% cream daily for 7 days
  - 100 mg vaginal suppository 100 mg daily for 7 days

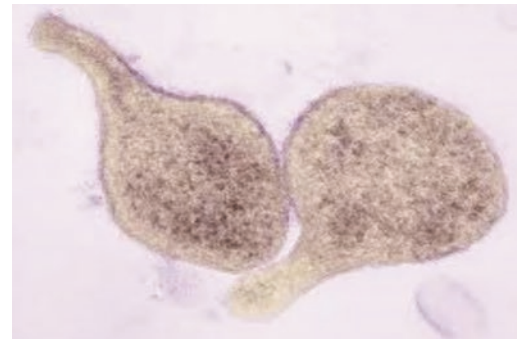

Fig. 22.8 Mycoplasma on culture examination

  - 200-mg vaginal suppository 200 mg daily for 3 days
- Nystatin 100,000 units vaginal tablets daily for 14 days.
- Complicated VVC—Clotrimazole cream/ointment 1%once daily for 10–14 days.

22.6.8.3 Use of Boric Acid

It should be avoided during pregnancy as intravaginal application of boric acid has been associated with a two-fold increase risk of birth defects when used during the first 4 months of pregnancy.

22.6.8.4 Douching

Douching is not used as it exacerbates symptoms.

22.6.8.5 Alternative Therapy

Bee Honey and Yogurt are used as complementary therapy for VVC in pregnancy. They are a rich source of Lactobacilli which demonstrate antibacterial activity.

22.6.9 Prevention and Screening

Screening for VVC and eradication of infection by treatment with clotrimazole during pregnancy reduce the risk of preterm delivery and other maternal and fetal complications.

22.7 Mycoplasma and Ureaplasma Infection

Ureaplasma urealyticum and *Mycoplasma hominis* belong to the *Mycoplasmataceae* family, which are characterized by limited biosynthetic abilities. They are commonly referred to as "Genital mycoplasma or Mycoplasma genitalium" as they are found in the urogenital tract of men and women. These organisms are attributed as a causative factor for cervicitis. Both Mycoplasma hominis and Ureaplasma urealyticum (MH and UU) are generally considered together because most of the literature and research related to these organisms has been developed together.

22.7.1 Pathogenesis

Mycoplasma is an intracellular parasite which lacks a cell wall and is covered with trilayered external membrane. It is a self-replicating microorganism which has a minute sized genomic structure. Out of 14 human species, three are pathogenic, i.e. *Mycoplasma hominis*, *M. genitalium*, and *M. pneumoniae*. *M. hominis* is a marker of sexual activity. It is more commonly seen in cervicovaginal cultures of sexually active women.

Ureaplasma is thought of as a more virulent organism. Based mainly on genome size, ureaplasmas comprise two distinct species as follows:

1. *Ureaplasma urealyticum* (formerly *U. urealyticum* biovar 2)
2. *Ureaplasma parvum* (formerly *U. urealytica* biovar 1)

The important steps in pathogenesis include:

Adhesion to host cells: The presence of mycoplasmal membrane adhesion protein or lipoprotein plays an important role in adhesion to host cells. The adherence of mycoplasma to host cells is a prerequisite for pathogenicity.

Host cell injury: After adhesion, the mycoplasma metabolites lead to cell injury and interfere with host metabolism.

Secretion of pro-inflammatory substances: Mycoplasmas activate macrophages and monocytes leading to secretion of major pro-inflammatory cytokines, tumor necrosis factor-a, interleukins (IL-1, IL-1b, IL-6, IL-8, IL-12, IL-16), and interferon. Both systemic inflammatory response and local inflammation are equally important in leading to abnormal pregnancy outcomes. Bacterial endotoxins and mycoplasma membrane lipoproteins also activate fetal membranes and decidua to produce cytokines.

Synthesis and release of prostaglandins: Endotoxins and cytokines stimulate release of prostaglandins which leads to synthesis of prote-

ase enzymes which subsequently lead to adverse pregnancy outcomes.

22.7.2 Clinical Manifestations

Most of the women are asymptomatic. Others may present with abnormal vaginal discharge, dyspareunia, post-coital bleeding, and pelvic pain. Mycoplasma infection increases the susceptibility to HIV infection.

22.7.3 Diagnosis

1. Detection of antimycoplasma antibodies: Diagnosis of mycoplasma infection of genital tract is confirmed by presence of antimycoplasma antibodies in women with intra-amniotic infection and postpartum fevers.
2. Molecular detection methods: Polymerase chain reaction has a high specificity. It is commonly used to detect the presence of these organisms.
3. Culture examination.

   Vaginal swabs are taken and sent for culture examination. Culture plates with specific culture medium is used for growth of *Ureaplasma* spp. and *M. hominis* (Mycoplasma agar).

22.7.4 Obstetric Consequences of Mycoplasma Infection

- Ectopic pregnancy: Previous PID due to mycoplasma or ureaplasma infection can cause damage to the fallopian tubes and lead to increased chances of an ectopic pregnancy.
- Abortion: Ureaplasma infection increases risk of late miscarriage in second trimester. Mycoplasma hominis can cause midtrimester abortions especially in the presence of abnormal vaginal flora.
- Preterm labor: Colonization of placenta with Ureaplasma urealyticum causes fetal and maternal inflammation and increases risk of preterm labor. Prostaglandins especially PGF2-alpha is increased in the amniotic fluid which leads to uterine contractions. Involvement of amnion evokes a greater intra-amniotic inflammatory response as compared to chorionitis.
- Chorioamnionitis: Ascending infection from lower genital tract penetrates amniotic cavity and causes fetal infection. Positive culture is seen in 32% of women presenting with PPROM. Detection of Ureaplasma spp. in the placenta is an independent risk factor for development of chorioamnionitis in deliveries <32 weeks of gestation.
- Postabortal salpingitis: This has been associated with *M. genitalium* colonization.
- Postabortal or postpartum fever: There is evidence, though less robust, that ureaplasmas cause postpartum or postabortal fever.
- Postpartum endometritis.

22.7.5 Neonatal Infection

Infant colonization results due to contact with an infected cervix and vagina during birth. Therefore, the incidence of colonization of infants delivered by cesarean section is less. In-utero infection with *M. hominis* and/or ureaplasmas is more common following rupture of membranes rather than with intact membranes.

- Congenital neonatal infection—The incidence of congenital fetal infection is more than it was previously recognized. One of every four preterm neonates of 23–32 weeks of gestation is born with bacteremia, which is frequently caused by mycoplasmas and ureaplasma. Vertical transmission of infection is uncommon with only one case reported in literature till now.
- Neonatal meningitis and septicemia.
- Bronchopulmonary dysplasia in neonates: Premature infant at the time of birth may be exposed to abnormal bacterial population.

This may lead to development of bronchopulmonary dysplasia. Currently available new techniques indicate that Ureaplasma parvum which now can be distinguished from U. urealyticum poses an increased risk for preterm birth and bronchopulmonary disease in the preterm neonate.
- Fetal respiratory distress syndrome.
- Intraventricular hemorrhage.

22.7.6 Treatment

Antibiotics are used to treat women with preterm prelabor rupture of membranes. Antibiotic treatment reduces the risks of maternal and neonatal infection, prolongs the pregnancy, and also improves neonatal outcome by limiting intra-amniotic bacterial load and subsequent reduction in the fetal inflammatory response.

22.7.6.1 Antibiotic Therapy

Mycoplasmas and ureaplasma have a trilayered external membrane, rather than a rigid cell wall. This makes them resistant to β lactam antibiotics. Clindamycin is active against *M. hominis* and is preferred for treatment during pregnancy. Use of clindamycin results in a significant reduction in the incidence of preterm delivery and LBW infants.

Clindamycin in combination with clarithromycin (which is highly active against ureaplasma) can be used. Antibiotics without evaluation of the vaginal microbial flora should not be used in pregnancy. Maternal postpartum or postabortal fever due to *M. hominis* and/or ureaplasma generally settles without treatment. If the fever is severe or persistent, administration of broad spectrum antibiotics as per the report of blood culture is given. The failure of treatment to prevent preterm labor is seen sometimes because of association between bacterial vaginosis (BV) and genital mycoplasmas.

22.7.7 Screening and Prevention

There are no recommendations for screening and treatment for *M. genitalium* for asymptomatic infection in pregnancy. But screening of symptomatic pregnant women is recommended in whom an adverse pregnancy outcome is suspected. They may be evaluated for presence of these organisms and administration of prompt treatment in case the screen is positive.

22.7.8 Conclusion

Vaginitis is a common reproductive tract infection which has a negative impact on pregnancy. The common causes of vaginitis include bacterial vaginosis, vulvovaginal candidiasis, and trichomoniasis. Bacterial vaginosis is a polymicrobial infection, diagnosed by Amsel's criteria and treated with oral/topical metronidazole or clindamycin. Trichomoniasis is a sexually transmitted disease, treated by oral/topical metronidazole. Both these infections lead to increased incidence of preterm labor, premature rupture of membranes, low-birth-weight infants, and postpartum endometritis. Vulvuvaginal candidiasis is caused by candida spp. Apart from the above complications, it also causes oral thrush, congenital cutaneous candidiasis, and neonatal sepsis. It is treated with oral or topical antifungals. Syndromic approach for vaginitis due to *T. vaginalis*, Candidia, and bacterial vaginosis is recommended by WHO in low resourse settings. It includes treatment with single dose therapies of broad spectrum antibiotics.

22.8 Syndromic Approach to Management of BV, Trichomoniasis, and VVC in Pregnancy (Fig. 22.9)

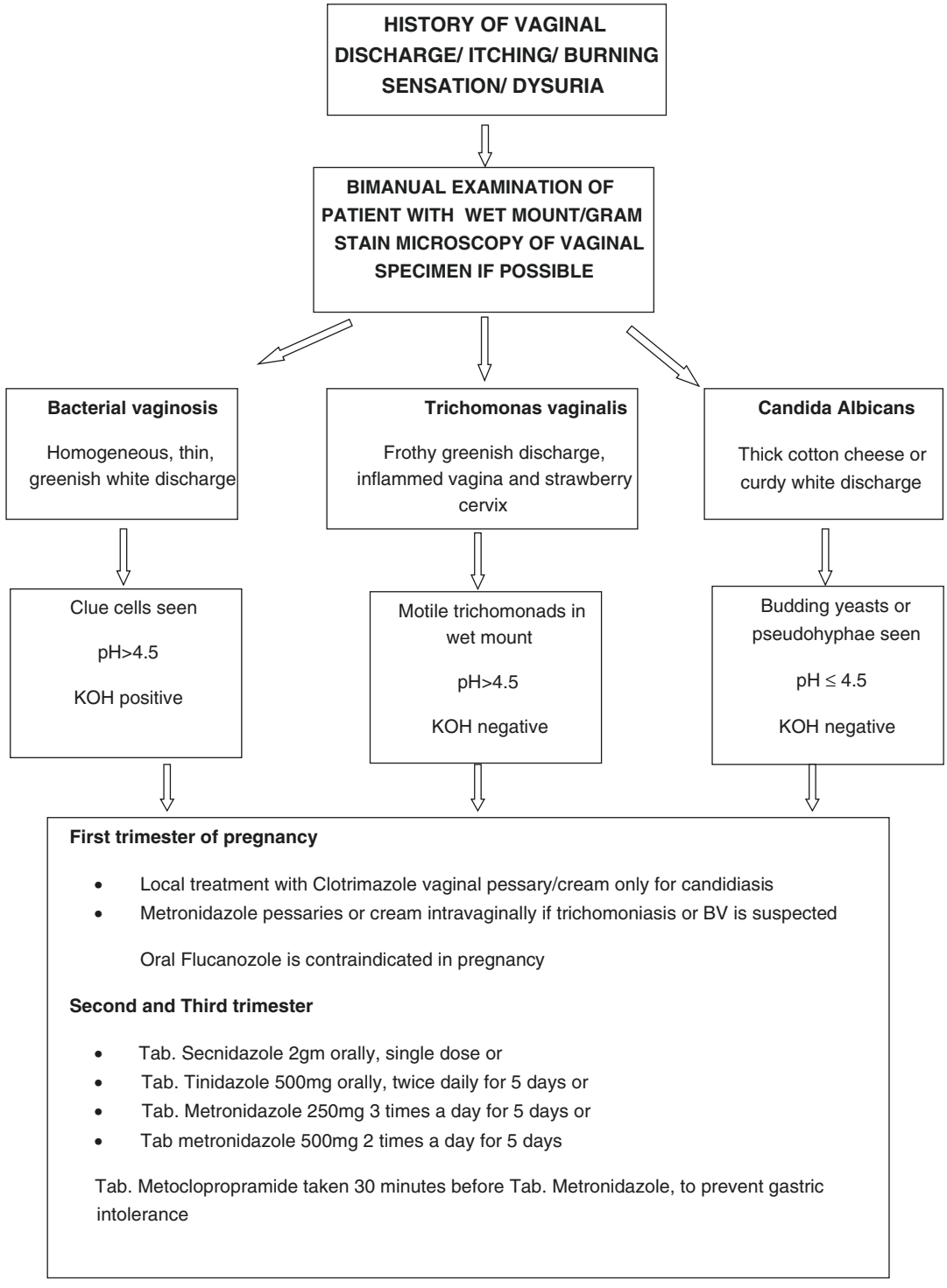

Fig. 22.9 Syndromic approach (guidelines for the management of sexually transmitted infections, WHO/HIV_AIDS/2001.01 WHO/RHR/01.10)

Key Points

- Vaginal infections have a negative impact on pregnancy outcome and are associated with increased incidence of perinatal and neonatal morbidity.
- Contributing factors for increased prevalence of vulvovaginal infections during pregnancy include low immunity status, hormonal changes, alteration in vaginal microbiome, increase in glycogen storage in vaginal cells, and excess moisture.
- Bacterial vaginosis, vulvovaginal candidiasis, and trichomoniasis are the most common causes of vaginitis.
- Bacterial vaginosis (BV) is a polymicrobial vaginal infection characterized by a shift in normal vaginal flora from predominantly aerobic to anaerobic. The Amsel's criteria is used for diagnosis of BV.
- The treatment of choice for BV is oral/topical metronidazole or clindamycin.
- *Trichomonal vaginitis* is a sexually transmitted disease caused by *T. vaginalis*, a flagellated anaerobic parasitic protozoan. It is characterized by greenish frothy discharge and strawberry cervix.
- TV is treated with topical clotrimazole in the first trimester. In the second and third trimester of pregnancy, oral metronidazole is used as the treatment of choice.
- Both BV and TV lead to increased incidence of preterm labor, premature rupture of membranes, low-birth-weight infants, and postpartum endometritis.
- Vulvovaginal candidiasis (VVC) is the second most common cause of vaginitis, after BV.
- Candida albicans is responsible for 80% of candida vulvovaginitis cases. Rest 20% cases are caused by non-albicans candida, like Candida tropicalis, Candida glabrata, and Candida parapsilosis.
- VVC is classified on the basis of severity as uncomplicated, complicated VVC, and recurrent VVC.
- Ureaplasma urealyticum and Mycoplasma hominis commonly cause cervicitis. They are implicated as a cause of ectopic gestation, abortion, preterm labor, and postpartum endometritis.
- Clindamycin is preferred for treatment for mycoplasma hominis infection during pregnancy.

  Clindamycin in combination with clarithromycin is recommended for use in pregnancy for ureaplasma infection.

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Part VII

Other Important Infections

Group B Streptococcus Infection

23

Aruna Nigam and Pragati Aggarwal

23.1 Introduction

Streptococcus agalactiae, also known as Group B streptococcus (GBS) is a β-hemolytic Gram-positive streptococci; it is a part of normal vaginal flora and lower gastrointestinal tract in 5–30% of women. It produces zone of hemolysis around the colonies [1] and is both an asymptomatic colonizer and an invasive pathogen. It is a major cause of infection in pregnancy, preterm birth, and neonatal infection. Infection is caused by vertical transmission of bacteria after rupture of membranes or during labor [2]. CDC guidelines for intrapartum antibiotic prophylaxis have reduced incidence of infection by 80% to 0.23 neonates per 1000 live births in 2015 [3].

23.2 Pathogenesis of GBS Infection in Pregnancy

Presence of bacteria as normal flora in vagina and rectum is the main source of infection in pregnancy. The close proximity of vagina and rectum enables accumulation of bacteria into the vagina from the intestine. Vaginal epithelium, mucus, low vaginal pH, antimicrobial peptides, antibodies, microbicidal immune cells, and vaginal microbiome dominated by lactobacilli act as protective factors against GBS infection [4]. This protective environment needs to be overcome by GBS for colonization. Pathogenicity of bacteria depends on host factors and bacterial factors (Table 23.1) [5]. Expression of bacterial factors is regulated by signal transduction system which responds to various host factors.

Table 23.1 Host and bacterial factors regulating GBS infection

Host factors	Bacterial factors
Production of maternal antibodies specific to GBS	Hemolytic pigment
Capsular polysaccharide	Superoxide dismutase
Mucosal immunity (T cells, B cells, neutrophils, macrophages, mast cells)	Cyclic di-AMP/CdnP
Vaginal epithelial exfoliation	HylB
Cervical mucus plug	HvgA
Mast cell chymase	C5a peptidase (ScpB)
Macrophage sialoadhesin	FbsA, FbsB, FbsC

23.2.1 Neonatal GBS Infection

If GBS organism is isolated from blood, cerebrospinal fluid (CSF), or another normally sterile site of neonate from birth through 6 days of age, it is called early-onset GBS infection (EOD GBS) [6].

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Late-onset GBS infection (LOD) is defined as isolation of GBS from a normally sterile site from 7 to 89 days of age [6].

23.3 Burden of Disease

Active Bacterial Core Surveillance (ABCs) conducted in 10 states of United States from 2006 to 2015 revealed that although GBS EOD declined over the years (0.37 cases per 1000 live births in 2006 to 0.23 cases per 1000 live births in 2015) but the GBS LOD incidence remained the same (0.31 cases per 1000 live births). Majority (94.7%) of the GBS EOD occur within 48 h of birth with prevalence of infection in term and very low birth weight baby being 45% and 25%, respectively. Both GBS EOD and LOD showed higher mortality in preterm infants as compared to term infants (19.2% vs 2.1% in GBS EOD and 7.8% vs 3.4% in GBS LOD) [3]. The median age at presentation with GBS LOD was 34 days (inter quartile range: 20–49 days) and bacteremia without focus was the most common form of disease [7].

A study was conducted in 195 countries of all live births in 2015 and it was estimated that 205,000 (uncertainty range [UR], 101,000–327,000) infants had early-onset disease and 114,000 (UR, 44,000–326,000) had late-onset disease, of whom a minimum of 7000 (UR, 0–19,000) presented with neonatal encephalopathy. There were at least 10,000 (UR, 3000–27,000) children with disability each year due to GBS disease. Furthermore, 33,000 (UR, 13,000–52,000) cases of invasive GBS disease in pregnant or postpartum women were seen. Up to 3.5 million preterm births may be attributable to GBS. Importantly, GBS is also a significant cause of death, with 57,000 (UR, 12,000–104,000) stillbirths and 90,000 (UR, 36,000–169,000) infant deaths estimated in 2015. IAP prevented an estimated 3000 (UR, 0–108,000) early neonatal deaths in 2015, mainly in high-income countries. Africa accounted for 54% of estimated cases and 65% of all fetal/infant deaths [8].

23.4 Risk Factors for EOD GBS [3, 7, 9]

1. Maternal vaginal-rectal colonization
2. GBS bacteriuria
3. GBS infection in prior births
4. Gestational age <37 weeks
5. Very low birth weight
6. Prolonged rupture of membranes
7. Intra-amniotic infection
8. Young maternal age
9. Maternal black race.

Maternal vaginal-rectal colonization is also associated with preterm labor [10], leading to delivery of infants at <37 weeks, which itself is risk factor for EOD GBS.

23.5 Clinical Features of GBS Infection

GBS infection is associated with adverse pregnancy outcomes, i.e. preterm prelabor rupture of membrane (PPROM), chorioamnionitis, fetal and neonatal infections (fulminant sepsis, pneumonia, bacteremia, meningitis, respiratory distress syndrome) [1]. Besides this it can also cause bacteriuria, pyelonephritis, osteomyelitis, postpartum mastitis, and puerperal infections.

GBS is the leading cause of neonatal sepsis in India [11, 12]. In neonates, septicemia presents as respiratory distress, fever, apnea, and hypotension. It usually develops within 6–12 h of birth. Late-onset disease caused by GBS usually manifests as meningitis within 1 week to 3 months after birth. The mortality rate, although appreciable, is less for late-onset meningitis than for early-onset sepsis, but neurological sequel can be seen in surviving infants of both early and late-onset disease [13].

23.6 Screening and Diagnosis

Universal screening of GBS colonization and intrapartum antibiotic prophylaxis is recommended to decrease burden of early-onset disease in newborn [14, 15]. RCOG does not recommend universal bacteriological screening for GBS. According to their view, there is no clear evidence to show that testing for GBS routinely would be beneficial [16].

23.6.1 Timing

It was initially described that sample for screening should be taken between 35 and 37 weeks [14]. But according to new recommendations by the American College of Obstetricians and Gynecologists (ACOG) screening should be done between 36 0/7 and 37 6/7. GBS colonization status at birth is most accurately predicted if GBS cultures are done within 5 weeks prior to delivery. Thereafter, the predictive value of these cultures decreases significantly [17]. This is the reason to wait till 36 0/7 weeks as it provides 5-week predictive window for screening culture up to 41 0/7 weeks.

23.6.2 Specimen Collection

A single swab sample from lower vagina (near introitus) and rectum is recommended without using speculum [18]. In lithotomy position, insert the swab stick 2 cm first in lower vagina (near introitus) without using speculum, then preferably from the same swab stick (two individual swabs can also be used) insert 1 cm into anal sphincter. Cervical, perianal, perirectal, or perineal specimens are not recommended as culture yield is very less from these sites [14].

23.6.3 Transportation to Laboratory

Flocked swab should be used to take vaginal-rectal sample. Use of traditional fiber swabs (Dacron, rayon, cotton) does not allow release of microorganisms which reduces sensitivity of test. Transport media used is liquid based non-nutritive medium such as Stuart and Amies transport media with or without charcoal. After taking sample it should be immediately inserted in transport media. It is recommended that sample should be transferred to testing laboratory within 24 h. If for any reason there is delay in transport, sample should be standard for antepartum GBS screening. Although, latex agglutination test or nucleic acid amplification test (NAAT) can also be used to detect GBS from vaginal-rectal samples. Most important step is to refrigerate to 4–8 °C so as to improve the yield [18].

23.7 Diagnosis

Culture-based testing remains standard for antepartum GBS screening, though latex agglutination test or nucleic acid amplification test (NAAT) can also be used to detect GBS from vaginal-rectal samples. Most important step is inoculate all vaginal-rectal swabs into a selective enrichment broth media and incubate for 18–24 h at 35–37 °C in ambient or 5% CO_2 conditions. When this is followed by NAAT it has shown increased sensitivity as compared to culture-based testing alone [19]. However, NAAT does not isolate bacteria so if the patient has known penicillin allergy, it should be mentioned in requisition form so that microbiologist can order culture-based testing to perform antibiotic susceptibility testing [17]. NAAT based method for GBS detection can also be used in a patient who has presented in labor without antepartum GBS screening test results, as a rapid screening test. It can be done in 1–2 h; however, this short time does not allow incubation with enrichment broth media which is necessary for maximizing sensitivity of test. Therefore, rapid testing with NAAT has reported failure rate of 7–10% [20]. Due to this, the American Society of Microbiology [18] does not recommend the use of NAAT without enrichment broth to rule out need for intrapartum GBS prophylaxis. Although, according to ACOG [15] it can be used in labor as it provides rapid results, however it cannot replace routine prenatal screening at 36 0/7–37 6/7 weeks of gestation.

23.8 Intrapartum Antibiotic Prophylaxis (IAP)

Universal screening of pregnant women with vaginal-rectal culture is recommended. Exceptions to this are [15]:

1. GBS bacteriuria identified at any time in current pregnancy
2. Pregnant women who have previously given birth to neonate with GBS EOD
3. Negative GBS culture in current pregnancy at 36 0/7 weeks of gestation or more
4. Prelabor cesarean section performed on women with intact membrane, regardless of GBS colonization status or gestational age
5. Negative vaginal-rectal culture at 36 0/7 weeks of gestation or more, regardless of any risk factors
6. Unknown GBS status at onset of labor, NAAT result negative, and absence of any risk factors (Table 23.2).

Table 23.2 Indications of intrapartum antibiotic prophylaxis [15]

During antepartum period, presence of any of these risk factors: 1. Previous history of neonatal GBS EOD 2. Positive GBS culture in current pregnancy at 36 0/7 weeks of gestation or more 3. GBS bacteriuria during anytime in current pregnancy.
During Intrapartum Period Unknown GBS colonization status or result awaited and presence of any of the risk factors: 1. Birth <37 weeks of gestation 2. Rupture of amniotic membranes >18 h 3. Intrapartum temperature >100.4 °F (38.0 °C) or higher[a] 4. Intrapartum NAAT result positive for GBS 5. Intrapartum NAAT result negative for GBS but above risk factors are present 6. Known GBS positive status in previous pregnancy.

Source: The American Association of Obstetricians and Gynecologists. Prevention of group B streptococcal early-onset disease in newborn. ACOG Committee opinion No. 797. Obstet Gynecol. 2020;135:51–72

[a]If intra-amniotic infection is suspected, intrapartum GBS prophylaxis should be replaced by broad spectrum antibiotics including an agent known to be active against GBS

23.8.1 Antimicrobial Agents

The role of IAP is to prevent neonatal early-onset GBS. It is achieved by maintaining adequate maternal drug levels (reduces neonatal GBS colonization), adequate fetal and neonatal levels (decreases risk of neonatal sepsis).

Intravenous Penicillin is the drug of choice, while intravenous Ampicillin is an acceptable alternative [15].

23.8.2 Women with Penicillin Allergy [15]

In women who report with penicillin allergy, the nature of allergy should be determined; it can be low risk or high risk.

23.8.2.1 Low-Risk Penicillin Allergy

- Nonspecific history (gastrointestinal symptoms, headache, vaginitis)
- Non-urticarial maculopapular rash without systemic symptoms; can be pruritic, typically occurs several days after initial exposure
- Pruritus without rash
- Family history of penicillin allergy without any personal history
- No recollection of symptoms or treatment of previous reported event.

23.8.2.2 High-Risk Penicillin Allergy

- Pruritic rash, urticaria, immediate flushing, hypotension, angioedema, respiratory distress
- Positive penicillin allergy test
- Recurrent reactions, reaction to multiple beta-lactam antibiotics
- Rare delayed onset cutaneous or systemic events.

Prenatal assessment for nature of penicillin allergy, further antibiotics for IAP should be determined (Fig. 23.1).

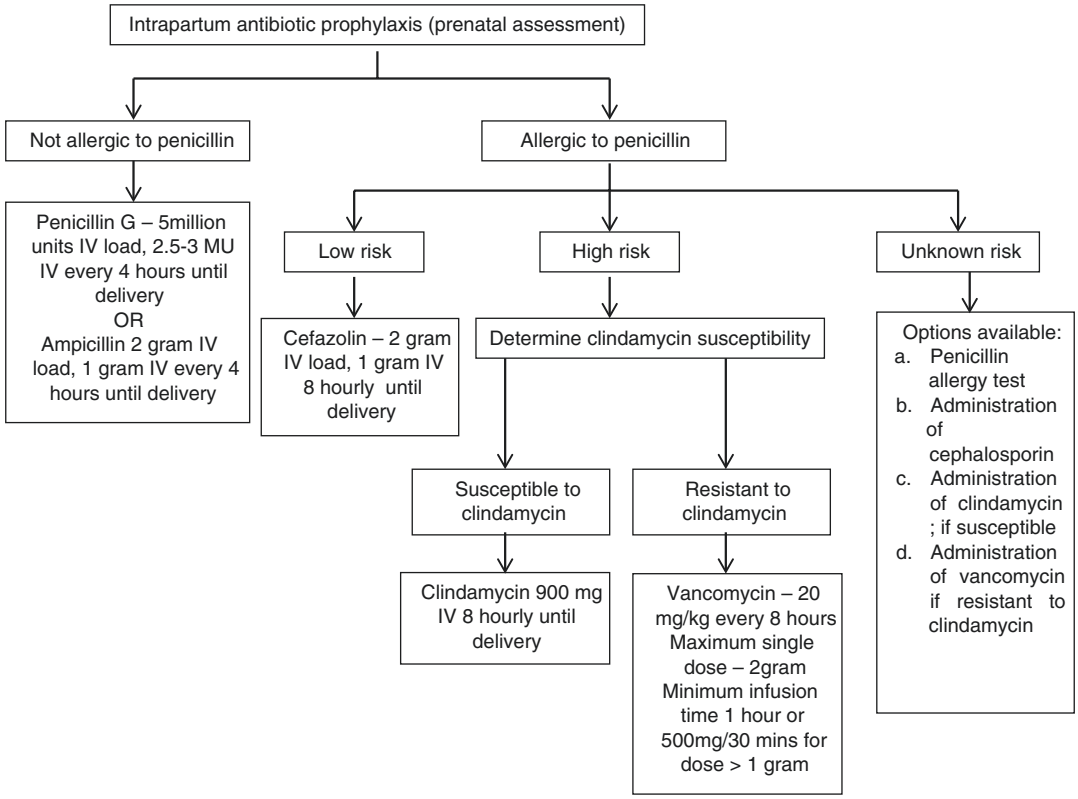

Fig. 23.1 Determination of intrapartum antibiotic prophylaxis against GBS [15]. Adapted from: Prevention of group B streptococcal early-onset disease in newborn. ACOG Committee opinion No. 797. Obstet Gynecol 2020;135:51–72

23.9 Special Conditions

23.9.1 GBS Bacteriuria [14, 15]

- Incidence of GBS bacteriuria >10^5 CFU/ml is 0.4–5% [21].
- GBS bacteriuria at any colony count detected at any time of pregnancy represents high vaginal-rectal colonization; therefore, it is an indication of IAP against GBS. Further screening with vaginal-rectal swab is not required at 36 0/7–37 6/7 weeks of gestation.
- GBS bacteriuria needs to be treated in antenatal period if it is symptomatic or colony count is >10^5 CFU/ml. There is no evidence that antenatal treatment of asymptomatic GBS bacteriuria <10^5 CFU/ml improves maternal and neonatal outcome [15].
- Asymptomatic GBS bacteriuria (>10^5 CFU/ml) in pregnancy has been associated with increased risks of pyelonephritis, low birth weight, and preterm birth.
- Treatment according to antibiotic sensitivity should be given. It has been shown to reduce the risk of pyelonephritis (RR 0.23; 95% CI 0.13–0.41) and low birth weight (RR 0.66; 95% CI 0.49–0.89), although no significant reduction in the rates of preterm birth has been demonstrated.
- Women with recurrent bacteriuria (same strain with significant colony counts cultured within 2 weeks of completing initial treatment) or reinfection (same or different strain with significant colony counts more than 2 weeks after completing treatment), including GBS, should be retreated according to antibiotic sensitivity [21].

23.9.2 Preterm Labor [14, 15]

If a patient reports with preterm labor less than 37 weeks, the algorithm to be followed is shown in Fig. 23.2.

- Vaginal and rectal swab is recommended in this patient if no previous culture is available or previous culture reported was more than 5 weeks back.
- If previous culture of preceding 5 weeks is available, result of that culture should be used to guide management.
- Antibiotic prophylaxis should be started after taking swab sample for GBS culture.
- Antibiotic prophylaxis should be continued if patient goes in true labor.
- It should be discontinued if onset of true labor does not occur and but GBS culture should be obtained.
- If culture reports are positive or not available at onset of labor, antibiotic must be started when labor starts.
- If culture reports are negative, antibiotics are not recommended, vaginal-rectal swab sample should be repeated if patient does not deliver within 5 weeks of previous culture reports or at 36 0/7–37 6/7 weeks of gestation.

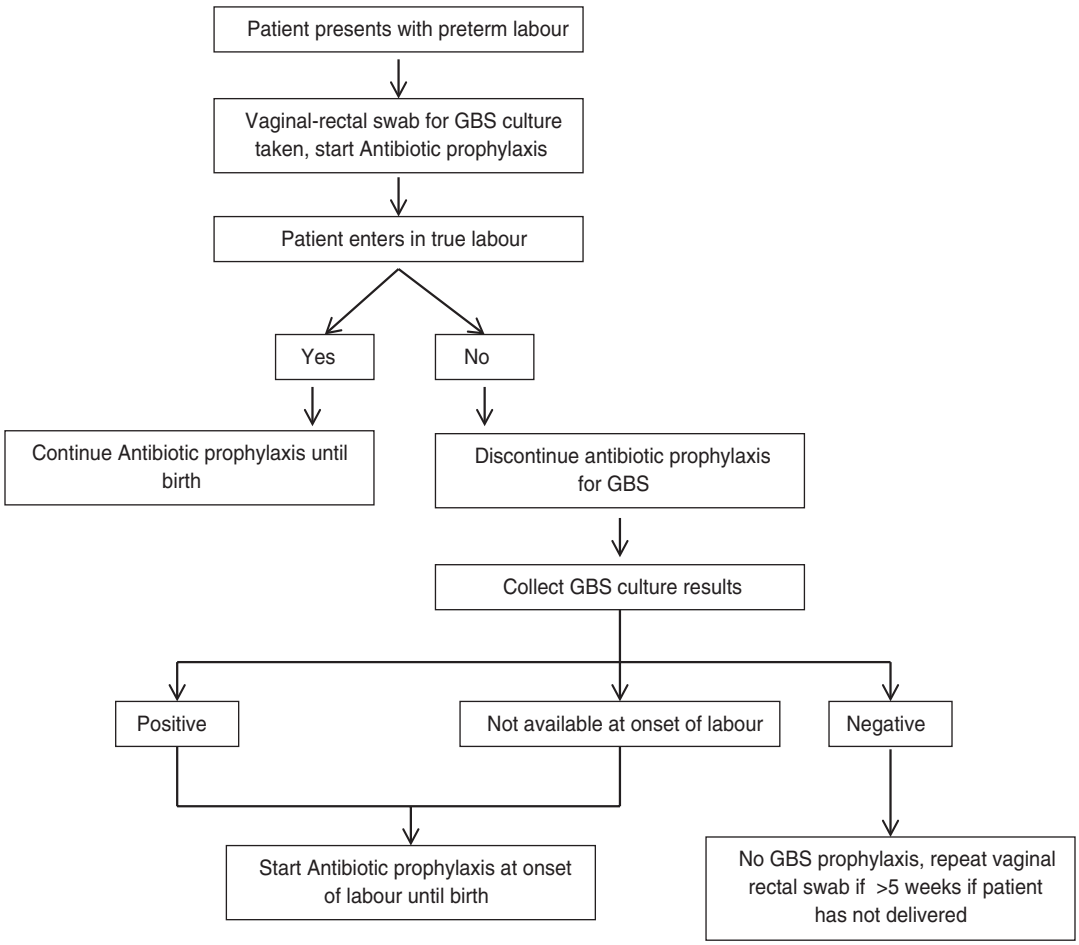

Fig. 23.2 Algorithm for antibiotic prophylaxis for GBS in patient presenting with preterm labor

23.9.3 Preterm Prelabor Rupture of Membranes (PPROM) [14, 15]

If a patient presents with PPROM, the following steps need to be taken:

- Vaginal and rectal swab for GBS culture should be taken if no previous culture for last 5 weeks is available; if culture preceding 5 weeks is available, it should be used for guiding management. GBS culture is valid for 5 weeks.
- If the patient has received antibiotics for positive GBS culture in last 5 weeks, GBS culture need not be repeated, intrapartum antibiotic prophylaxis has to be given whenever labor occurs [15].
- Patient should be started with latency intravenous antibiotics for 48 h [22].
- If patient presents after 34 weeks gestation, delivery should be considered [22, 23].
- If patient goes in labor, antibiotic prophylaxis should be continued.
- If expectant management is considered, intravenous latency antibiotic should be continued for 48 h followed by 5 days oral antibiotics to complete a 7-day course* [22].
- At any stage if intra-amniotic infection is suspected, antibiotics should be upgraded to broad spectrum antibiotics, which should include coverage against Group B Streptococcus [24].
- If patient goes in labor before collection of GBS culture reports or it comes out to be positive, GBS antibiotic prophylaxis should be started.
- If culture reports are negative, intrapartum antibiotic prophylaxis is not required.
- Repeat vaginal-rectal swab should be taken if patient remains pregnant for more than 5 weeks or at 36 0/7–37 6/7 weeks of gestation (Fig. 23.3).

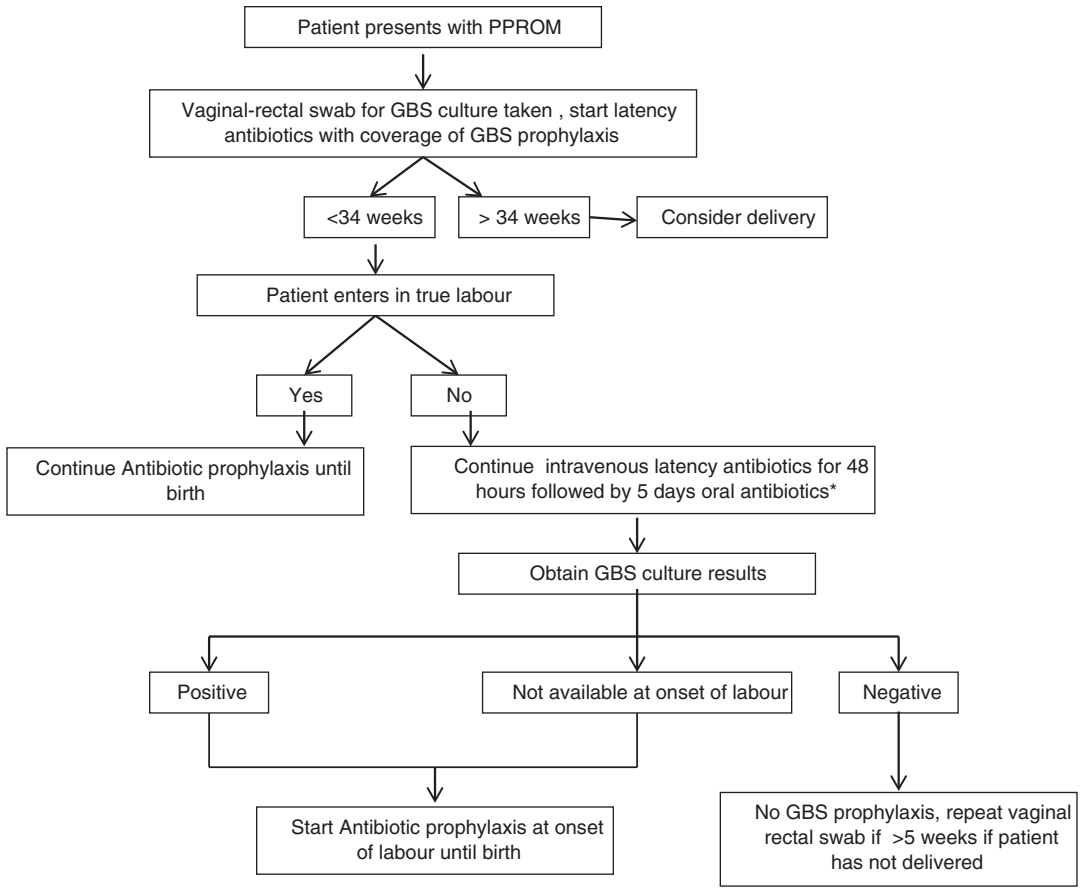

Fig. 23.3 Algorithm for antibiotic prophylaxis for GBS in patient presenting with PPROM

23.9.4 Elective Cesarean Birth

IAP for GBS is not recommended if cesarean section is done before onset of labor and without rupture of membranes, even if GBS culture is positive for colonization. Recommendation of giving prophylactic antibiotics before skin incision to prevent post-operative infection is not changed [25].

23.9.5 Unknown Culture Status at Term During Labor (Fig. 23.4) [15]

In this condition, three factors should be considered for guiding management.

1. Presence of high-risk factors (Rupture of amniotic membranes >18 h, intrapartum temperature >100.4 °F (38.0 °C) or higher)
2. Molecular based testing (Rapid NAAT)
3. History of GBS colonization in previous pregnancy or GBS bacteriuria in current pregnancy.

If there is history of GBS colonization in previous pregnancy or GBS bacteriuria at any gestation in current pregnancy, IAP is recommended.

Presence of maternal high-risk factors at term during labor is independently associated with increased risk of neonatal GBS. So it is considered as indication for intrapartum antibiotic prophylaxis, regardless for NAAT results.

NAAT should be performed, if available, antibiotic prophylaxis should be started with positive results.

23.10 Neonatal Group B Streptococcus Disease

Following algorithm (Fig. 23.5) should be followed, to detect GBS disease early in potential babies [7, 14].

- Complete diagnostic evaluation should be performed for every newborn presenting with neonatal sepsis; antibiotic therapy should be initiated.

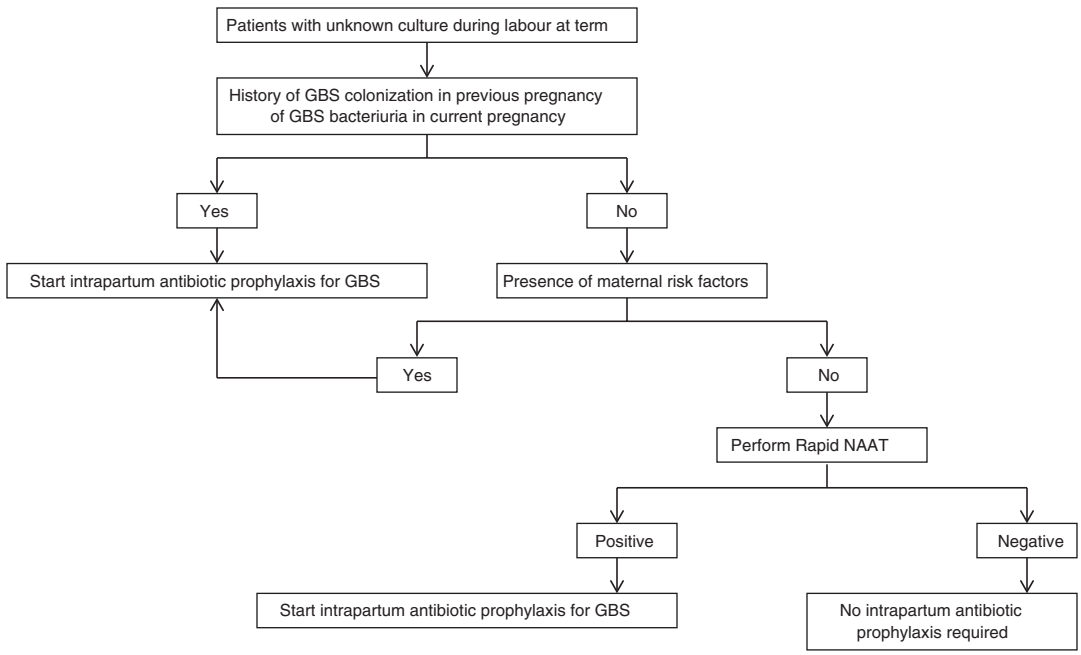

Fig. 23.4 Algorithm for antibiotic prophylaxis for GBS in patients with unknown culture status

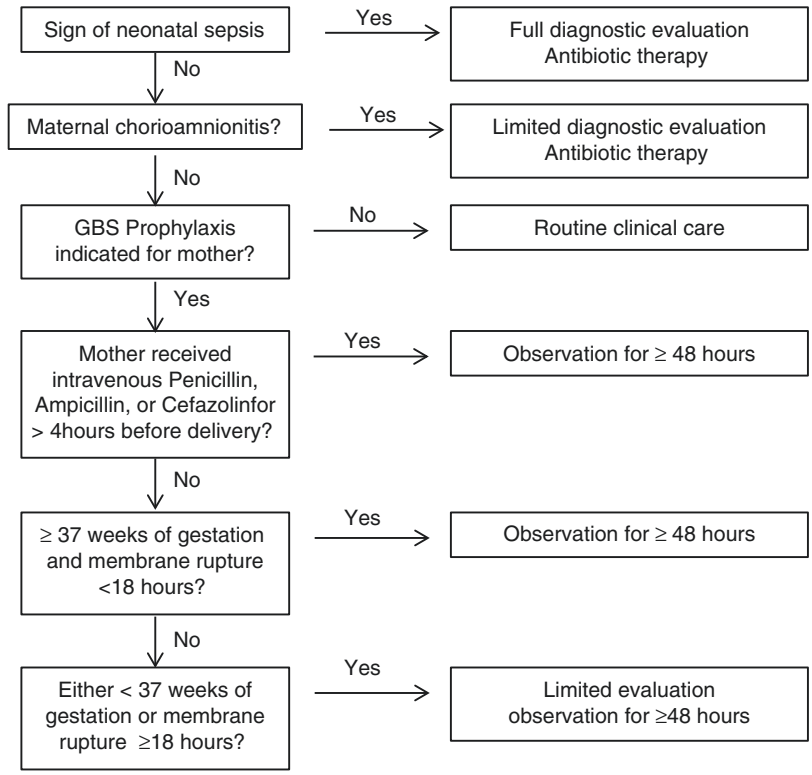

Fig. 23.5 Algorithm for management of GBS infection in newborn

Table 23.3 Antibiotic therapy in neonate [7]

		Bacteremia		Meningitis	
Age of neonate		Ampicillin	Penicillin G	Ampicillin	Penicillin G
Gestational age < 34 weeks	Post natal age ≤ 7 days	50 mg/kg12 h	50,000 U/kg12 h	100 mg/kg8 h	150,000 U/kg8 h
	Post natal age > 7 days	75 mg/kg12 h	50,000 U/kg8 h	75 mg/kg6 h	125,000 U/kg6 h
Gestational age > 34 weeks	Post natal age ≤ 7 days	50 mg/kg8 h	50,000 U/kg12 h	100 mg/kg8 h	150,000 U/kg8 h
	Post natal age >7 days	50 mg/kg8 h	50,000 U/kg8 h	75 mg/kg6 h	125,000 U/kg6 h

Source: Puopolo KM, Lynfield R, Cummings JJ. Management of Infants at Risk for Group B Streptococcal Disease. American Academy of Pediatrics, Pediatrics. 2019;144(2): 1–17.

- The complete diagnostic workup will include a complete blood culture (CBC), including total and differential leukocyte and platelet count. In neonates with abnormal respiratory signs, a chest radiograph is also advised. If there is suspicion of sepsis, then a lumbar puncture is performed if the newborn is stable enough to tolerate the procedure.
- Antibiotic therapy for neonate has been described in Table 23.3.
- Healthy neonate born to a mother with history of chorioamnionitis should also be investigated and treated with antibiotics. These neonates require limited diagnostic evaluation which includes a CBC including differential leukocyte count and platelet count. Chest radiograph or lumbar puncture is not required.
- Healthy neonates with no history of maternal chorioamnionitis and no indication for GBS

prophylaxis should be managed as per routine clinical care.

- Babies born to mothers who have received GBS prophylaxis (penicillin, ampicillin, or cefazolin) for more than 4 h prior to delivery should be kept under observation for 48 h. If these babies develop any signs of sepsis during observation, a full diagnostic evaluation should be conducted and antibiotic therapy should be started.
- For neonate born at ≥37 weeks gestation, with no history of maternal chorioamnionitis and with no signs of sepsis, home monitoring can be recommended after 24 h if the following criteria is met—ready access to medical care, the care giver can understand and fully comply with instructions for home observation, and other discharge criteria have been met. If any of these conditions is not met, the neonate should be observed in the hospital for at least 48 h.
- A well appearing neonate of more than 37 weeks of gestation and membrane rupture of less than 18 h, whose mothers have not received or inadequately received GBS prophylaxis, should be observed for 48 h. No antibiotic therapy is required.
- A well appearing neonate with either less than 37 weeks gestation or rupture of membranes more than 18 h should undergo limited diagnostic evaluation and should be kept in hospital for observation for at least 48 h, until other discharge criteria are met.

23.10.1 Recommendations for Neonatal Antibiotic Therapy [7]

- Combination of ampicillin and an aminoglycoside is the primary recommended therapy for infants up to 7 days of age.
- Broad spectrum antibiotics should be added empirically especially in cases of neonates with very low birth weight, if there is strong suspicion for ampicillin-resistant infection.
- Ampicillin and ceftazidime together are recommended in infants between 8 and 28 days of age who are not critically ill with no evidence of meningitis. In infants of 29–90 days of age, ceftriaxone therapy is recommended.
- For all previously healthy infants in the community from 8 to 90 days of age, if there is evidence of meningitis or critical illness, vancomycin should be added to expand coverage, including for β-lactam-resistant Streptococcus pneumoniae.
- Penicillin G is the drug of choice for group B streptococci, with ampicillin as an acceptable alternative therapy.

Key Points

1. Group B streptococcus is a β-hemolytic Gram-positive streptococcus, which is present normally in vagina and lower gastrointestinal tract. It becomes pathogenic when there is imbalance between host and bacterial factors.
2. It can cause group B streptococcus disease in neonate; early and late onset. Universal screening of GBS colonization and intrapartum antibiotic prophylaxis is recommended to decrease burden of early-onset disease in newborn.
3. Screening should be done by vaginal-rectal swab sample at 36 0/7–37 6/7 weeks of gestation.
4. GBS bacteriuria and history of neonatal GBS are direct indications for intrapartum antibiotic prophylaxis.
5. IAP is not required in patients undergoing elective cesarean section without going in labor and without rupture of membranes at any gestation.
6. Intravenous penicillin is drug of choice; intravenous ampicillin is an acceptable alternative.
7. Injection Cefazolin is given in patients with low-risk allergy to penicillin.
8. In high-risk allergy, susceptibility for injection clindamycin should be checked. If resistant, injection vancomycin is recommended.
9. For neonatal GBS, injection ampicillin or penicillin is recommended; aminoglycoside can be added in sick neonates.

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Urinary Tract Infections in Pregnancy

24

Divya Pandey and Zeba Khanam

24.1 Introduction

The physiological changes in urinary tract during pregnancy promote urinary stasis and vesicoureteral reflux. These changes along with underlying preponderance of urinary tract infections (UTIs) in pregnancy continue to be a challenging clinical problem to gynecologists. It may involve lower tract (acute cystitis) or upper tract (acute pyelonephritis). This chapter will cover UTIs in pregnancy including acute cystitis, acute pyelonephritis, and asymptomatic bacteriuria. The symptomatology ranges from asymptomatic to urgency, frequency, nocturia, hematuria, supra pubic pain, flank pain, and systemic symptoms (fever with chills and rigors, nausea and vomiting). Their diagnosis and treatment remains crucial from Obstetrics point of view considering the adverse maternal and fetal outcomes associated with their presentation.

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24.2 Classification of UTI in Pregnancy

Urinary tract infection may be classified as asymptomatic bacteriuria, acute cystitis, and pyelonephritis. (Table 24.1; Fig. 24.1)

24.3 Epidemiology of UTI in Pregnancy

UTIs are among the most common medical conditions during pregnancy. *Asymptomatic bacteriuria* usually presents early in pregnancy and affects 2–7% of all pregnant women [1, 2]. A

Table 24.1 Classification of urinary tract infections in pregnancy

Asymptomatic bacteriuria	Acute cystitis	Pyelonephritis
Defined as persistent colonization of the urinary tract by significant number of bacteria in women without urinary symptoms	It is distinguished from asymptomatic bacteriuria by the presence of symptoms such as dysuria, urgency, frequency, nocturia, hematuria, and suprapubic discomfort in afebrile women with no evidence of systemic illness	Significant bacteriuria in the presence of systemic illness and symptoms such as flank or renal angle pain, pyrexia, rigor, nausea, and vomiting

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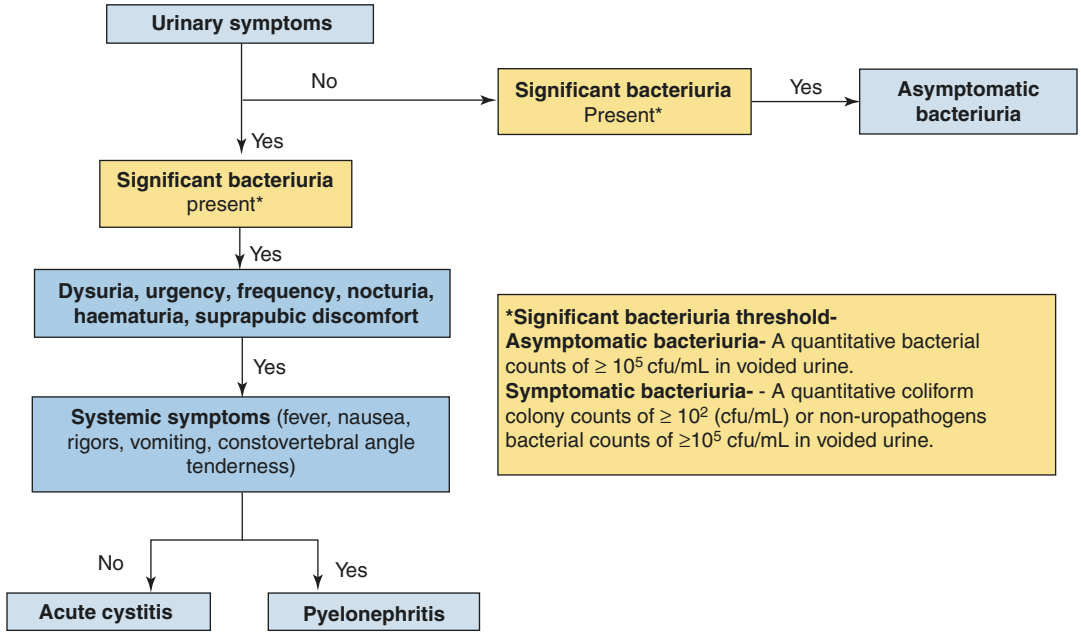

Fig. 24.1 Classification of urinary tract infections in pregnancy

prior history of urinary tract infection, presence of urinary tract anomaly, diabetes mellitus, high parity, and low socioeconomic status may predispose to asymptomatic bacteriuria of pregnancy [3, 4]. While in 20–35% of the untreated cases, it may evolve to a symptomatic urinary tract infection, in timely treated cases this risk is reduced to 70–80% [5, 6].

Acute cystitis represents inflammation of the bladder wall. Accurate incidence of acute cystitis is largely unknown since majority of women get treatment on an empirical basis without a urine culture and antimicrobial sensitivity report. It may complicate 1–2% of all pregnancies.

Pyelonephritis represents infection of a renal papilla, which may involve multiple papillae in untreated cases and seldom the entire renal cortex in neglected cases. A *pyonephrosis* represents infection of the whole kidney. It may lead to a perinephric abscess when the renal capsule ruptures. Initially in women with pyelonephritis lower urinary tract symptoms may predominate due to early stage acute cystitis. The incidence of pyelonephritis in pregnant women is reported to be 0.5–2% [7, 8]. It presents typically during second and third trimesters (90% cases) in unattended nulliparous young pregnant females (<20 years age) with a history of smoking, pre-existing sickle cell trait, or overt diabetes [7–9]. The recurrence rate of pyelonephritis in the same pregnancy is 23% [10]. Pyelonephritis may be associated with preterm delivery and anemia (due to hemolysis secondary to endotoxins). In severe complicated cases it may lead to multi-organ failure secondary to Gram-negative septicemia, septic shock, and acute respiratory distress syndrome (20% cases) [7].

24.4 Etiopathogenesis of UTI

Urine is normally sterile. The bacteriostatic properties of urine are secondary to its acidic pH, high osmolality, and urea levels. Urinary tract infections are 14 times more common in females than males due to their short and straight urethra, continued contamination of distal urethra with vaginal and rectal bacterial flora, incomplete evacuation of bladder during voiding, and easy traumatization of the distal urethra during intercourse.

Further in pregnancy this risk is increased many fold due to:

- Increase in bladder volume
- Decrease in detrusor muscle tone
- Ureteric dilatation (right more than left) due to ureteric smooth muscle relaxation under the effect of progesterone
- Pressure from the expanding uterus (90% women).

The above changes lead to urinary stasis, compromised ureteric valves, and vesicoureteral reflux which facilitates bacterial colonization and ascending infection. Lowered mucosal interleukin-6 levels and serum antibody responses to *E. coli* antigens from the accompanying immunosuppression of pregnancy also favor *E. coli* colonization of the urinary tract. Glycosuria (seen in 70% of pregnant women), aminoaciduria, and a urine osmolality fall during pregnancy further favor bacterial proliferation of urothelium in a pregnant woman. A gravid distended uterus may make maintaining hygiene difficult which may exacerbate urinary tract infection. There is higher rate of infection with increased maternal age and lower socioeconomic status. Associated urinary tract anomalies, maternal diabetes, and sickle cell disease also increase risk of urinary infections manifold. Any medical intervention during pregnancy like urethral instrumentation, catheterization may also predispose to urinary infection (Table 24.2). Gram-negative enteric bacteria can easily survive in urine as opposed to the commensal vaginal and perineal microflora (Fig. 24.2).

Table 24.2 Risk factors for UTIs in pregnancy

Physiological changes in pregnancy favoring urinary tract infections
Increase in bladder volume
Decrease in detrusor muscle tone
Ureteric dilatation
Immunomodulation of immune system from cell-mediated to an increased humoral response
Glycosuria
Aminoaciduria
Fall in urine osmolality
Factors predisposing to urinary tract infection in pregnancy
Physiological changes of pregnancy
Poor hygiene
Advanced maternal age
Lower socioeconomic strata
Urinary tract anomalies
Maternal diabetes and sickle cell anemia
Urethral instrumentation and catheterization

24.5 Microbiology

Urinary tract infection results from either *ascending genitourinary infection* (most common) or from hematogenous spread. *E. coli* is the most common causative organism found in 70% of asymptomatic and symptomatic bacteriuria in both pregnant and non-pregnant women. Other microorganisms implicated are *Klebsiella* (3%), *Enterobacter* species (3%), *Proteus* (2%), Gram-positive organisms (including Group B *Streptococcus)* in 10% and extended-spectrum beta-lactamase (ESBL)-producing strains [11, 12]. A mixed growth of greater than one species or the presence of *Lactobacillus* or *Cutibacterium* (or *Propionibacterium*) *acnes* indicate contamination of the specimen with vaginal or skin flora. However, significance of similar persistent finding is unknown (Table 24.3).

24.6 Screening for Asymptomatic Bacteriuria in Pregnancy

As per the Infectious Disease Society of America (2019), US preventive Services Task Force (2019) and Canadian Task Force on Preventive Health Care (2018), all pregnant women should be screened for asymptomatic bacteriuria with a urine culture at the first prenatal visit and preferably at 12–16 weeks' gestation [1, 13, 14]. Other societies have also made similar recommendations [1, 15]. In low-risk women re-screening is not advised, but it may be done in women at high risk for infection; in women with history of urinary infections, presence of urinary tract anomalies, diabetes mellitus, sickle cell anemia, or preterm labor. The screening tests for diagnosing an asymptomatic bacteriuria.

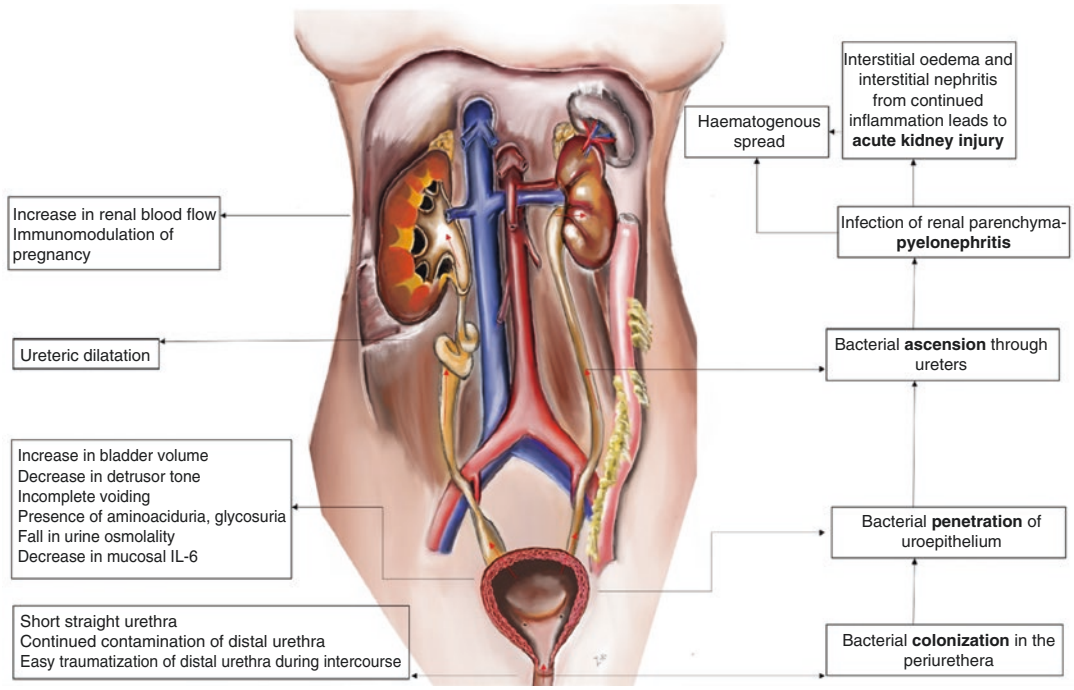

Fig. 24.2 Pathogenesis of urinary tract infections in pregnancy

Table 24.3 Causative microorganisms

Microorganisms causing UTIs	
Gram Negative Bacilli (*E. Coli*—most common, *Proteus mirabilis*, *Klebsiella pneumoniae*, and *Enterobacteriaceae*)	*E. Coli* is implicated in 80–90% of urinary tract infections Urea splitting *Proteus*, *Klebsiella*, and *Enterobacteriaceae* form urinary stones which act as reservoirs for bacterial colonization
Gram-positive Cocci	Coagulase-negative cocci—*Staphylococcus saprophyticus* is the second most common causative organism. Group B hemolytic *streptococci* are encountered infrequently but hold clinical importance. *Staphylococcus aureus* are inoculated hematologically into the urinary tract
Mycobacterium group	Are typically inoculated hematologically into the urinary tract
Nonbacterial causes	*Chlamydia* species Fungal infections, such as *Candida albicans*

Table 24.4 Urine Sample collection for screening and diagnosis of urinary tract infections

- Routine catheterization for specimen collection is not recommended
- Spreading the labia and collecting a mid-stream urine (second portion of the voided urine after discarding the initial stream)—MSSU is sufficient
- Clean-catch urine (after local cleansing of the urethral meatus and surrounding mucosa) is of little value

How to collect urine specimen: While collecting urine specimen, care should be taken to minimize chances of contamination. Though it seems that the collection of, "*clean-catch mid-stream*" (i.e., *clean-catch* after local cleaning of urethral meatus and peri-meatal mucosa; *Mid-stream*, collecting second part of voided urine after discarding the initial part) is the best approach, yet, various studies have suggested that a MSSU (mid-stream specimen of urine) sample, not necessarily clean-catch is sufficient and recommended for screening and diagnosis of asymptomatic and symptomatic bacteriuria in pregnancy (Table 24.4).

The various tests used for screening for asymptomatic bacteriuria are listed in Table 24.5.

Table 24.5 Screening tests for asymptomatic bacteriuria

	Advantages	Disadvantages
Urine culture and sensitivity	• "Gold standard screening test." Excellent sensitivity and specificity • Quantified assessment of the concentration of bacteriuria • Identification of the organism involved and antibiotic sensitivity testing to guide effective therapy • Strict attention must be given to sample collection, storage, and laboratory evaluation • Routine MSSU screening in early pregnancy (RCOG Grade A recommendation) [16]	Time taking and costly
Urine microscopy	Yield results fast; low cost	High false-negative rate (19.4%) of Gram staining and microscopy Not useful as a screening test
Reagent strip analysis	Quick results; low cost	High false negative rate (52.8%) Not recommended as a screening test
Other urine-based screening tests • Interleukin-8 test • Rapid enzymatic test • Chromogenic Limulus Amoebocyte Lysate Assay • Semi-automated urine screen *(Bac-T-screen®:Vitek Systems, Biomeriux Vitek Inc., Hazelwood, MO, USA)* • The dip-slide quantitative kit *(Uricult®: Orion Diagnostica Oy, Espoo, Finland)*		Not recommended as screening test

24.7 Diagnosis of UTI in Pregnancy

The definitive diagnosis of urinary tract infection in pregnancy is typically made after positive urine culture test. Antibiotic sensitivity testing may then be used to treat the offending organism. Urinalysis may be of little importance. However, the presence of nitrite on urinalysis in a symptomatic woman may signify significant bacteriuria warranting a definitive culture report to target the offending microorganism. The threshold value of bacterial count on urine culture for diagnosing urinary tract infections in pregnancy is summarized in Table 24.6.

The gold standard test for diagnosing pyelonephritis has been renal biopsy but it is not useful in practical scenario. A combination of symptoms, full blood count, inflammatory markers, renal function tests, blood culture, urine culture, and sensitivity testing is sufficient in making a diagnosis of pyelonephritis (Table 24.7).

Differential diagnosis of symptomatic urinary tract infection may include gonococcal and non-gonococcal urethritis, chemical cystitis, physiological response of urinary system to pregnancy, nephrolithiasis, chorioamnionitis, and other systemic infections (Table 24.8).

Table 24.6 Definition of significant bacteriuria in pregnancy

Threshold values of bacterial counts on urine culture (significant bacteriuria) for diagnosis of urinary tract infections in pregnancy		
Asymptomatic bacteriuria	Acute cystitis	Pyelonephritis
Significant bacteriuria in absence of urinary symptoms is suggestive of asymptomatic bacteriuria Significant bacteriuria is defined as isolation of the same bacterial strain in quantitative counts of $\geq 10^5$ *colony-forming units (cfu/mL)* in two consecutive voided urine specimens or isolation of one bacterial species in a single catheterized urine specimen in a quantitative count of $\geq 10^2$ *cfu/mL* In clinical practice a single MSSU sample with bacterial counts of $\geq 10^5$ cfu/mL is sufficient to initiate treatment.	Significant bacteriuria with associated dysuria, urgency, frequency, nocturia, hematuria, and suprapubic discomfort in afebrile women with no evidence of systemic illness signifies acute cystitis A quantitative coliform colony count of $\geq 10^2$ *cfu/mL* in voided urine is taken as threshold for significant bacteriuria For non-uropathogens—a high threshold of $\geq 10^5$ *cfu/mL* bacterial count is used for significant bacteriuria	Significant bacteriuria in presence of systemic illness (fever, rigors, nausea, and/or vomiting) and symptoms such as flank or renal angle pain signifies pyelonephritis Threshold significant bacteriuria is similar to those for acute cystitis.

Table 24.7 Tests for urinary tract infections

Urine culture and antibiotic susceptibility	Recommended test
Reagent based dipstick test	Presence of nitrite in urine of symptomatic women suggests significant bacteriuria
Urinalysis	*Acute cystitis*—Pyuria is invariably present; Hematuria may be present *Pyelonephritis*—Pyuria/bacteriuria is typically present. However, in absence of pyuria but with positive symptoms and cultures, urinary tract infection cannot be ruled out
Blood culture	Recommended only in cases with signs of sepsis or serious underlying medical conditions such as diabetes or sickle cell disease
Serum lactate levels	May help to determine severity of disease in cases of severe sepsis or septic shock.
Renal imaging	Useful in cases of severe illness, history of renal colic, renal stones, diabetes, prior urological surgery, evidence of immunosuppression, repeated episodes of pyelonephritis, or urosepsis
Others—Full blood count, inflammatory markers, and renal function tests	

Table 24.8 Differential diagnosis of acute cystitis and pyelonephritis

Acute cystitis	Pyelonephritis
Physiological changes of pregnancy Urinary urgency and frequency is common in first and third trimester	**Nephrolithiasis** Presents with flank pain and abnormal urinalysis. Fever is uncommon in absence of complications. Renal imaging may depict a stone
Vaginitis True bacteriuria is absent in contrast to acute cystitis	**Chorioamnionitis** Presents with fever and/or back pain. However, in contrast to pyelonephritis, there is premature rupture of membranes, uterine tenderness, and/or foul smelling amniotic fluid
Gonococcal urethritis Presence of acute urethral syndromes (dysuria, frequency, pyuria, and hematuria) without significant bacteriuria Urethral discharge is characteristic	Bacteriuria is characteristically absent
Non-gonococcal urethritis (Chlamydia, Mycoplasma, Gram-negative bacteria associated) Presence of dysuria in absence of significant bacteriuria	**Other maternal infections** Influenza, pneumonia, appendicitis—may present with back pain and fever Bacteriuria is typically absent
Non-urethral, non-urinary tract infections Intra-amniotic infection Vulvitis Vaginitis Cervicitis secondary to Herpes simplex virus	**Placental abruption** Back pain and uterine tenderness are usually present Vaginal bleeding may be present There is no fever Woody hard abdomen viz a viz soft and non-tender abdomen seen in cases of acute pyelonephritis
Chemical cystitis	

24.8 Maternofetal Outcomes of UTI in Pregnancy

The long-term prognosis of asymptomatic bacteriuria and urinary tract infections in pregnancy is excellent.

However, in untreated cases of asymptomatic bacteriuria there is high risk of adverse maternal, fetal, and perinatal outcomes in form of symptomatic cystitis, pyelonephritis, preeclampsia, preterm labor, prematurity, and low birthweight, neonatal sepsis, and UTI in present pregnancy [17].

Untreated bacteriuria, but not acute cystitis, may be associated with preterm birth, low birth weight, and preeclampsia [5, 18–23].

Although fetal bacteremia after maternal urinary tract infection is rare, it may lead to fetal cerebral hypoperfusion secondary to direct endotoxin damage, maternal dehydration, and anemia.

Upper urinary tract infections, if left untreated, may culminate into low birth weight babies, prematurity, preterm labor pains, pregnancy induced hypertension, maternal anemia, intrauterine growth retardation, amnionitis, and higher rates of cesarean deliveries. There is 30% risk of neonatal urinary tract infection in a pregnant woman with UTI [24, 25]. In the worst case scenario, acute pyelonephritis may lead to maternal acute respiratory distress syndrome, sepsis, septic shock, and maternal death. There is 1.31-fold rise in preeclampsia in women with urinary tract infections [26]. It is postulated that asymptomatic renal scarring after childhood urinary tract infection may lead to preeclampsia in these women.

Group B *Streptococcus* (GBS), an important causative organism of early-onset neonatal sepsis, when found in significant titers in the urine of a pregnant woman may increase risk of chorioamnionitis [27]. The pathogenesis behind GBS bacteriuria and chorioamnionitis might be explained by pore formation in placento-fetal barrier through its attachment to epithelial cells and release of B-hemolysin/cytolysin. Another pathogen widely implicated in causing chorioamnionitis secondary to urinary tract infection similar to GBS, is *Ureaplasma urealyticum*.

Table 24.9 Maternofetal outcome of asymptomatic bacteriuria in pregnancy

Maternal outcome	Symptomatic cystitis (up to 30% cases) Pyelonephritis (up to 50% cases) Preterm labor and delivery Preeclampsia Anemia Chorioamnionitis Postpartum endometritis
Fetal and neonatal outcomes	Prematurity Low birth weight Increased perinatal mortality Fetal growth restriction Stillbirth Mental retardation and developmental delay secondary to direct bacterial endotoxin damage and fetal cerebral hypoperfusion

Arachidonic acids, phospholipase A2, and prostaglandins produced by uropathogens cause softening of cervix and calcium influx into uterine myometrial smooth muscle cells. The result is increasing uterine contractility and commencement of preterm labor pains. GBS B-hemolysin is responsible for preterm labor pains in selected women.

Vertical transmission of GBS during delivery or membranes rupture may lead to neonatal sepsis and pneumonia. Hence, it is advocated that a pregnant woman with a previously GBS affected neonate should receive parenteral antibiotic treatment for any level of CFU/mL of GBS detected in urine as soon as labor ensues or membrane ruptures.

Owing to the adverse effects on pregnancy and its outcome (Table 24.9) and high rate of progression to complicated UTI, asymptomatic bacteriuria in pregnancy warrants treatment.

24.9 Management of Urinary Tract Infection in Pregnancy

24.9.1 Asymptomatic Bacteriuria (Fig. 24.3)

According to Cochrane review, treatment of asymptomatic bacteriuria may reduce risk of pyelonephritis, preterm delivery, and low birth-

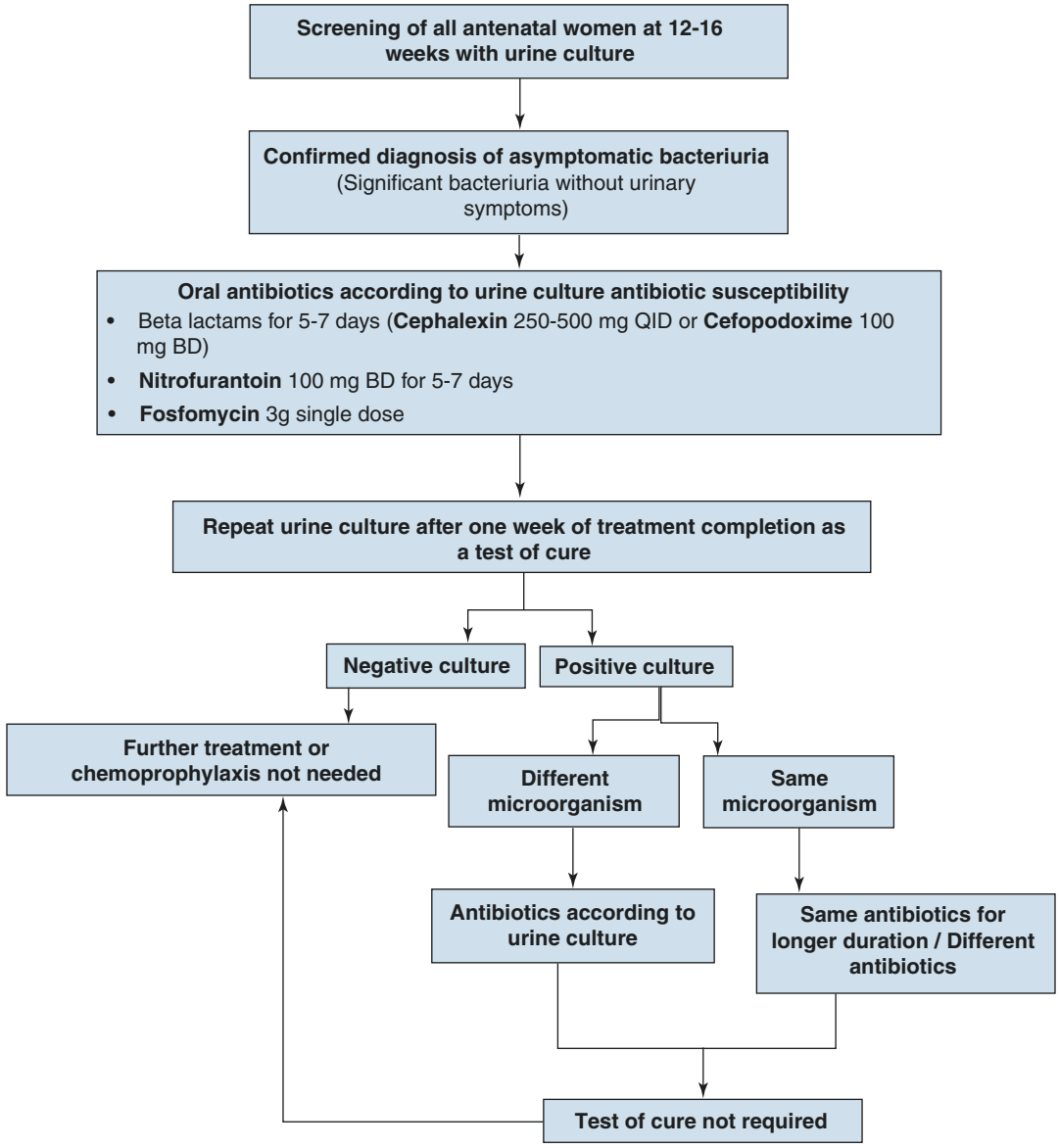

Fig. 24.3 Management of asymptomatic bacteriuria in pregnancy

weight in pregnant women [28]. Antibiotics are initiated according to urine culture reports; beta-lactam antibiotics, nitrofurantoin, and fosfomycin are useful antibiotics. Duration of treatment is unknown though short-course therapy is recommended over long course treatment. Single-dose treatment, except in case of fosfomycin, is usually ineffective. Another Cochrane review has emphasized superiority of standard short-course treatment of 4–7 days over a single-dose regimen. However, efficacy of 3–5 days' regimen is unknown [29] (Table 24.10). A *repeat culture should be obtained as a test of cure* (performed a week after completion of therapy). If repeat culture is negative, no treatment is required in asymptomatic cases. If repeat culture is positive with bacterial counts $\geq 10^5$ cfu/mL, repeat antibiotic treatment should be given according to antimicrobial susceptibility. In case of same microorganism as the previous test, a longer

Table 24.10 Summary of recommendations on screening, diagnosis, and treatment of asymptomatic bacteriuria in pregnancy

RCOG, 2008 [30]	• Screening of all women by urine culture should be performed in early pregnancy, despite cost • Treatment should be guided by urine culture and sensitivity reports • Antibiotic treatment should be continued for 7 days
Cochrane review, 2015 [29]	• A single-dose regimen may be less effective than a standard short-course (4–7 days) regimen for treatment. Data on efficacy of 3–5 days regimen is not known
ACOG Committee Opinion No. 717 [31]	• Pregnant women should not be denied appropriate treatment because untreated infections can commonly lead to serious maternal and fetal complications • Treatment should be guided by urine culture and sensitivity reports • Antibiotic treatment should continue for 7 days as shorter courses are not as effective during pregnancy • Cultures showing mixed Gram-positive bacteria, *lactobacilli*, and *Staphylococcus* species (other than *S. saprophyticus*) may be presumed to be contaminants and need not be treated • Penicillins, erythromycin, and cephalosporin have not been found to be associated with an increased risk of birth defects • The evidence regarding an association between nitrofurantoin and sulfonamide classes of antibiotics and birth defects is mixed. Prescribing sulfonamides or nitrofurantoin in the first trimester is still considered appropriate when no other suitable alternative antibiotics are available. During the second and third trimesters, sulfonamides and nitrofurantoin may continue to be used as first-line agents for the treatment and prevention of urinary tract infections and other infections caused by susceptible organisms. Sulfonamides and nitrofurantoin are contraindicated in patients with G6PD deficiency
Canadian Task Force on Preventive Health Care, 2018 [29]	• Pregnant women should be screened once during the first trimester with urine culture for asymptomatic bacteriuria (weak recommendation; very low-quality evidence) • It applies to pregnant women who are not experiencing symptoms of a urinary tract infection and are not at increased risk for asymptomatic bacteriuria
United States Preventive Services Task Force, 2008 [32]	• Screening for asymptomatic bacteriuria with urine culture for pregnant women at 12–16 weeks gestation or at their first prenatal visit, if later. (Grade A: evidence)
The National Institute for Health and Care Excellence, UK, 2008 [33]	• Pregnant women should be screened for asymptomatic bacteriuria in first trimester of pregnancy (Grade A Recommendation: consistent, good-quality patient-oriented evidence) • Pregnant women who have asymptomatic bacteriuria should be treated with antimicrobial therapy for 3–7 days (Grade B Recommendation: inconsistent or limited-quality patient-oriented evidence)

course of same antibiotics may be used or an altogether different antibiotic may be started. A test of cure is not warranted in such cases.

Treatment for non-uropathogens (*lactobacillus*) is started only when it grows as a single isolate on consecutive cultures.

24.9.2 Acute Cystitis

Increasing oral fluid intake is usually advised as a first-line treatment in symptomatic urinary infection in pregnancy. However, there is little evidence to support it. Moreover, it may worsen the urinary frequency and dysuria of acute cystitis [30]. A Cochrane systematic review determined that there was no good-quality evidence to suggest that cranberry juice is an effective treatment option in relieving symptoms of acute cystitis [34]. Benefits of using urine alkalinizing agent are not also proven. Moreover, it should be avoided considering risk of maternal hypernatremia. Simple analgesics may relieve suprapubic discomfort and dysuria of acute cystitis. However, teratogenic profile of these drugs should always be kept in mind. There is a little evidence to support topical local anesthetics to reduce dysuria symptoms. Empiric antibiotic therapy is usually started with presence of consistent symptoms and pyuria on urinalysis. For empiric therapy, cefpodoxime, amoxicillin-clavulanate, fosfomycin, or nitrofurantoin may be used.

For women at risk for or who have an infection with ESBL-producing *Enterobacteriaceae*, nitrofurantoin and fosfomycin are good oral options. Definitive treatment is subsequently modulated according to urine culture reports. No particular drug regimen is recommended over other for acute cystitis. Optimal duration of treatment for acute cystitis in pregnancy is uncertain. Short courses of antibiotics (usually 3–7 days) are preferred. Single-dose therapy is reserved only for fosfomycin. A RCOG review determined that 7–10-day course of an appropriate antimicrobial is usually sufficient to eradicate acute cystitis infection. A consensus opinion on efficacy of shorter antibiotics course and single-dose antibiotic regimen for uncomplicated infections is not available. The concern here is persistent infection and progression to pyelonephritis in under-treated cases [30].

Test of cure is usually performed a week after completion of therapy. Primary treatment failures or relapses should be treated with a full 7-day course of a different antimicrobial in accordance with sensitivity testing. Other underlying factors should also be considered [30]. Figure 24.4 shows management of acute cystitis in pregnancy.

Chemoprophylaxis may be required in cases of recurrent cystitis or in women who are at high risk for urinary complications, for example, women with diabetes or sickle cell disease (Table 24.11).

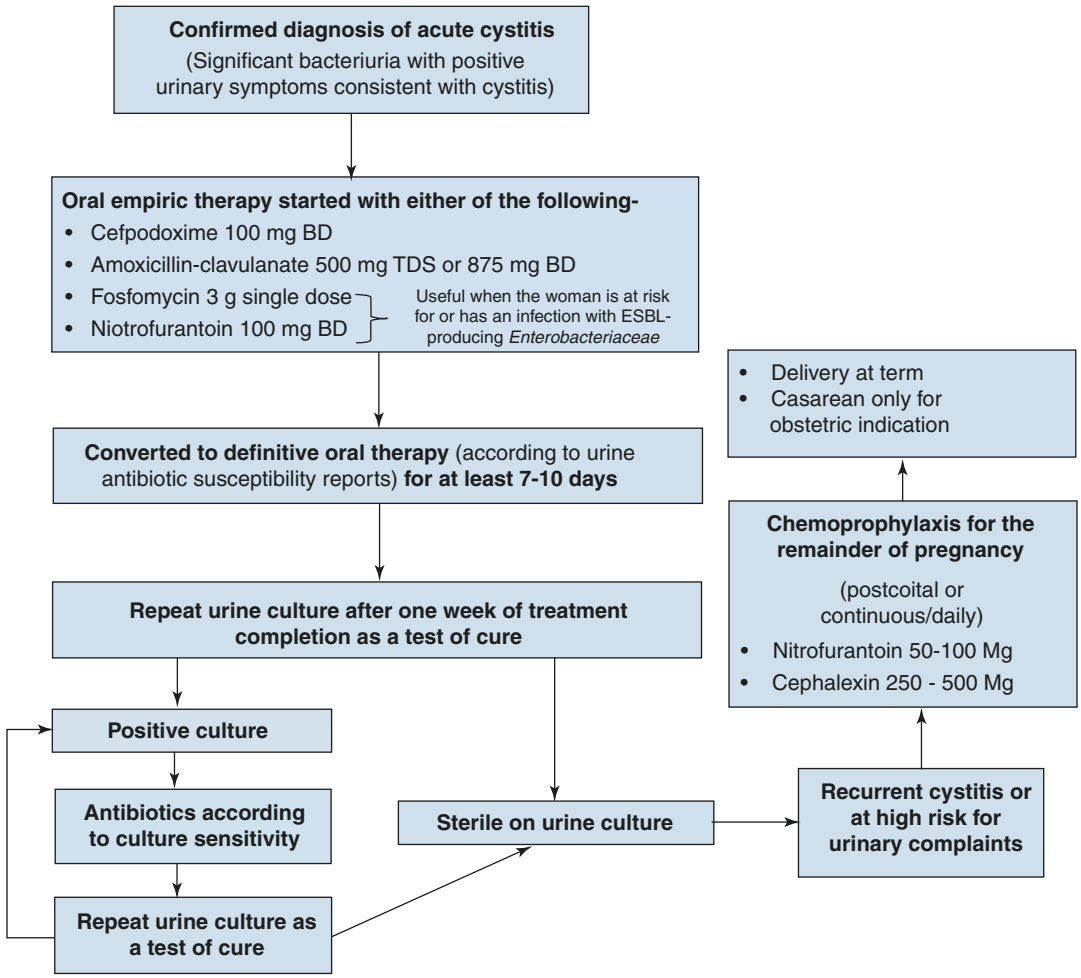

Fig. 24.4 Management of acute cystitis in pregnancy

Table 24.11 Chemoprophylaxis for recurrent cystitis

Asymptomatic bacteriuria	Acute cystitis	Pyelonephritis
Suppressive or prophylactic antibiotics for persistent or recurrent asymptomatic bacteriuria are not recommended	With recurrent cystitis (three or more episodes during pregnancy) antimicrobial prophylaxis for the rest duration of pregnancy is recommended. In women with high risk for urinary complications, e.g. pre-existing diabetes or HbS trait, prophylactic antibiotics may be started after first episode of acute cystitis. Prophylaxis can be postcoital if it is sexually related (in most cases) or continuous/daily in form of oral **low-dose nitrofurantoin** (50–100 mg) or **cephalexin** (250–500 mg)	Recurrent pyelonephritis occurs in 6–8% of pregnant women. **Low dose nitrofurantoin** (50–100 mg orally at bedtime) or **cephalexin** (250–500 mg orally at bedtime) is instituted for rest of the pregnancy. On later culture it is advised to look for breakthrough bacteriuria and treatment should be instituted according to the culture reports

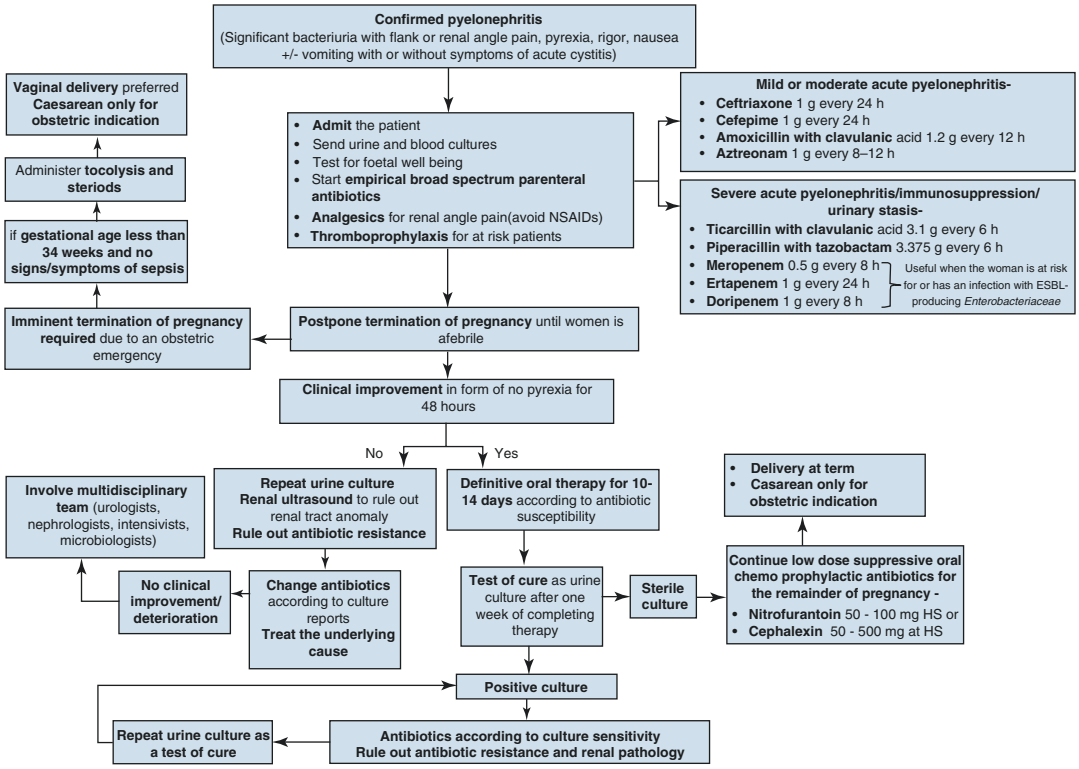

Fig. 24.5 Management of a case of pyelonephritis in pregnancy

24.9.3 Pyelonephritis (Fig. 24.5)

In-patient treatment with parenteral empirical antibiotics (broad spectrum beta-lactams) is the main line of treatment. Parenteral antibiotics should be continued until the woman is afebrile for 24–48 h and there is visible clinical improvement. Outpatient management and oral antimicrobial treatment may be considered in selected uncomplicated pregnancies with minimal symptoms, without any underlying medical illness, anomalies of urinary tract, signs of sepsis,

or a history of a recent antibiotic use. A comprehensive maternofetal workup should be done. Blood and urine samples for culture should be collected and vaginal swabs for microorganism culture should be taken. Subsequently, empiric treatment should be started. Parenteral, broad spectrum beta-lactams are the preferred antibiotics for initial empiric therapy of pyelonephritis; later narrow spectrum antibiotics are administered according to urine culture findings. Fluoroquinolones and aminoglycosides (often used for pyelonephritis in non-pregnant women) should be avoided in pregnancy. In women with a history of infections with ESBL-producing *Enterobacteriaceae* (or other risk factors), carbapenem (except imipenem) is used for empiric therapy. Once the woman is afebrile for 48 h, she can be switched to a definitive oral therapy (beta-lactams or trimethoprim—sulfamethoxazole) for 10–14 days guided by culture susceptibility results. She may be discharged then on oral therapy. It is important that antimicrobials should be continued for at least 10 days since there have been reports of relapses when treatment was stopped earlier at 7 days. Some clinicians may favor a longer duration treatment for 14–21 days. However, evidence on longer duration treatments regimens is limited and hence not advocated. Nitrofurantoin and fosfomycin are not useful in treatment of pyelonephritis since they do not reach therapeutic levels in kidneys (Table 24.12).

Table 24.12 Treatment of pyelonephritis in pregnancy

Mild or moderate acute pyelonephritis	Ceftriaxone 1 g every 24 h Cefepime 1 g every 24 h Amoxicillin with clavulanic acid 1.2 g every 12 h Aztreonam 1 g every 8–12 h
Severe acute pyelonephritis/ immuno-suppression/urinary stasis	Ticarcillin with clavulanic acid 3.1 g every 6 h Piperacillin with tazobactam 3.375 g every 6 h Meropenem 0.5 g every 8 h Ertapenem 1 g every 24 h Doripenem 1 g every 8 h

It is important to re-evaluate treatment if the woman is not responding within 24–48 h of parenteral therapy and once culture and sensitivity results become available. If symptoms persist beyond first 24–48 h of treatment, a repeat urine culture and renal ultrasound are required. Simple analgesics usually suffice for renal angle pain but opiates may be required in severe cases, or for an associated renal colic. Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided, considering risk of oligohydramnios, premature fetal ductus arteriosus closure and maternal risks of gastric mucosal ulceration and reduced renal perfusion.

Thromboprophylaxis in form of graduated compression stockings and low molecular weight heparin should be used if the woman has reduced mobility or she is on bed rest.

Following management of acute phase, *suppressive antibiotic therapy* is continued for the remainder of pregnancy in order to prevent recurrence (Table 24.11).

In cases where prophylactic antibiotics are not received, woman should be followed up monthly with urine cultures reports. The most common reason for initial treatment failure and clinical deterioration is resistance to antimicrobial treatment. In all cases of treatment failure, one must exclude underlying pathology or renal tract anomaly. Renal calculi may lead to persistent infection. Appropriate imaging must be employed to explore all causes of treatment failure.

If there is maternal deterioration or she is unresponsive to conventional treatment, concerned specialists (urologists, nephrologists, intensivists, and microbiologists) should be involved in decision-making. Initial investigation and resuscitation should ensue as soon as signs and symptoms of severe sepsis or septic shock become evident.

If induction of labor or cesarean delivery is planned in a woman with pyelonephritis, it should be delayed until the woman is afebrile, except in cases of maternofetal emergency.

The risk of preterm labor increases significantly during an episode of acute pyelonephritis. Where gestational age is less than 34 weeks, tocolysis and steroids should be administered, except in the setting of sepsis where ARDS and pulmonary edema may be precipitated. Algorithm for management of a case of acute pyelonephritis is shown in Fig. 24.5.

24.9.4 Recurrent Urinary Tract Infections in Pregnancy

Urinary tract infections may recur in 4–5% of all pregnancies. The risks of developing pyelonephritis and its potential consequences are same as for primary infection. The exact etiology remains uncertain but reinfection by coliforms from the vaginal reservoir may be secondary to sexual activity.

In all such women—

- Urinary tract anomalies must be excluded
- A postpartum evaluation should be done
- Long-term, low dose antimicrobial cover, or single postcoital doses (cephalexin 250 mg or nitrofurantoin 50 mg) are given for the remainder of the pregnancy.

24.10 Antibiotics Used for UTI in Pregnancy

In pregnancy, increased glomerular filtration rates due to increased maternal plasma volume reduce serum antibiotic concentrations. This is especially true for ß-Lactam antibiotics (penicillins and cephalosporins). The accompanying polyuria and increased urinary frequency further reduce concentration of antibiotics within the urinary tract. Hence, antibiotics dosages should be increased or hydrophilic drugs should be prescribed to ensure efficacy of the treatment. It is always imperative to look out for the causative organism and its resistance profile trends in the local antenatal population. Table 24.13 highlights common antibiotics, their dosages and side-effects in treatment of urinary tract infections in pregnancy.

Table 24.13 Antibiotic usage for treatment of urinary tract infections in pregnancy

Drugs	Dosage	Precautions
Penicillin group of drugs	Amoxycillin-500 mg orally TDS or 875 mg BD for 5–7 days Amoxicillin-clavulanate-500 mg orally TDS or 875 mg BD for 5–7 days	Not very effective against Gram-negative organisms
Cephalosporins	Cephalexin-250–500 mg orally QID for 5–7 days Cefpodoxime-100 mg orally BD for 5–7 days	Ceftriaxone should be avoided near delivery for risk of kernicterus in fetus
Carbapenems: • Meropenem • Ertapenem • Doripenem		Imipenem is associated with birth defects in animal model. Hence, not used in pregnant population
Nitrofurantoin	100 mg orally BD for 5–7 days	Generally safe except for a very small risk (0.0004%) for hemolytic anemia with glucose-6-phosphate dehydrogenase (G6PD) deficiency in mother and fetus and infrequent reports of associated birth defects It should be avoided during first trimester and last trimester Does not achieve therapeutic levels in kidneys so should not be used if pyelonephritis is suspected
Fosfomycin	3 g orally as single dose	Does not achieve therapeutic levels in kidneys. Hence, not useful for treatment of pyelonephritis
Trimethoprim-sulfamethoxazole	800/160 mg (one double strength tablet) BD for 3 days	Can be used in mid-trimester Trimethoprim is a folate antagonist and may cause birth defects if used during first trimester Sulfamethoxazole may cause birth defects and kernicterus if used during third trimester It is not recommended during first and last trimester of pregnancy
Aminoglycosides Fluoroquinolones Tetracycline	Avoided during pregnancy due to associated teratogenicity	

24.11 Conclusion

Urinary tract infections are the commonest cause of preventable bacterial infections in pregnancy. They can range from asymptomatic bacteriuria to acute cystitis and pyelonephritis and can have significant effect on maternal and fetal outcomes. UTI during pregnancy has been found to be associated with preeclampsia, preterm labor, and fetal growth restriction. Antenatal screening of pregnant women for UTI, its early recognition and timely treatment can help in preventing associated maternal and fetal morbidity and mortality.

Key Points

- Screening for asymptomatic bacteriuria should be done at least once at 12–16 weeks gestation with a mid-stream urine for culture. *Escherichia coli* is the predominant causative organism found in both asymptomatic and symptomatic bacteriuria in pregnant and non-pregnant women.
- In 30–40% women, asymptomatic bacteriuria may lead to symptomatic urinary tract infection. Untreated cases may be complicated by preterm birth, low birth weight, and perinatal mortality.
- The diagnosis of acute cystitis is made by the findings of significant bacteriuria (coliform colony counts of $\geq 10^2$ (cfu/mL) or non-uropathogenic bacterial colony counts of $\geq 10^5$ cfu/mL) in voided urine sample in the presence of new onset dysuria, frequency, or urgency and the absence of systemic signs and symptoms.
- Acute pyelonephritis is diagnosed by presence of significant bacteriuria, flank pain, nausea/vomiting, fever (>38 °C), and/or costovertebral angle tenderness, with or without the typical symptoms of cystitis. It is associated with poor maternofetal outcomes.
- Management includes antibiotic therapy according to urine culture results. Antibiotics used are beta-lactams, nitrofurantoin, and fosfomycin.
- Test of cure is required in form of a sterile urine culture on follow-up. With recurrent cystitis, prophylactic or suppressive antibiotics are given in addition to retreatment.

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Gastroenteritis in Pregnancy: Relevance and Management

25

Neha Sharad and Sruthi Bhaskaran

25.1 Introduction

The estimated monthly prevalence of diarrhea among adults is 3–7% [4]. Prevalence of acute infection is reported to be 3.5–5% during pregnancy [5]. Pregnancy is associated with dramatic anatomic and physiological changes that have the potential to create unique conditions potentiating gastrointestinal (GI) discomfort. Nausea and vomiting are common during the first 20 weeks of pregnancy. Nausea and vomiting occurring after 20 weeks of gestation or when accompanied with fever, diarrhea, headache, or severe abdominal pain are not normal in pregnancy.

As per WHO, *Diarrhea* is defined as the passage of three or more loose or liquid stools per day (or more frequent passage than is normal for the individual). Diarrhea may be further defined as *acute if <2 weeks, persistent if 2–4 weeks, and chronic if it is of more than 4 weeks duration* [2]. More than 90% of cases of acute diarrhea are caused by infectious agents; and are often accompanied by vomiting, fever, and abdominal pain. Incidence is same in all trimesters of pregnancy [2]. A study conducted in Sweden suggests that as many as 1/3rd women will experience this condition during their pregnancy [5]. Acute gastroenteritis in pregnancy is associated with adverse outcomes such as miscarriage, premature rupture of membranes, preterm birth, growth restriction, and still birth [5].

While less common than constipation, diarrhea or more frequent stools can be a normal physiologic occurrence during pregnancy, particularly at term as a precursor to labor. However, diarrhea can also be a symptom of a more serious cause and therefore should not be ignored, particularly if it is profuse, watery, bloody, accompanied by other symptoms such as fever or severe abdominal pain, or if it lasts more than 48 h [6]. When nausea and vomiting in pregnant women are accompanied by diarrhea, GI infection potentially is a causative factor [6].

As pregnancy in itself is an immunocompromised state hence pregnant women may be more vulnerable to complications, so there should be a lower threshold for investigation, admission, and treatment because with subsequent progression to critical illness there are subsequent risks to fetus from both maternal illness and treatment.

25.2 Anatomic and Physiological Changes During Pregnancy

Almost every organ system of the body in pregnancy is associated with physiologic and anatomic changes including the GI tract. While these changes are adaptive, rather than pathologic, they

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are often implicated in the discomfort that pregnant women experience.

As the uterus enlarges to become an intraabdominal organ, it leads to the displacement of the abdominal organs (intestines and stomach) [7]. The lower esophageal sphincter, which normally helps in preventing acid and stomach contents from moving upwards due to decrease in its tone, allows gastric contents to move up into the esophagus. As the pregnancy advances, gastric pressure increases progressively, increasing the potential for gastroesophageal reflux [8]. The frequent incidence of constipation is due to pressure on the sigmoid colon from the enlarging uterus creating a mechanical barrier, contributing to the frequent incidence of constipation [9]. Small bowel also has diminished motility during pregnancy.

Adding to the effects of these anatomic changes in pregnancy are hormonal effects that carry the potential to greatly influence the GI system:

- Increased levels of hormones such as progesterone causes decrease in sphincter tone leading to delayed gastric emptying and increase in gastric volume which contributes to nausea, vomiting, and gastrointestinal reflux disease [10].
- Increased levels of progesterone also causes decreased peristalsis in the GI tract leading to gastrointestinal reflux disease, constipation, and hemorrhoids [10].
- Gastric acidity is increased because of higher production of gastrin by the placenta.
- Pregnancy induced diarrhea may be due to elevated levels of prostaglandins [11].

25.3 Risk Factors

1. In the developing world the most common risk factor is poor literacy and low socioeconomic status [12]
2. Ingestion of unhygienic food and water contaminated with pathogens from human or animal feces [4]
3. Immunocompromised states.

25.4 Etiology of Gastroenteritis

The causes of diarrhea can be classified as physiological, acute infections, and non-infectious causes (Fig. 25.1).

Gastrointestinal illness that is abrupt in onset in an otherwise healthy person is most often caused by infectious agents. The infectious causes can be categorized into *bacterial, viral, and parasitic infections.*

In developed countries most common infective agents for acute diarrhea are viral. Acute viral infections are most commonly caused by *rotavirus, norovirus, sapovirus, and astrovirus*. Viral gastroenteritis is often spread among family members [6].

Bacterial infections can be spread by human contact, food, and contaminated water. In acute bacterial infection most common causative agents are *Escherichia coli followed by Shigella, Vibrio, Listeria monocytogenes, Salmonella, and Campylobacter* [1].

Acute parasitic infectious agents include *Giardia intestinalis, Cryptosporidium, Entamoeba histolytica, and Dientamoeba fragilis* [1].

Clostridium difficile is often the causative agent when diarrhea follows recent antibiotic use due to the alterations to the normal bowel flora caused by the antibiotic [6]. In pregnant women whose diarrhea is accompanied by other flu like symptoms like fever, back pain, chills *listeria* as a cause must be considered, particularly if there has been a recent outbreak of foodborne illness due to this bacteria [13].

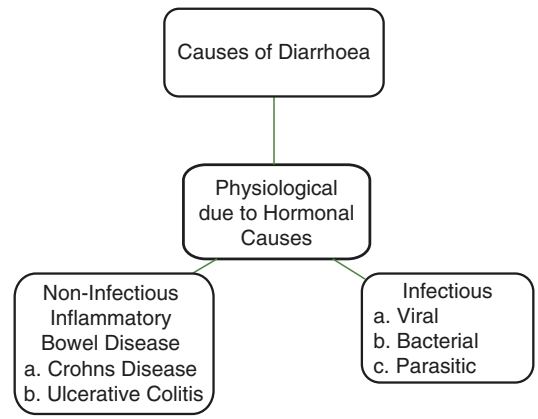

Fig. 25.1 Causes of diarrhea in pregnancy

25.5 Symptoms and Pathophysiology of Infective Diarrhea

Symptoms may be mild and usually self-limiting; but can be severe, leading to dehydration and even preterm labor pains. Common symptoms include loose stools, myalgia, fatigue, fever, headache, nausea, vomiting, blood and mucus in stools.

The mechanisms which have been proposed to cause diarrhea are:

- A change in active ion transport by decreased sodium absorption or increased chloride secretion
- Change in intestinal motility
- An increase in luminal osmolarity
- An increase in tissue hydrostatic pressure [14].

The pathophysiology underlying acute diarrhea by infectious agents produces specific clinical features that may also be helpful in diagnosis (Table 25.1). Profuse watery diarrhea secondary to small bowel hypersecretion occurs with ingestion of preformed bacterial toxins, enterotoxin producing bacteria, and enteroadherent pathogens like *Clostridium perfringens*, Giardia, *Escherichia coli*, and *Staphylococcus* [2].

Diarrhea associated with marked vomiting and minimal or no fever may occur abruptly within a few hours after ingestion of the preformed bacterial toxins and enterotoxin producing bacteria. On the other hand, vomiting is usually less; abdominal cramping or bloating is greater, and fever is higher with the enteroadherent pathogens. Cytotoxin producing and invasive microorganism all cause high fever and abdominal pain. Invasive bacteria and *Entamoeba histolytica* often cause bloody diarrhea known as dysentery [2] (Table 25.1).

Table 25.1 Association between pathophysiology of causative agents and clinical features in acute infectious diarrhea [2]

Pathobiology	Incubation period	Emesis	Abdominal pain	Fever	Diarrhea
Toxin producers 1. *Staphylococcus* 2. *C. perfringens* 3. *E. coli* (enterotoxin) 4. *B. cereus*	1–72 h	3–4+	1–2+	0–1+	3–4+watery
Enteroadherent 1. *E. coli* 2. *Giardia* 3. Helminths	1–8 days	0–1+	1–3+	0–2+	1–2+, watery, mushy
Cytotoxin producers 1. *C. difficile* 2. *E. coli* (hemorrhagic)	1–3 days	0–1+	3–4+	1–2+	1–3+ watery then bloody
Inflammatory minimal 1. Rotavirus 2. Norovirus	1–3 days	1–3+	2–3+	3–4+	1–3+, watery
Inflammatory variable 3. *Salmonella* 4. *Campylobacter* 5. *Vibrio*	1–11 days	0–3+	2–4+	3–4+	1–4+watery or bloody
Inflammatory severe 6. *Shigella* 7. *E. coli* 8. *Entamoeba histolytica*	1–8 days	0–1+	3–4+	3–4+	1–2+, bloody

B. cereus—Bacillus cereus; *C. difficile—Clostridium difficile*; *C. perfringens—Clostridium perfringens*; *E. coli—Escherichia coli*

25.6 Diagnosis and Assessment

History: One of the important tools for assessment is a thorough history which should be elicited from the patient to assess when the diarrhea started, frequency of stools, passage of blood in stools, back pain, myalgia, and abdominal pain including its nature and severity. History of any other additional symptoms like nausea, vomiting, and fever, any history of recent travel, recent antibiotic use, similar complaints in other family members, and any past history of chronic diarrhea should also be elicited (Box 25.1).

Clinical assessment: The woman should be evaluated for the degree of dehydration, abdominal signs suggesting an acute abdomen, uterine contractions indicating premature labor and fetal well-being. Concerning signs and symptoms include: profuse watery diarrhea with dehydration, grossly bloody stools, fever>101 °F, duration > 48 h without improvement, signs of volume depletion (rapid pulse, dry mucous membranes), recent antibiotic use, new community outbreaks, associated severe abdominal pain, and diarrhea in the immunocompromised patients [15]. Most episodes of acute diarrhea are mild and self-limiting.

Box 25.1 Salient Points in History

- Onset and duration of symptoms
- Frequency and nature of stools
- Consistency, volume, and color of stools
- Passage of blood in stools
- Associated symptoms like fever, myalgia, back pain, nausea, and vomiting
- Abdominal pain (onset, nature, site)
- Recent travel history
- Recent antibiotic use
- Similar complaints in other family members
- Past history of any chronic diarrhea

25.6.1 Laboratory Investigations

Investigations to evaluate a patient with acute gastroenteritis include:

- Complete hemogram—To evaluate baseline hemoglobin and total leucocyte count to rule out infection.
- Serum electrolytes—To evaluate dyselectrolytemia due to loose stools, vomiting, and dehydration
- Kidney function tests including blood urea and serum creatinine
- Blood culture and sensitivity—To detect any possible causative pathogen
- Urine routine microscopy and culture
- Stool examination for ova, cyst, and culture. The cornerstone of diagnosis in those suspected of severe acute infectious diarrhea is microbiologic analysis of stool (Fig. 25.2a,b).
- Ultrasound for the fetal well-being
- Inflammatory markers—Various markers are now being evaluated for acute gastrointestinal infections including C-reactive protein (CRP) level and blood neutrophil count.
- C-reactive protein—CRP has been assumed to be a marker of bacterial infections [16, 17]; however, it can also be used to distinguish between bacterial and viral infections [18]. Recently, other markers of infections have also been introduced as possible candidates for routine clinical use, such as lipopolysaccharide-binding protein (LBP), an acute phase protein [19], and interleukin-6 (IL-6).
- Lipopolysaccharide-binding protein—LBP binds the lipopolysaccharide (LPS) of Gram negative bacteria to form an LPS–LBP complex. This complex after binding to CD14 and Toll-like receptors results in initiation of pro-inflammatory cytokine production [20, 21]. LBP could, therefore, be an ideal candidate as a biomarker for gastrointestinal bacterial infections.

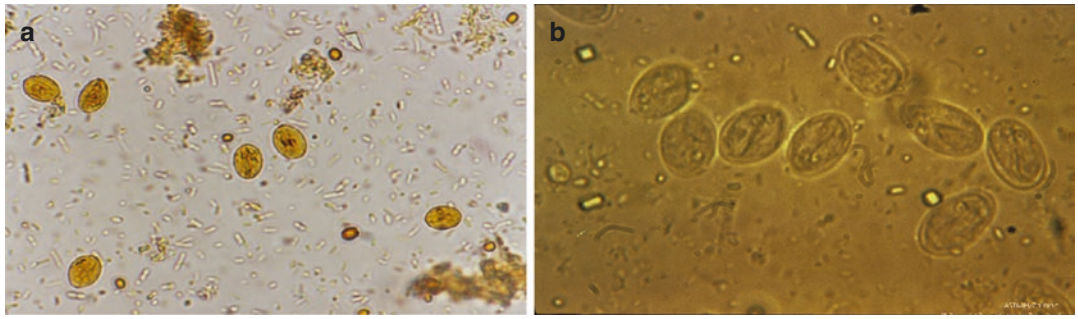

Fig. 25.2 Stool for ova/cyst of (**a**) *Entamoeba histolytica* (**b**) *Giardia*

- Interleukin 6—During early phase of inflammatory processes plasma concentrations of IL-6 get elevated [22, 23]. IL-6 levels correlate with the severity of sepsis and inflammation [24] and play a major role in inducing the synthesis of acute phase proteins, such as CRP and LBP [25]. Thus, IL-6 is also a potentially interesting marker to evaluate during the early phase of infection.

In a study by Elsing et al., lipopolysaccharide based protein (LBP), C-reactive protein (CRP), WBC, and IL-6 levels were used as markers for infection to differentiate between viral and bacterial infection. They found LBP and CRP to be increased in bacterial infections. LBP and CRP appeared to be superior as compared to WBC and IL-6 as a diagnostic marker for bacterial gastrointestinal infections [26]. These markers can be used to prevent unnecessary use of antibiotics in cases of viral gastrointestinal infections.

Fig. 25.3 WHO ORS Solution (for adults)

25.7 Treatment

The mainstay of treatment should focus on supportive therapy, dietary changes, and maintenance of hydration.

25.7.1 Fluid and Electrolyte Replacement

The most common risk associated with diarrhea, particularly in vulnerable populations such as pregnant women, is dehydration and so fluid and electrolyte replacement is an essential part of treatment. Fluid replacement alone may suffice for mild cases. Unless the diarrhea is accompanied by vomiting, this can usually be accomplished orally with extra fluids such as water, clear juices, decaffeinated beverages, or broth. Foods high in fat and lactose should be avoided whereas bland foods and foods low in fiber may be beneficial. A more restrictive diet such as BRAT diet (banana, rice, apple sauce, toast) may be recommended and has been shown to decrease the nausea associated with diarrheal episodes.

Rehydration solutions (ORS) containing both glucose and salt are recommended (Fig. 25.3). The World Health Organization recommends oral

rehydration solutions as it is based on the sodium/glucose coupled active absorption mechanism. These solutions are beneficial as they contain sodium and glucose and are formulated with a concentration and osmolality similar to luminal fluid [27]. Patients should also be advised to minimize or avoid caffeine, alcohol, and sugary beverage intake, because these products may also worsen pre-existing diarrhea.

If the diarrhea is more severe and in profoundly dehydrated patients, intravenous rehydration is required. Mainstay of treatment in such women is intravenous hydration using normal saline or ringer lactate with potassium supplements in amounts to restore maternal blood volume and to ensure uteroplacental perfusion. Monitoring of vital signs and urine output are important for monitoring signs of sepsis syndrome [28].

25.7.2 Adsorbents

Adsorbents such as attapulgite, kaolin, polycarbophil, and pectin are used for symptomatic relief in mild diarrhea. They have a non-specific mechanism of action. There is little evidence of their efficacy, and they may not alter stool frequency, stool fluid losses, or the duration of diarrhea. These compounds may adsorb nutrients, toxins, drugs, bacteria, and digestive enzymes in the GI tract [14]. According to the FDA, polycarbophil is the only effective adsorbent agent. Polycarbophil may modify watery stool output by absorbing up to 60 times its weight in water [29]. Adverse effects of adsorbents are constipation, bloating, and fullness [14]. These products are pregnancy category B drugs [27].

25.7.3 Digestive Enzymes

Lactobacillus acidophilus is a digestive enzyme that helps shorten the course of diarrhea by restoring the normal flora. It may prevent changes in fecal flora and the resulting diarrhea associated with antibiotics [14]. Limited data suggests no link between lactobacillus use and congenital abnormalities, but further research is needed [30].

25.7.4 Antibiotics

Antibiotics are not routinely recommended as most of the episodes are self-limiting. Judicious use of antibiotics is appropriate in selected instances of acute diarrhea and may reduce its severity and duration. In moderately severe non-febrile and non-bloody diarrhea, antimotility and anti-secretory drugs such as loperamide can be given as last resort to control symptoms; such agents should be avoided with febrile dysentery which may be exacerbated or prolonged by them.

For moderate to severely ill women, some recommend empirical treatment with antibiotics, most commonly ciprofloxacin. When specific pathogens are identified, they can be treated if required. Syndromes for which treatment is usually unnecessary include those caused by *Escherichia coli*, Staphylococcal species, *Bacillus cereus*, and Norwalk like virus. Severe illness caused by *Salmonella spp* is treated with ciprofloxacin or trimethoprim-sulfamethoxazole; infection by *Campylobacter spp* with Azithromycin; *Clostridium difficile* with oral Metronidazole or Vancomycin; and *Giardia spp* and *Entamoeba histolytica* with metronidazole [4, 31]. Cases of moderately severe diarrhea with fecal leukocytes or gross blood may best be treated with empirical antibiotics rather than evaluation (Table 25.2).

Table 25.2 Treatment of acute gastrointestinal illness [28]

Prevention	Hand washing Avoidance of contaminated foods
Non-pharmacological treatment	Hydration with salt/sugar-containing fluids bland foods, avoid milk and high fat-containing foods, BRAT diet (banana, applesauce, rice, and toast)
Pharmacological treatment *Toxin producers* 1. *Staphylococcus* 2. *C. perfringens* 3. *E. coli* 4. *B. cereus*	Antibiotics as indicated for infectious diarrhea caused by bacteria 1. None 2. None 3. Ciprofloxacin 4. None

Table 25.2 (continued)

Enteroadherent 1. *E. coli* 2. *Giardia* 3. Helminths	1. Ciprofloxacin 2. Tinidazole 3. As detected
Cytotoxin producers 1. *C. difficile* 2. *E. coli*	1. Metronidazole 2. None
Inflammatory 1. Rotavirus, norovirus 2. *Salmonella* 3. *Campylobacter* 4. *Vibrio* 5. *Shigella* 6. *E. coli* 7. *Entamoeba histolytica*	None Ciprofloxacin Azithromycin Doxycycline Ciprofloxacin Ciprofloxacin Metronidazole
Anti-secretory/motility drug Inflammatory bowel disease	Loperamide—initial dose of 4 mg followed by 2 mg after each loose stool not to exceed 16 mg/day (avoid if caused by bacteria or if diarrhea is bloody) Sulfasalazine—3–6 gm daily in divided doses

25.7.5 Ultrasonography

Lastly after initial resuscitation, ultrasound for fetal assessment should be done for fetal well-being.

Treatment of acute diarrhea is detailed in Fig 25.4. Treatment of chronic diarrhea should be in the context of therapy for the underlying disorder.

25.8 Maternal and Fetal Outcomes

Maternal—Gastroenteritis is rarely life-threatening, but causes significant distress and also impairs quality of life. There is a risk of premature rupture of membranes and preterm labor pains. Some studies have shown that there is a risk of chronic hypertension and increase in mean arterial pressure in early pregnancy among women who experience gastroenteritis after exposure to bacterial contaminated drinking water [32].

Fetal—There is an increase in prevalence of miscarriage, low birth weight, and premature birth and there is a risk of still birth also in women who suffer from gastroenteritis in pregnancy [5].

Ludvigsson et al. [5] in their study on effect of gastroenteritis at different gestations during pregnancy on neonatal outcome did not find any significant difference in the duration of pregnancy in both the groups. However, a substudy analysis found that gastroenteritis during months 4, 5, and 7 of pregnancy was associated with an increased risk of preterm birth. They also inferred that three or more episodes of gastroenteritis during pregnancy may increase the risk for preterm birth. The mechanism of preterm birth in women with gastrointestinal disease is unknown. It could be similar to the reasons in inflammatory bowel disease and celiac disease, i.e. intestinal inflammation and suboptimal nutrition. Though there was no effect on birth weight, infants born to mothers with gastroenteritis during the 8th month were at increased risk (adjusted analysis) to require neonatal hospital care.

25.9 Novel Corona Virus

The emerging pandemic due to corona virus has also been implicated for the gastrointestinal manifestations in pregnant women in addition to the respiratory symptoms [3].

According to the evidence, gastrointestinal manifestations have also been observed in some patients suffering from COVID-19. One hypothesis in this regard is the use by the coronavirus of human angiotensin-converting enzyme 2 (ACE-2) receptors located on intestinal cells, hepatocytes, and cholangiocytes [33]. Another possible mechanism is that changes in the composition and function of the gastrointestinal tract and respiratory tract flora can affect each other. This effect is called the "gut-lung axis" and can help explain why patients with COVID-19 often have gastrointestinal symptoms [34]. Sellevoll et al have discussed a case of a woman who was admitted with acute abdominal pain and suspected cholecystitis with no symptoms of respi-

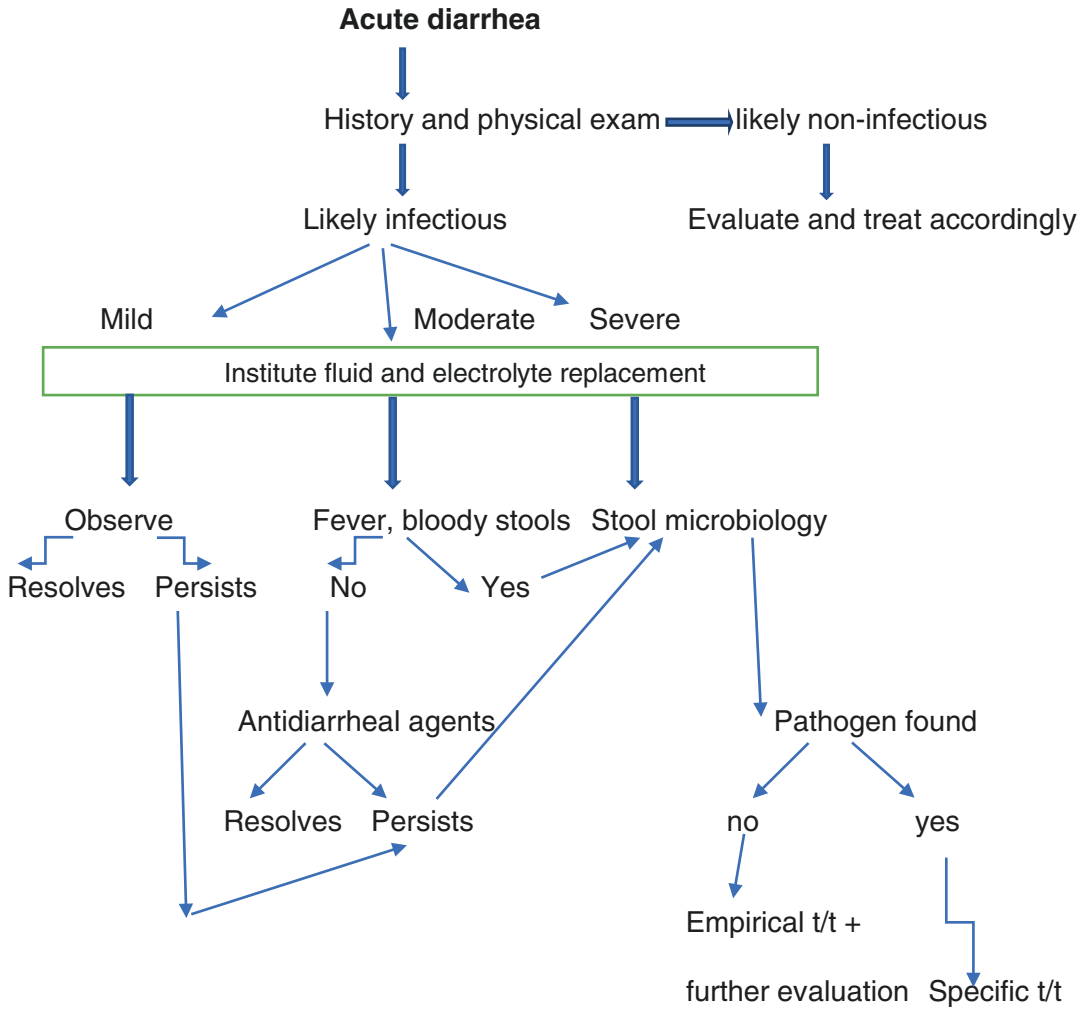

Fig. 25.4 Algorithm for the management of acute diarrhea [2]

ratory infection, but eventually, a coronavirus test was positive [35]. Findings from some studies on pregnant women infected by SARS-CoV-2 have indicated gastrointestinal symptoms such as diarrhea, abdominal pain, nausea, and vomiting in addition to respiratory symptoms [34, 36]. The most common GI manifestation in such women was found to be diarrhea followed by abdominal pain. Treatment is same based on the symptoms and is usually self-limiting. Management of COVID-19 infection in pregnancy has been discussed in detail in Chap. 22.

25.10 Conclusion

Gastrointestinal system disorders can manifest as a variety of symptoms in a pregnant woman. Mostly pregnant women experience one or more GI discomfort throughout their pregnancy. The common manifestations are heart burn, gastroesophageal reflux disease (GERD), constipation, diarrhea, hemorrhoids, and pica. The etiology of diarrhea in a pregnant female can be physiological, non-infectious, and infectious. Usually, the symptoms are self-limiting

and can be managed conservatively but if along with diarrhea there are other symptoms like abdominal pain, fever, nausea and vomiting, or dehydration, then a need for evaluation for the cause and treatment accordingly is essential. Management could be either non-pharmacological or pharmacological. When drug therapy is needed, it is important to identify the best medication for each situation and use them judiciously.

The antibiotic regimen should be used very cautiously as in most cases the cause is viral gastroenteritis. Hydration therapy remains the mainstay of treatment including oral clear fluids, ORS, and intravenous hydration. Blood and stool culture play a vital role in bacterial and parasitic gastroenteritis. Although diarrhea is self-limiting in most cases, assessment is very important to identify the women who need to be admitted as it can have detrimental impact on maternal and fetal health.

The emerging Novel corona virus is also seen to cause GI symptoms in pregnant women along with the respiratory manifestations. The most common GI symptom is diarrhea followed by abdominal pain, nausea, and vomiting. The symptoms are usually self-limiting and are managed conservatively.

As this disease is mostly food and water borne, hence proper hygiene and hand washing are essential for its prevention.

Key Points

1. Pregnant women are susceptible to nausea, vomiting, gastroesophageal reflux, constipation, and diarrhea at rates similar to or higher than the general population.
2. Normal hormonal and structural changes associated with pregnancy are responsible for most of the pregnancy induced gastrointestinal disorders.
3. Mostly the symptoms of acute gastroenteritis are mild and usually self-limiting and resolve by supportive therapy like diet modification and hydration.
4. Evaluation is needed when diarrhea is associated with fever, symptoms lasting longer than 48 h, new community outbreak, or patient presents with shock.
5. When symptomatic remission cannot be achieved with non-pharmacologic therapy, pharmacological treatment may be instituted, but the potential teratogenic side effects must be considered.
6. Risk of low birth weight and preterm birth increases due to preterm labor pains which can manifest as a consequence of gastroenteritis.
7. The emerging corona virus is also implicated in causing GI symptom of diarrhea and abdominal pain along with the usual respiratory symptoms.

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Listeriosis

26

Nidhi Arora

26.1 Introduction

Listeriosis is a sparse foodborne illness caused by a gram-positive bacterium called *Listeria monocytogenes*. The disease was first identified in laboratory animals as early as 1926. A decade later, Burn identified it as a cause of perinatal infections in humans in 1936 [1]. The name "Listeria" was coined under the name of the Father of antisepsis, Lord Joseph Lister, in 1940 [2]. The bacteria are ubiquitous in nature. It usually infects the population that is at the extremes of the age, i.e., newborns and elderly, immunosuppressed patients, pregnant women and sometimes can affect previously healthy individuals. In comparison to the general population, listeriosis is seen 13–20 times more commonly in pregnant women, and infections in pregnant women contribute to 16–27% of all listeria infections [3–5]. Most of the times, the infection is seen in otherwise healthy pregnant women with no prior risk elements [6].

26.2 Epidemiology

L. monocytogenes is known to cause foodborne illness reported in sporadic cases, outbreaks, and food recalls all over the world. It became one of the major pathogens causing foodborne illnesses in 1980s which actually resulted in the execution and further improvisation of surveillance strategies in the Western world [7]. Overall, due to the extensive reporting, microbiological surveillance through reference laboratories and systematic food quality control procedures, there was significant decrease in the cases, especially in pregnancy. However, recently new changes were observed in the overall epidemiology of the disease.

A recent large outbreak (2017–2018) caused by this bacterium in South Africa (the largest outbreak worldwide) had an effect on a wider population over a wider geographical area as compared to that caused by the usual local foodborne illness. There were more than 1000 laboratory-confirmed cases with more than 200 case fatalities with 42% infected [8]. The source of the illness was identified as "polony" that is an instant processed meat. The strain of listeria associated with the outbreak was also recognized in the processing environment of the manufacturer of this processed meat. The outbreak had a widespread impact affecting more than 15 African countries [9]. The factor responsible for such a large distribution of the disease was mainly because of the widespread distribution of the processed food product across national as well as international borders.

The largest outbreak in the USA was reported in 2011, which affected multiple states with alto-

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gether 147 people being affected. This outbreak has accounted for the largest number of deaths (n = 33) as seen by any foodborne illness in the USA in greater than the last 80 years. The food product identified was the whole cantaloupe melons from a single farm [10].

Over the last few years, there has been a recent change in the foods/food products identified as sources of Listeria outbreaks, and there has been involvement across the borders, national as well as international. This can be attributed to the free exchange of goods, including food (processed as well as unprocessed), its constituents, and the processing supplies across states as well as countries. The main factors responsible for these mass food outbreaks are the microbiological characteristics of this pathogen, its ability to survive, grow, and then multiply in different environments [11].

The most common vehicles of transmission of Listeria infection are dairy associated products like unpasteurized milk, soft cheese (like queso fresco, feta and camembert), cooked and processed instant meats and sausages, refrigerated foods like seafood, pates, and spreads. The recent outbreaks have challenged our old time understanding of the foods associated with this infection, and foods like raw sprouts and whole cantaloupe melons have been added to the list now [12–14].

Listeria infection is a considered as a notifiable disease in some countries. The Center for Disease Control and Prevention estimates that approximately 1600 cases occur annually and considers L. monocytogenes as the third leading cause of death from foodborne illness in the USA, causing about 260 deaths [15]. On the European front, 28 European countries documented 2206 confirmed human cases of listeriosis and 270 deaths in 2015. This large number accounted for the highest yearly deaths since 2008, making this disease the most severe human zoonotic disease under European Union (EU) Surveillance [16].

26.2.1 Listeriosis in Pregnancy

Listeriosis in pregnancy is associated with significant morbidity, including fetal loss and severe neonatal infection. The incidence of listeriosis in pregnant women is reported as 11% in Italy, 12% in UK, 16.9% in USA, and 17.7% in France [17]. Mylonakis et al. [6], in their case series of 11 pregnant women affected with listeriosis, along with a review of 222 cases from the literature, observed that around 1 out of 5 pregnancies resulted in spontaneous miscarriage or still birth, and around 66% of the infants who survived had neonatal listeriosis [6]. The reported case fatality rate from Listeria is around 60% for fetal or early neonatal infection vs. around 35% for late-onset neonatal infection [15].

Listeriosis during pregnancy is seen more commonly in certain ethnic groups. It is seen more frequently in Hispanic women as compared to non -Hispanic women in USA [6, 18], in women with African origin as compared to French origin [19] and in non-English women compared to those born in the UK [20].

26.3 Microbiology and Pathogenesis

The only species of listeria that is commonly associated with infection in humans is *Listeria monocytogenes*. Rare cases of infection with *Listeria ivanovii* and *Listeria grayi* have also been reported [21, 22]. *L. monocytogenes* is an aerobic and facultative anaerobic, intracellular gram-positive bacillus that is beta hemolytic with characteristic tumbling motility, which can be visualized on light microscopy [23, 24]. On gram staining, Listeria can be mistaken with other gram positive bacilli like diplococci, diphtheroid, enterococci or H influenzae [23]. Because of its intracellular nature, gram staining is not a preferred method for diagnosing Listeria. It is ubiquitous and can survive through wide temperatures

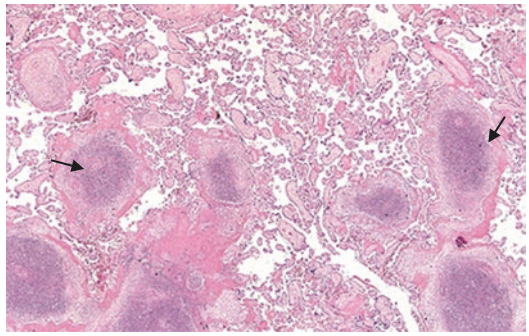


Fig. 26.1 Listeria placentitis: Histopathological image of placenta showing microabscesses with neutrophilic infiltration

varying from 4 to 37 °C. At room temperature, it is highly motile and can replicate actively in diverse medium: soil, water, vegetable decaying matter and animal feed, making them its primary habitat. It can also grow well in low temperatures, allowing it to survive and grow in refrigerated food like deli meats and soft cheese.

Listeria grows easily in most of the commonly used culture media like broth or blood agar. It usually does not need enrichment media when specimen is obtained from aseptic sites. However, if specimen is obtained from the vagina or is a stool culture, selective media are required to inhibit the growth of other commensals inhabiting such sites [25, 26]. On histopathology of infected placental specimens' micro abscesses are found (Fig. 26.1). The mode of transmission is the consumption of foods contaminated with the organism.

26.3.1 Genomic Characterization of Strains of *Listeria Monocytogenes*

Isolates of L. monocytogenes have been grouped into lineages, PCR serogroups, multilocus sequence typing (MLST), clonal complexes (CCs), and core genome MLST (cgMLST) sub lineages and types (CTs) [27, 28]. Overall, 13 serotypes are recognized in literature. A difference in the virulence of these lineages and subtypes have been noted. In particular, hypervirulent MLST clones with high clinical frequency have been identified, such as CC1, CC2, CC4, and CC6 (belonging to lineage 1 and serotype 4b) [29]. Maury et al. [29] reported that these particular strains were seen more commonly in maternal-neonatal listeria infection isolates in France, were also more frequently isolated from milk products [29]. The most common association was seen with CC4 type, 20% of these were obtained from maternal-neonatal infections. On the contrary, CC9 and CC121 (lineage 2) are the most common isolates obtained from food and are rarely seen in maternal-neonatal infections [30]. This is seen because of the difference in the virulence observed in the different groups and their adaptability to the mammalian gut. Of note, CC1, CC4, and CC6 adapt and replicate well and thereby are hypervirulent in comparison to isolates CC9 and CC121 that are hypovirulent as seen in the mouse model of listeria infection. It is seen that these strains are hypovirulent since they express a short and non-functional InlA [29, 30]. The CC4 strain also exhibits placental tropism when used for intravenous inoculation rather than the usual strains (CC7 and CC9) used for reference in experiments [30].

26.3.2 Pathophysiology

The incubation period of listeria infection varies between 24 h and 70 days, with a median of 21 days. The infection results after consumption of food contaminated with the bacteria. The bacteria penetrates through the enteric mucosa into the systemic circulation. Both innate and acquired immune responses help in combating this infection. The immune system responsible for protecting against listeria is cell-mediated immunity, where the circulating T-cell lymphokines activate the local macrophages leading to the removal of the bacteria from the circulation [31–33]. Interleukin (IL)-18 appears to play a role in protection against Listeria by enhancing bacterial clearance, even in the absence of interferon

(IFN)-gamma, and by stimulating macrophages to secrete tumor necrosis factor (TNF) and nitric oxide [32]. On the other hand, factors that impair macrophage survival or function are associated with increased susceptibility to listeria infection. Pregnancy is associated with decreased cell-mediated immunity, thereby providing home to this virulent bacterium. The pregnant uterus gets inoculated by the circulating listeria leading to placental involvement. Once infected, the ability of the bacterium to survive intracellularly makes the placenta a perfect reservoir resulting in active multiplication and increasing overall active bacterial load.

26.3.3 Placental Tropism

It has been seen that maternal-neonatal (MN) Listeriosis with *L monocytogenes* does not correlate well with any immunosuppressed state apart from the pregnancy itself. The clinical manifestation of listeriosis in pregnant women is usually mild with no mortality from listeria itself but has high rate of complications and mortality in fetus and neonates. This may indicate a high affinity of listeria for placental tissue [19].

Experimental studies using in vitro, ex vivo, and in vivo models have helped in understanding the pathophysiology of placental infection of this bacterium. Human placenta is formed with cytotrophoblasts that are epithelial cells that join together and form the syncytiotrophoblast (SYN). This SYN layer comes in straight contact with maternal blood, and this is called hemochorial placentation. Studies using human placental explants of the first and third trimester have shown that L. monocytogenes invades the extravillous trophoblasts (EVT), [34] and syncytiotrophoblasts (SYN) [35] in these explants. Along with that, immunohistochemical studies have shown that it is seen in SYN of placental specimens acquired from women infected with listeriosis.

Multiple studies have documented that listeriosis is most often reported in late second and third trimesters. These studies support the fact that this organism's mode of entry to the placenta is the SYN [19].

The more common incidence of listeriosis in the late second or third trimester can be explained by many factors.

The most important explanation of this association is that the human placenta becomes hemochorial only in the second trimester [36]. Also, there could be a low-grade infection due to the long incubation period of L. monocytogenes in the placenta, which actually becomes the home for this bacterium and further causes multiplication and reinfection [37]. Another hypothesis could be the increase in the percentage of cardiac output to the uterine blood flow, which increases as the pregnancy advances, thereby increasing the chances of seeding into the placenta. Along with that, there is an increase in the critical immune tolerance mechanisms at the maternal-fetal interface in advanced gestation. Listeriosis is also more often seen to affect multiple fetuses (with increased physiological burden), thereby suggesting that the increased physiological burden of advanced gestation can also be a possible explanation [38].

Contrary to these above explanations, one should remember that there might be an underreporting of listeria in early pregnancy losses since the products of conception are not often sent for culture and histopathology, resulting in underreporting. Also, as in early pregnancy, placenta directly invades the decidua, i.e., the uterine wall, making EVT as the portal of entry for L. monocytogenes during that period.

The entry of this bacterium into the host cells is species specific. In vivo studies have reported InlA and InlB are the two proteins of *L. monocytogenes*, which are crucial in invasion of epithelial cells used for culture. Their receptors are also host specific. InlA interacts with E-cadherin (hEcad, adherens junction protein human) while InlB interacts with hepatocyte growth factor receptor (c-Met in human, mouse, and gerbil) [39, 40]. As previously mentioned, the histological sections obtained from cases of MN listeriosis (human) depicted SYN and villous stroma [35]. Ecad and c-Met are both seen on the surface of SYNs and EVT (Fig. 26.2). InlA interacts with

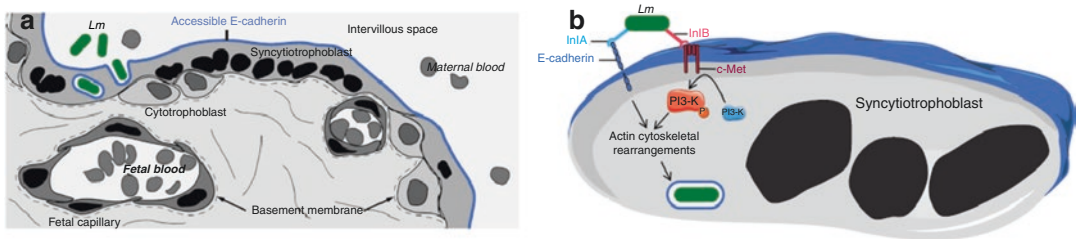


Fig. 26.2 Pathogenesis of Listeria infection of Placenta. InlA and InlB dependent breaching of the placental barrier by Listeria monocytogenes. (**a**) The placental barrier between the maternal blood and the fetus lies in an epithelium, the syncytiotrophoblast, which results from the fusion of underlying cytotrophoblast cells. Syncytiotrophoblast expresses E-cadherin, which is accessible for bacteria in the maternal blood. (**b**) Listeria monocytogenes adheres to syncytiotrophoblast via InlA interaction with Ecad. InlB is required for L. monocytogenes entry by activating PI3-K via c-Met in the syncytiotrophoblast, leading to the actin cytoskeleton rearrangements needed for bacterial internalization

Ecad to adhere the bacteria on the host cell, and then InlB interacts with c-Met and thereby activates PI3-K (phosphoinositide 3 kinase) in the syncytiotrophoblast, which helps in its internalization. The potential role of InlA can be emphasized by the epidemiological fact that 100% of the clinical isolates associated with MN listeriosis demonstrate a non-truncated InLA in comparison to the isolates from the cases of bacteremia (93%) or those obtained from food (65%) [19, 30, 41].

To summarize, MN listeriosis is due to the organism's specific placental tropism that is subsequent to the interaction of InlA and InlB with their respective species-specific receptors at the placental surface. Other pathogenic factors like Listeriolysin O (LLO), which is a pore-forming toxin that helps the organism to avoid its internalization vacuole and modifies host signaling pathways [42] and ActA (Actin assembly-inducing protein) that arbitrates actin polymerization that leads to the creation of comet cells which helps in movement of Listeria intercellularly [43]. Both these molecules play important role in their intracellular survival and multiplication.

26.4 Clinical Manifestations (Table 26.1)

Severe maternal disease due to Listeria in pregnancy is rare, though it has been reported. Most of the women present with mild to minimal symptoms or may be asymptomatic as well. In most case studies, fever has been reported as the most common symptom. It can affect all three trimesters in pregnancy equally, and the overall outcome depends upon the stage of pregnancy affected. Theoretically, co-morbidities affecting the cell-mediated immune system, for example, HIV, diabetes, and use of immunosuppressed agents, may predispose pregnant women to this infection, but most of the cases reported are seen in healthy pregnant women with no predisposing risk factors [6]. As mentioned above in the text, infections are more often seen in the late second or third trimester.

Table 26.1 Clinical manifestations of listeria in pregnancy and neonatal period

Pregnant women	Neonatal infections
• Influenza-like symptoms: fever, malaise, headache • Gastrointestinal symptoms • Back pain • First trimester: Miscarriage • Second/third trimester: Preterm labor, Stillbirth, Meconium stained amniotic fluid, Neonatal infections	*Congenital/Early onset infection (0–7 days):* • Sepsis • Congenital pneumonia and respiratory distress • Skin rash • Neurological symptoms • Jaundice • Disseminated granulomatous lesions called granulomatous infantisepticum • Death (60%) *Late-onset infection (8–28 days)* • Meningitis • Sepsis • Death (20%)

26.4.1 Maternal Manifestations

The estimated incidence of listeria in pregnancy is 3–4 per 100,000 cases. It usually presents with nonspecific flu-like illness with symptoms: fever, myalgia, headache, backache, vomiting, diarrhea, or sore throat, leading to delay in the diagnosis. Women with confirmed listeriosis are more likely to have fever (71% vs. 28%), flu-like symptoms (42% vs. 9%), preterm labor (100% vs. 1.7%), and premature contractions (57% vs. 5%) compared to suspected listeriosis [44]. Mortality is rare in pregnant women, but the outcomes in the fetus as well the newborn can be potentially grave.

26.4.2 Fetal Infection

Listeria is one of the infections that has shown a high transmissibility rate from the mother to the fetus in the intrauterine period. Close to 95% of the mother infected with listeria can transmit the infection to the fetus in the first 14 days of infection [45]. Compared to other common infections like TORCH, Listeria is not teratogenic with no associated fetal anomalies based on the current literature. It however carries significant morbidity and mortality compared to infection in the neonatal period, with multiple studies reporting a high rate of fetal losses in the early pregnancy: 65% compared to 26% in the second or third trimester [15]. In a study looking at the 166 cases of listeria infection acquired during pregnancy, the fetal mortality rate was 100%, 71%, and 5% with infection acquired in the first, second, and third trimester, respectively [46]. The reason for high mortality in the first trimester is not very well clear and is most likely confounded due to better reporting of cases resulting in fetal losses and missing out on the mild or moderate infection due to the nonspecific clinical presentation of the listeria in the pregnancy (flu-like illness).

26.4.3 Listeria in Newborn Period (0–28 Days) or Neonatal Listeriosis

The incidence of listeria in the newborn period is about 8 per 100,000 live births, with an overall reported fatality rate of 20–30% [47]. Infection in a newborn can be transmitted by different routes: trans-placental by infected amniotic fluid or perinatal through the vagina [48]. Early onset within first 7 days can present with neonatal pneumonia and respiratory distress (61%), fever (48%), neurological symptoms (24%), skin rash (20%) and jaundice (5%) [6]. The rate of mortality in early onset is significantly high compared to late-onset (60% vs. 20%) [6]. The infants in late-onset cases (days 8–28) are usually term and are born to asymptomatic mothers with no perinatal complications, with meningitis more commonly reported (90%) compared to early onset [49]. Maternal demographics and outcomes in both early and late-onset cases are comparable, while the overall yield of listeria detection is higher in the early onset cases. The maternal blood culture or genital culture is usually positive for Listeria (44–90%) in the early onset cases [50].

26.4.4 Granulomatosis Infantiseptica

It is a widespread presentation of *Listeria monocytogenes* where diffuse granulomas are seen in various systemic organs like liver, spleen, lungs, kidneys, and brain of the fetus or neonate. There can be associated skin lesions. Mortality is very high in these cases [51]. On histopathological examination of the placenta, there is distinctive chorioamnionitis with acute villitis along with macro abscess formation. Listeria can be seen clearly within the amniotic epithelium with Gram stain or silver methenamine stain. It is considered as a pathognomonic for Listeriosis [52].

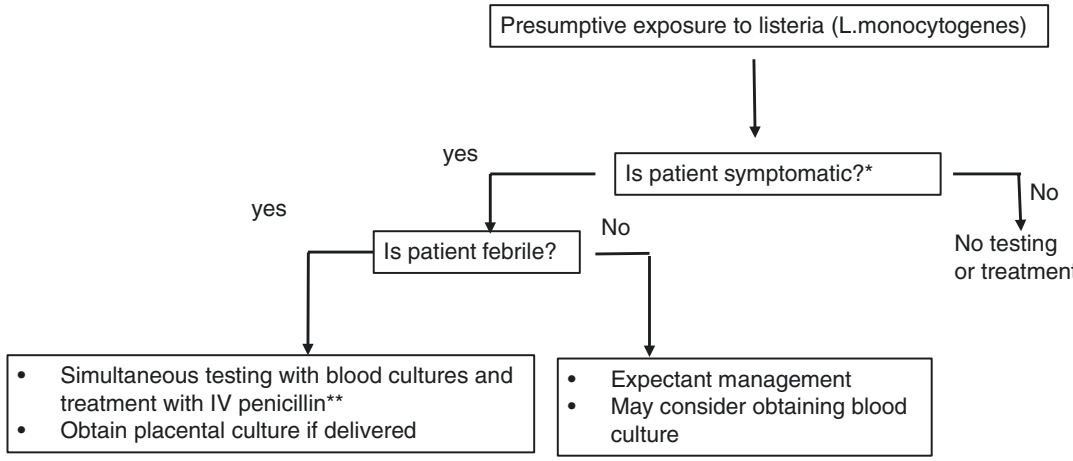
26.5 Diagnosis

Listeriosis can be diagnosed by obtaining cultures from sterile areas like amniotic fluid, blood, or cerebrospinal fluid [53]. Gram staining is not a very sensitive method to diagnose Listeria infection. It gives results in only 33% of cases. It is thereby important to inform the microbiologist about the clinical suspicion of the diagnosis, which can improve the yield from cultures obtained from the contaminated sites like the vagina or rectum [25, 26]. It is always recommended that if a pregnant woman presents with fever and there is a high suspicion of Listeriosis, blood is the specimen of choice. If the amniotic fluid is obtained following amniocentesis, it is mostly meconium stained. Gram-positive rods are seen on staining. Stool culture has not been advocated as a screening or diagnostic specimen for Listeriosis during pregnancy. This is because bacteria are usually present in the food and the environment. It is frequently shed in stool with fecal carriage of around 5% and may not indicate true infection resulting in poor sensitivity for the diagnosis of listeriosis. Polymerase chain reaction (PCR) and antibody testing for listeria are not available currently. Once the diagnosis is confirmed in any individual, it should be reported to appropriate authorities since it is considered as a notifiable disease in many countries.

The aim of listeria infection detection and treatment is to improve the fetal and neonatal outcomes. Guidelines from various countries (Ireland [54], USA [18], Canada [55], and Australia [56, 57]) have been approached to compile in this chapter (Table 26.2). All of these guidelines are based on expert opinions. They have divided the pregnant women with presumed

Table 26.2 Guidelines on the management of women with presumptive exposure to *L. monocytogenes* (from mildest to the most aggressive approach), left to right [58]

	Country			
Symptoms	Ireland [54]	USA [18]	Canada [55]	South Australia [56, 57]
Asymptomatic	No testing, No fetal surveillance, Counsel regarding potential symptoms	No testing, No fetal surveillance, Counsel regarding potential symptoms	No testing, No fetal surveillance, Counsel regarding potential symptoms	Consider to start antibiotic therapy—oral amoxicillin/ampicillin (2–3 g/day for 7 days)
Mildly symptomatic	Consider blood Culture, Consider antibiotic Therapy, Consider fetal surveillance	Consider antibiotic Therapy, Consider fetal surveillance	Stool for routine culture, Consider stool cultures, Counsel regarding potential symptoms	Start antibiotic therapy—oral amoxicillin/ampicillin (2–3 g/day for 7 days)
Severe infection: febrile with or without other symptoms consistent with Listeria	Simultaneously test by blood culture and start the antibiotic therapy, Obtain placental cultures after delivery. If blood culture results negative, consider whether to continue the antibiotic therapy based on clinical status	Simultaneously test by blood culture and start the antibiotic therapy, Obtain placental cultures after delivery, If blood culture results negative, consider whether to continue the antibiotic therapy	Two sets of blood cultures taken from different sites, Another set of blood culture after 48 h if the previous cultures are negative, Culture of other potentially involved anatomic site (e.g., joint, pleural, pericardial fluid, sputum)	Start antibiotic therapy—Intravenous amoxicillin/ampicillin (4–6 g/day for 14 days)



Abbreviation: IV, intravenous. *Symptoms include flu-like symptoms, such as myalgia, abdominal or back pain, nausea, vomiting, or diarrhea;
**Trimethoprim with Sulfamethoxazole should be used if patient is allergic to penicillin

Fig. 26.3 Management of pregnant women with presumptive exposure to listeria

infection with listeriosis into three different groups. The following recommendations from the American College of Obstetricians and Gynecologists (ACOG), Fig. 26.3 [18] are described in the text, whereas all the others are enumerated in Table 26.2.

1. *Asymptomatic Pregnant Women*

For women who are asymptomatic and their only complaint is a possible exposure to Listeria during an outbreak or when noted during recall, no testing is recommended. However, they should be kept on follow-up and should be asked to report if they have symptoms in the 2 months following the exposure. Also, no fetal monitoring is required in such cases, and regular antenatal care is provided.

2. *Mild Symptoms with Listeria-Like Illness Without Fever*

Limited evidence is available to support management in this subgroup. When a pregnant woman presents with gastrointestinal or flu-like symptoms, i.e., myalgias, nausea, vomiting and/or diarrhea with a history of eating food that could be contaminated like Listeria, but does not have fever, then she can be managed using two approaches. The first approach is expectant management, like in asymptomatic pregnant women with a note for follow-up in case she develops fever or symptoms worsen. Another approach is to test the patient followed by treatment if she comes as positive. The test of choice should be blood culture. At the time of delivery, placental cultures can be sent. Of note, it is important to inform the microbiologist with the suspicion of listeria as the causative organism, which helps in increasing the yield of the testing.

Again, the need for treatment is based on clinical judgment; some clinicians would like to initiate the treatment with intravenous penicillin without waiting for the results, while others would prefer to wait for the definitive diagnosis and then start the treatment. There is no data to prove the superiority of either of the above lines of treatment.

3. *Fever With/Without Other Listeria-Like Symptoms*

It is recommended to screen and treat the pregnant women with a history of possible exposure to listeria if she presents with fever (temperature > 100.6 °F). The other symptoms and signs of listeriosis may or may not be present at the time of presentation. With no other identifiable

causes of fever in such women, listeria infection should be presumed, and the appropriate treatment should be initiated. Blood cultures at presentation and placental cultures at delivery should be sent. Since the blood culture has a low sensitivity (0–55%) for listeria, the continuation of treatment if the cultures are negative should be individualized based on the overall clinical status of the patient. Amniocentesis can be considered if the patient is clinically stable, and the laboratory should be informed for the targeted amniotic fluid culture. A multidisciplinary team assessment involving an Infectious diseases specialist and Maternal-fetal specialist is also warranted.

26.6 Treatment

Listeria can survive and grow within host cells, so the infection may not respond favorably to bacteriostatic antibiotics. High dose of Intravenous (IV) ampicillin (6–12 g/day) for 14 days is the recommended treatment of choice. In case of the previous history of penicillin allergy, Trimethoprim with Sulfamethoxazole IV (200–320 mg for 14 days) is the first line of treatment, followed with IV erythromycin (4 g/day for 14 days) or IV vancomycin (1 g/day for 14 days) as a second line of treatment. In an afebrile pregnant woman with a history of exposure to listeria, a 14 days oral amoxicillin regimen of 1 g three times a day is suggested. Initiating a program of fetal surveillance seems prudent for women in whom listeriosis is diagnosed or strongly suspected because of exposure and fever with or without other symptoms, although studies and data do not exist to point to one best plan for such testing.

26.7 Prevention and Surveillance

Prevention and increased surveillance are essential for reducing the fetal and neonatal complications. Different agencies have recommended the following guidelines to minimize the exposure to Listeria:

26.7.1 Infection Prevention in Pregnancy (Table 26.3)

The following recommendations for the prevention of Listeriosis in pregnancy are available on the Center for Diseases Control and Prevention (CDC) website (https://www.cdc.gov/listeria/prevention.html).

Health Protection Surveillance Centre, HPSC Ireland, describes various food safety measures to prevent foodborne illnesses.

Foods should be used for a short period of time and read the labels for dates of manufacture and dates of expiry, including the directions for storage.

Raw meat should be cooked properly and through and through till the center.

Separate uncooked meat from cooked food, vegetables, and ready to eat things.

All fruits, vegetables, and fruits should be washed properly before consuming, including those which are to be peeled and cut items.

Once used, the cutting materials (board, knives, peelers) should be washed properly.

Refrigeration temperatures should be checked periodically.

While heating food in microwave follow instructions given by manufacturer.

Table 26.3 CDC recommendations for pregnant women for food safety to prevent Listeriosis during pregnancy

Foods to be avoided while being pregnant
• Hot dogs, lunch meats, cold cuts (when served chilled or at room temperature; heat to internal temperature of 74 °C [165 °F] or steaming hot)
• Refrigerated pâté and meat spreads
• Refrigerated smoked seafood
• Raw (unpasteurized) milk
• Unpasteurized soft cheeses such as feta, queso blanco, queso fresco, Brie, queso panela, Camembert, and blue-veined cheeses
• Unwashed raw produce such as fruits and vegetables (when eating raw fruits and vegetables, the skin should be washed thoroughly in running tap water, even if it will be peeled or cut)

Data from Centers for Disease Control and Prevention. Listeria (listeriosis). Prevention. Available at: http://www.cdc.gov/listeria/prevention.html. Retrieved July 25, 2014 [18]

Once reheated, food should be consumed. Leftover should not be kept for reuse. If cooked food is to be consumed again, it should be cooled and then refrigerated readily.

If the pregnant women cannot avoid contact with ewes during lambing time, hand hygiene can be really helpful in preventing infection.

26.8 Conclusion

Listeriosis is a foodborne illness caused by *Listeria monocytogenes* which is a gram-positive bacterium. The estimated incidence of listeria in pregnancy is 3–4 per 100,000 cases. Maternal infection manifests as non-specific flu like syndrome to febrile illness, but in 95%cases transplacental infection of the fetus is seen within 14 days of the infection. It is an important cause of fetal demise in the first trimester and is responsible for upto 30% fetal mortality in the newborn period. For symptomatic patients, intravenous ampicillin for 14 days is the treatment of choice and all pregnant women should follow CDC food safety guidelines for prevention of listeriosis.

Key Points

1. Listeriosis is primarily a foodborne disease. It is caused by an intracellular organism which is seen to affect individuals with depressed cell-mediated immune system.
2. Pregnant women are more prone to this infection, so they need to be informed regarding the avoidance of possible foods that are at risk of contamination with the organism, and this should be a part regular antenatal counseling.
3. Listeria is usually asymptomatic in pregnant women but can present with flu-like illness. Its effects on fetal and neonatal life can be devastating, and fatality rates vary between 20 and 30% in the newborn period.
4. For asymptomatic pregnant women who report exposure to a potential food product involved in a food recall or outbreak, no testing or treatment is recommended. She should be followed up for 2 months post-exposure for symptoms.
5. Nonfebrile pregnant women with mild flu-like illness can be managed with two acceptable approaches. First approach is to a have a close follow-up for at least 2 months for fever or other signs and symptoms. The other approach is to evaluate for listeria infection and treat if positive along with fetal surveillance.
6. In case of febrile symptomatic women with high clinical suspicion, testing, and treatment should be promptly initiated.
7. In countries where Listeriosis is a notifiable disease, all positive cases should be notified to appropriate authorities.
8. Pregnant women should be given leaflets to read about Listeria infection and measures that can be taken to prevent it during pregnancy.

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Dermatological Infections During Pregnancy

27

Bhawuk Dhir and Archana Singal

27.1 Introduction

Cutaneous infections during pregnancy are an important part of antenatal care due to their frequent occurrence. The immune responses by the maternal immune system are curbed to permit the survival of her fetus. The altered immune response during pregnancy leads to a higher risk of appearance of occult infections or occurrence of new ones. This is attributed to the high estrogen levels, which causes impaired maternal cellular immunity.

As a result of this altered immune response, infections during pregnancy have the following implications:

- Clinical features as well as progression of the disease may be altered.
- There is risk of certain complications which may pose risk to maternal and fetal health. For instance, congenital malformations due to varicella infection and increased size of genital warts may pose a hindrance for normal delivery.
- Further, the pharmacological approach to the management is often challenging during pregnancy. Most treatment recommendations are based on animal trials. Recent changes in FDA labelling of drugs from the previous pregnancy categories have allowed the prescriber to discuss options with patients in a more lucid manner.
- The altered immune responses during pregnancy cause a decline in the cell-mediated immune response at the maternal fetal axis and subsequent tipping towards Th2 (Fig. 27.1).

Various infections encountered during pregnancy have been classified as under (Table 27.1).

27.2 Viral Infections

27.2.1 Herpes Simplex Virus Infection

27.2.1.1 Introduction and Etiology

Human herpes viruses are a family of DNA viruses, which includes herpes simplex virus types 1 and 2 (HSV-1, HSV-2), Varicella Zoster virus (VZV), Epstein–Barr virus (EBV), Cytomegalovirus (CMV), and Human herpes virus types 6–8. Among these, Herpes simplex

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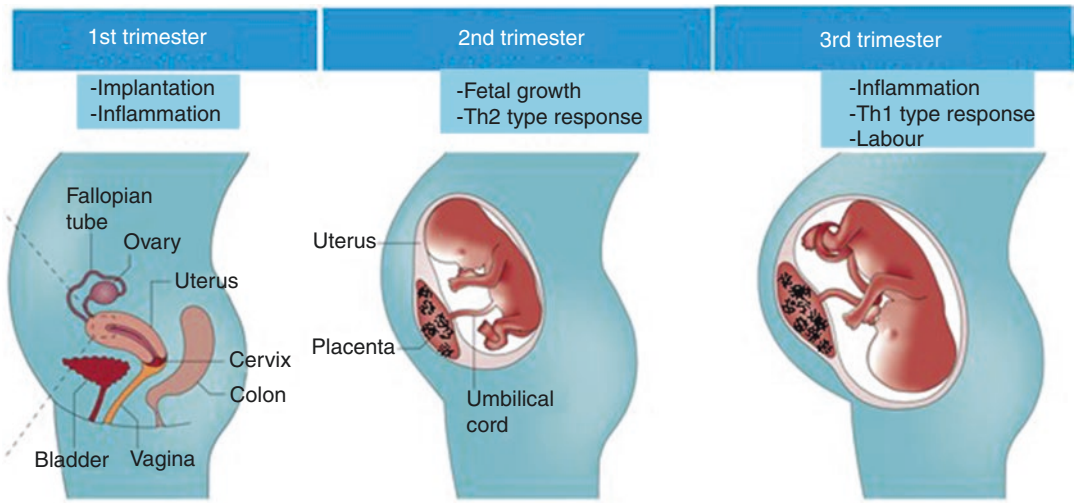

Fig. 27.1 The dynamic immunologic changes during pregnancy

virus type 1 and 2 are important pathogens that need special attention during pregnancy.

HSV-1 is the primary etiologic agent of herpes labialis, gingivostomatitis, and keratoconjunctivitis. In most cases, HSV-2 has genital preponderance, and most genital infections with HSV are due to HSV-2. However, HSV-1 infections are becoming increasingly common as a cause of oral and genital infections, particularly among adolescents and young women. Besides the mother, it poses risks to the fetus and newborn.

27.2.1.2 Epidemiology

Herpes virus is ubiquitous. Genital herpes is one of the most common sexually transmitted infections. Up to 21% of women may have serologic evidence of HSV-2 infection [1]. Reported figures from the USA estimate 1.6 million new HSV-2 infections in adults. During pregnancy, new HSV-1 or 2 cases have an incidence of about 2% [2]. Close to 10% of women without any serologic evidence of prior herpes, have spouses who are seropositive, putting them at risk of herpes during pregnancy [3].

The incidence of neonatal herpes is unknown, but older figures suggest up to 80% of affected infants were born to women with no stated past HSV infection.

27.2.1.3 Pathogenesis

The transmission of viral particles occurs via direct contact with an incubation period ranging from 2 to 12 days. Infection is initiated when the virus makes contact with mucosa or chafed skin. Following the cellular invasion, there is cellular replication in the epidermis and dermis, which causes inflammation and cellular damage.

In most members of the Herpes family, the virus invades the sensory neurons during the primary infection, and then the infection becomes latent in the sensory ganglia. Reactivation of viral replication occurs and may manifest clinically as recurrent ulcerative lesions or sub-clinically as asymptomatic viral shedding. Type-specific antibodies to the viral proteins develop within 2–3 weeks of infection and persist.

When HSV-1 or HSV-2 is identified from lesions in people who do not have any evidence of antibodies to either viral form in the serum, a clinical hypothesis of *primary infection* is confirmed. When one viral type is detected in lesions of individuals with evidence of antibodies to the other viral type in the serum, a *nonprimary first-episode infection* is confirmed. *Recurrent infection* is suspected when individuals with evidence of antibodies to either HSV 1 or 2 in serum have the same viral isolate from the lesion.

Table 27.1 Classification of dermatologic infections in pregnancy

Bacterial	Viral	Fungal	Parasitic	STI (Sexually transmitted infections)
• Gram-positive – Folliculitis,Furunculosis, Abscess – Streptococcal vulvovaginitis – Staphylococcal scalded skin syndrome – Erythrasma, Pitted keratolysis, trichomycosis axillaris • Gram Negative – Meningococcal – Pseudomonal pyoderma, ecthyma gangrenosum – Bartonella – Tularemia, Plague, Melioidosis, etc. • Mycobacterial – Leprosy – Lupus vulgaris – Tuberculosis verrucosa cutis – Lichen scrofulosorum – Scrofuloderma • Anerobic and others – Actinomycosis – Nocardiosis	• DNA virus – Human herpes Virus Herpes simplex virus (HSV 1 & 2) Varicella (Chicken Pox HHV-3) Herpes Zoster (HHV-3) Epstein–Barr virus (HHV-4) Cytomegalovirus (HHV-5) Human herpesvirus type 6,7,8 – Human Papilloma virus (Genital Warts) – Molluscum Contagiosum	• Dermatophytic • Non-dermatophytic	• Scabies • Head louse • Leishmaniasis • Toxoplasmosis	• Bacterial – Gonorrhea – Chlamydia – Chancroid – Donovanosis – Nongonococcal urethritis/cervicitis – Bacterial vaginosis • Spirochetes – Syphilis – Endemic Treponematoses—Yaws, pinta, bejel – Lyme Disease • Viral – Genital Herpes – Human Papilloma virus (HPV) – Molluscum contagiosum – HIV (Human immunodeficiency virus) • Parasitic – Trichomoniasis – Pediculosis Pubis – Scabies

Neonatal herpes is usually acquired intrapartum through exposure to the virus via the maternal genital tract. Approximately 1/3rd to 1/2 of cases of neonatal herpes are caused by HSV-1 [4]. It can be disseminated (25%) , central nervous system disease (30%), or limited to the skin, eyes, or mouth in 45% of cases. Major concern with neonatal herpes is the high mortality, reported at 30% for disseminated infections. Long-term neurologic sequelae are seen in 20% of survivors of neonatal herpes (Box 27.1).

Box 27.1 Complications of Herpes simplex virus infection during pregnancy

Maternal	Fetal
Viral shedding and transmission to neonate	Neonatal herpes
Disseminated disease	Fulminant encephalitis
Encephalitis	Congenital anomalies
Abortions	Microcephaly
	Neonatal chorioretinitis

27.2.1.4 Clinical Features

HSV infections have a wide range of clinical features. The primary infection is usually much more severe, symptoms typically occurring 3–7 days after exposure.

Maternal genital herpes presents with multiple grouped vesicles, which soon rupture to leave behind grouped, polycyclic erosions (Fig. 27.2). Primary episode may lead to a protracted clinical illness with severe genital ulcers and CNS involvement. Occasionally, there may be excruciatingly painful, erosive vulvitis or vaginitis. This can be followed by recurrent episodes, which are less common after HSV-1 infection. There can be intermittent asymptomatic viral shedding with clinically silent infection.

Oral HSV infections in pregnancy are relatively rare. Majority of primary orolabial infections are asymptomatic. In symptomatic cases, mouth and lips are the common sites of involvement (Fig. 27.3). Typical ulcerations at any oral mucosa are accompanied by lymphadenopathy and systemic symptoms. Available literature indicates that HSV-1 gingivostomatitis in the first,

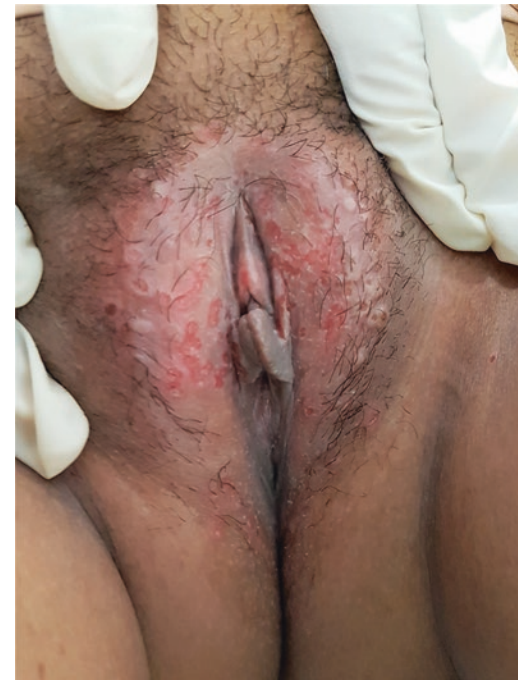

Fig. 27.2 Genital Herpes—Multiple grouped erosions in a polycyclic pattern over the vulva

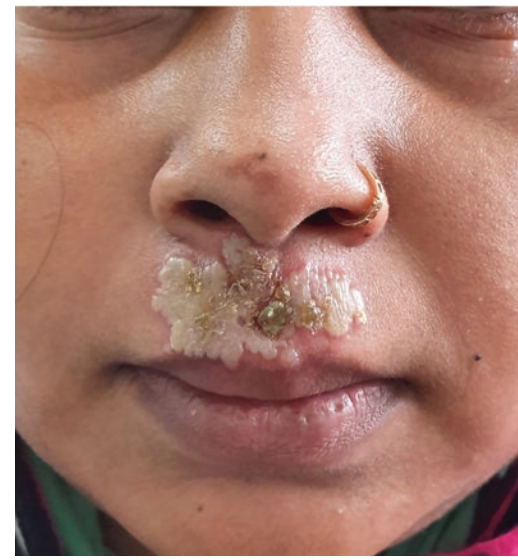

Fig. 27.3 Herpes labialis—Multiple, grouped polycyclic vesicles over the lip

second, and third trimester of pregnancy is not associated with harmful fetal effects. HSV infection needs to be differentiated from other conditions associated with similar manifestations (Box 27.2).

Box 27.2 Differential diagnosis of HSV infection

Orolabial herpes	Genital herpes
• Aphthous stomatitis • Erythema multiforme • Stevens–Johnson syndrome • Behcets disease • Fixed drug eruption • Erosive lichen planus • Herpangina	Other causes of genital ulcer disease such as: Syphilitic chancres Chancroid Lymphogranuloma venereum Traumatic ulceration Aphthous ulcer

27.2.1.5 Diagnosis

Tzanck smear—As an initial modality, smear prepared from the floor of the vesicle/erosion and stained with Giemsa may demonstrate the presence of multinucleate giant cells (MNGC). However, cytologic detection of these cellular changes is an insensitive and nonspecific method of diagnosing genital HSV and, therefore should not be relied on as per CDC recommendations.

Cell culture and PCR are the favored tests for HSV diagnosis. Unfortunately, the sensitivity of viral culture is low, particularly for recurrent cases, and drops rapidly as lesions begin to recover. Nucleic acid amplification tests, including PCR assays for HSV DNA, are more sensitive.

HSV serology—Type-specific serologic assays that reliably differentiate between HSV-1 and HSV-2 antibodies can be beneficial for patients who have a clinical history that indicates HSV but do not present with active lesions or whose lesions have negative culture or PCR results.

Maternal screening for HSV by serology and providing seropositive patients with suppressive antiviral cover has been suggested as an approach to reduce the incidence of neonatal Herpes. However, multiple analyses on cost-effectiveness of such screening programs have revealed high costs ($200,000–$4,000,000) to prevent a single case of neonatal herpes and hence not recommended as per the latest guidelines published by ACOG (2020) [5].

27.2.1.6 Management

Management includes mainly three oral antiviral drugs; acyclovir, valacyclovir, and famciclovir. Of these, acyclovir has maximum evidence for use in pregnancy. Both animal and human evidence indicates that it is safe in pregnancy, even during the first trimester, and that it can effectively minimize viral shedding and lesion persistence. Valacyclovir is a prodrug of acyclovir and is swiftly altered to acyclovir after metabolism in the liver. Further, it has better bioavailability, less frequent dosing and hence, improved patient adherence. Therefore, valacyclovir is presumed to retain the safety benefits of acyclovir. Data on Famciclovir in pregnancy is scarce and not enough to recommend its use during pregnancy.

Management of herpes infection in pregnancy is discussed in detail in Chap. 16.

ACOG Recommendations for the management of herpes in pregnancy include:

- Women with a primary or nonprimary first-episode outbreak in pregnancy, as well as women with a clinical history of genital herpes, should be given a choice for suppressive therapy beginning at 36 weeks of gestation (*Level of recommendation B*) [5].
- Otherwise, for primary outbreaks that occur in the third trimester, the extension of antiviral therapy until delivery may be contemplated.
- Cesarean delivery is required in women with active genital lesions or prodromal symptoms, such as pain over the vulva or burning, because these symptoms suggest active viral shedding (*Level of recommendation B*) [5].
- For women with a history of HSV infection but no active genital lesions or prodromal signs during labor, a cesarean is usually not recommended. But, for females with a primary or nonprimary first-episode genital herpes in third trimester, cesarean delivery may

be offered due to the possibility of prolonged viral shedding.

- Cesarean delivery is not endorsed for women with non-genital lesions (e.g., lesions on back, thigh, or buttock). (*Level of recommendation C*). These lesions may be covered with an occlusive dressing, and the patient can give birth vaginally.

27.2.2 Varicella Zoster Virus (HHV-3)

27.2.2.1 Introduction

HHV-3 (VZV) is the etiologic agent of Varicella (Chicken Pox), and its reactivation leads to herpes zoster (Shingles). Varicella infection during pregnancy can lead to several potentially life-threatening complications for the fetus and mother.

27.2.3 Varicella in Pregnancy

Primary Varicella infection may occur for the first time during pregnancy in a seronegative patient. Usually, the course during pregnancy is more serious, especially during third trimester, with implications for both mother and the fetus.

27.2.3.1 Epidemiology

Around 15 cases per 1000 individuals occur per year in non-immune populations, resulting in a seropositivity of about 95% of young adults [6, 7].

27.2.3.2 Clinical Features

It usually presents with classical features and poses less diagnostic uncertainty. After a prodrome of mild fever, myalgia, and malaise, there is appearance of erythematous, pruritic macules and papules, which have a cephalocaudal progression. These lesions rapidly evolve into clear vesicles with erythematous halo. Subsequently, older vesicles evolve to form pustules and crusts. The hallmark of Varicella is pleomorphism, wherein lesions in various stages of evolution are seen concurrently.

Table 27.2 Summary of maternal and fetal complications in Varicella

Maternal complications	Fetal complications
Secondary bacterial infection of the skin	Congenitalvaricellasyndrome—Cutaneous scars in a dermatomal pattern, limb hypoplasia, microphthalmia, cataract, and chorioretinitis
Scarring	CNS defects—microcephalus, cortical atrophy, or encephalitis
Pneumonia	Low birth weight (80%)
Hemorrhagic exanthema	Developmental delays (50%)
CNS sequelae—encephalitis	Urogenital abnormalities
Hepatitis	Gastrointestinal abnormalities
Glomerulonephritis	Cardiovascular abnormalities
Myocarditis	
Pancreatitis	
Vasculitis	

The risk of viral pneumonia complicating primary varicella in pregnant females is 10%, varying with severity of exanthem and increasing gestational age. This life-threatening complication carries a mortality rate of 10%. Further, there is risk of hepatitis and encephalitis as well (Table 27.2).

27.2.3.3 Diagnosis

Diagnosis is usually clinical, and bedside tests such as *Tzanck smear* demonstrate multinucleate giant cells, which help confirm the diagnosis.

PCR, Immunohistochemical can also help in confirming the diagnosis.

Fourfold increase in the VZV titer in convalescent serum relative to the acute serum *is diagnostic of VZV*. As a result, serology is only useful in retrospect.

27.2.3.4 Differential Diagnosis

The diagnosis is usually straightforward. Rarely, disorders such as PLEVA (pityriasis lichenoides et varioliformis acuta), vesicular viral exanthems (e.g., due to coxsackie virus), disseminated HSV infection, rickettsial pox, drug eruptions, bullous insect bite reactions, and even scabies may cause diagnostic dilemma.

27.2.3.5 Management

Management depends on several determinants—Duration of disease, Gestational age and presence of complications such as pneumonia.

- The first step is to isolate the patient to prevent spread to other patients in the labor room.
- In case the duration is less than 24 h and gestation beyond 20 weeks, the patient should be started on Acyclovir 800 mg 5 times a day.
- In case of disseminated infections, such as pneumonia, hemorrhagic blisters, or prolonged fever, the patient should be started on intravenous acyclovir (10–15 mg/kg/day, three times a day for 7–10 days). Cesarean section should be considered in case of respiratory insufficiency in the mother to minimize maternal and fetal risks. Although Acyclovir can readily cross the placenta, it has not been found to be teratogenic (Pregnancy category B). The chance of spontaneous abortion with a primary varicella infection is around 8%.

27.2.3.6 Congenital Varicella Syndrome (CVS)

Maximum risk of Congenital varicella syndrome (CVS) is between 13 and 20 weeks. Common malformations include cutaneous scars in a dermatomal pattern, limb hypoplasia, microphthalmia, cataract and chorioretinitis. The CNS may be involved in 30% of cases where microcephalus, cortical atrophy, or encephalitis may occur. Further, low birth weight (80%) and developmental delays (50%) are seen. Other rarer abnormalities include the urogenital, gastrointestinal, and cardiovascular systems. The risk of CVS is often overestimated. The estimated transplacental infection rate is around 25%, and about 1–2% of these cases lead to congenital varicella syndrome [8]. Termination of pregnancy may be considered in cases with major CNS anomalies or limb defects. Serial monitoring with high-resolution ultrasound, MRI, IgM against VZV and VZV-specific DNA guides the management strategy. For neonates born with CVS, despite an early high mortality of 30%, long-term outcomes are often favorable. Neonates afflicted by the syndrome should receive intravenous Acyclovir to retard the progression.

27.2.3.7 Seronegative Woman with Potential Exposure to Varicella

A significant exposure to varicella is said to occur if:

1. Living in the same house as a patient suffering from herpes zoster or varicella.
2. Direct contact for a duration greater than 5 min with a patient with active varicella or uncovered herpes zoster, or.
3. Staying in the same room with a patient of varicella or herpes zoster for over 15 min [9].

After such an exposure, if there is no exanthem evident in the pregnant female, an urgent evaluation of the serostatus by an ELISA test is warranted. If the IgG titre is <1:64, the patient is presumed to be susceptible to varicella. An immediate passive immunization with Varicella Zoster Immune Globulin (VZIG) should be done (latest by 96 h of exposure) at any time during pregnancy. Dosing recommendations vary with single IM dose of 0.2 mL/kg being used in the USA and intravenous administration of 1 mL/kg of VZIG in Europe. This approach can thwart the outbreak or at least the serious complications of varicella in the pregnant woman. However, its efficacy regarding the prevention of congenital varicella syndrome in neonates is not established. A milder progression of neonatal varicella may be seen after maternal administration of VZIG. There are no known fetal risks from the administration of immunoglobulin.

27.2.4 Herpes Zoster (HZ) in Pregnancy

27.2.4.1 Epidemiology

People with a history of varicella have a 20% lifetime risk of developing zoster. The annual incidence of HZ in the USA and Europe is 2.5/1000 persons between ages 20 and 50 years,

5/1000 between ages 51 and 79 years, and 10/1000 in those >80 years of age.

If the primary episode of VZV occurs during the second or third trimester during pregnancy, up to 20% of the offspring may develop neonatal or infantile herpes zoster, which is attributable to the inadequately developed cellular immunity [10]. It may occur as early as 2 weeks after birth up to first year of life [11]. With little to no discomfort or scarring, the course is normally uneventful and self-limiting.

27.2.4.2 Pathogenesis

Following primary VZV infection, the virus remains inactive in the dorsal root ganglion. This latent phase may last for several decades. Reactivation of latent VZV in dorsal root ganglia leads to herpes zoster. As it is generally associated with localized viremia, the risk of transplacental transmission is low. In addition, the mother usually has protective antibodies which get transferred to the fetus.

27.2.4.3 Clinical Features

In the majority of patients, HZ starts with a prodrome of itching, tingling, stinging, hyperesthesia, and/or intense pain. Occasionally, the intense pain can give rise to diagnostic confusion with myocardial infarction, acute abdomen or toothache. Sometimes, these symptoms arise without any subsequent cutaneous lesions, a phenomenon known as "zoster sine herpete." However, on most occasions, patients experience painful eruptions on an erythematous base with clustered vesicles distributed in a dermatomal pattern (Fig. 27.4). Thoracic dermatomes are involved most commonly followed by ophthalmic, cervical, and lumbosacral. The lesions may occasionally involve more than one dermatome and can cross the midline.

27.2.4.4 Complications

The maternal and fetal complications associated with HZ infection are summarized in Table 27.3.

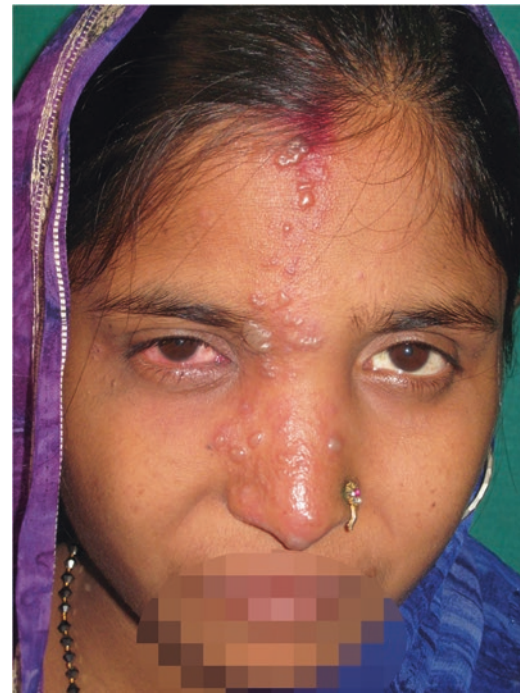

Fig. 27.4 Herpes zoster in pregnancy—Multiple grouped vesicles and bullae in V1 dermatome (Trigeminal nerve)

Table 27.3 Summary of the potential maternal and fetal complications

Maternal	Fetal
• Disseminated HZ	• Neonatal or infantile herpes zoster
• HZ Oticus	• Disseminated herpes zoster
• Hemorrhagic zoster and mucosal involvement	
• HZ Ophthalmicus—conjunctivitis, (epi)scleritis, keratitis, uveitis, acute retinal necrosis, optic neuritis, visual loss	
• Ramsay Hunt syndrome—Facial nerve paralysis, loss of taste in anterior 2/3rd of the tongue, tinnitus, hearing loss and vertigo	
• Peripheral motor neuropathy	
• Diaphragmatic weakness (C3–5)	

27.2.4.5 Diagnosis

The diagnosis is usually clinical. However, diagnostic modalities such as Tzanck smear, PCR, and immunohistochemistry may be utilized for confirmation as in varicella infection.

27.2.4.6 Differential Diagnosis

Important differentials include zosteriform HSV infections, bacterial skin infections (e.g., cellulitis, bullous impetigo), contact dermatitis, and phytophotodermatitis.

27.2.4.7 Management

- As the neutralizing antibodies are transferred from the mother to the fetus and the viremia is usually localized, systemic therapy with an antiviral agent or a VZIG is not necessary.
- However, in case of disseminated HZ, HZ Oticus/ophthalmicus, hemorrhagic zoster and mucosal involvement, intensive therapy is warranted:
  - Intravenous therapy with acyclovir 10–20 mg/kg three times a day.
- Usually, varicella zoster immunoglobulin (VZIG) is not required as there is only a localized viremia.

An algorithm for diagnosis and management considerations in pregnancy is summarized in Fig. 27.5.

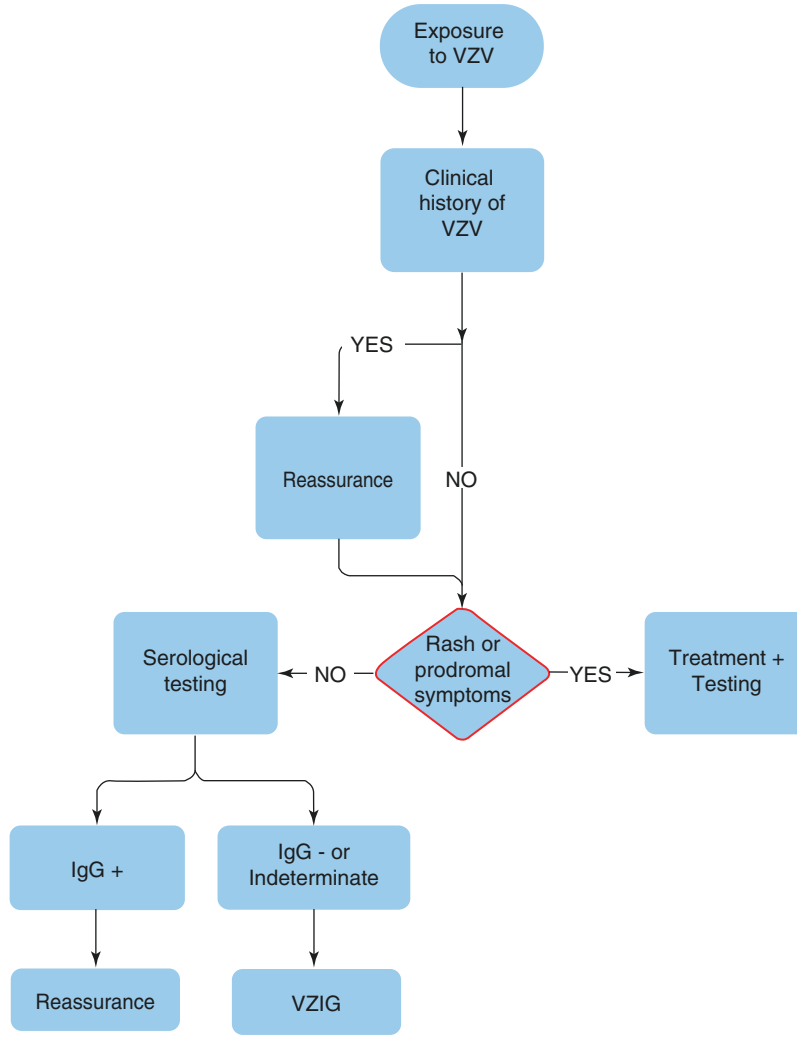

Fig. 27.5 Approach to management of herpes zoster in pregnancy

27.2.5 Human Papilloma Virus (HPV)

27.2.5.1 Introduction

Human papillomaviruses (HPVs) comprise a large group of more than 150 genotypes that infect the epithelia of skin or mucosa and most commonly cause warts. Infection with the common cutaneous HPV types 1, 2, 4, 27, 57, etc., is regarded to have no oncogenic potential. A considerable burden of cancers and anogenital warts are ascribed to high-risk HPV types.

Condylomata acuminata (genital wart) is caused by HPV types 6 and 11 in 90% cases. Rarely, types 16, 18, 31, 33, and 35 have also been implicated and can be associated with foci of high-grade squamous intraepithelial lesions (HSIL), especially in persons who have HIV infection.

27.2.5.2 Epidemiology

A small number of specific HPV types are responsible for cutaneous warts, with a prevalence of up to 30% in the population [12].

HPV infection of the genital tract is among the most common viral sexually transmitted disease worldwide. The estimated prevalence in the USA is around 40% in those ages 19–59 years. However, since the introduction of the quadrivalent HPV vaccine, the prevalence of HPV types 6, 11, 16, and 18 in cervicovaginal specimens has decreased in young girls aged 14–19 years, declining from 11.5% in the pre-vaccine era (2003–2006) to 5% in the years 2007–2010 [13].

27.2.5.3 Clinical Features

Clinical manifestations of cutaneous HPV infection depend on the HPV type isolated, the anatomic site, and the immune status of the host. Table 27.4 summarizes common clinical types of HPV infection and their cause.

Common warts generally present as hyperkeratotic, exophytic, dome-shaped papules, or plaques that are usually associated with HPV-1, 2,4,27, or 57. These typically present on fingers and the dorsal surface of hands. Their management do not usually pose any additional challenges during pregnancy.

Table 27.4 Clinical manifestations and associated human papillomavirus (HPV) types

	Frequently detected HPV Types	Less frequently detected HPV Types
Skin lesions		
Common, palmar, plantar, myrmecial, and mosaic warts	1, 2, 27, 57	4, 29, 41, 60, 63, 65
Flat warts	3, 10	28, 29
Butcher's warts	7	1, 2, 3, 4, 10, 28
Digital squamous cell carcinoma and Bowen disease	16	26, 31, 33, 34, 35, 51, 52, 56, 73
Epidermodysplasia verruciformis (EV)	3, 5, 8	9, 12, 14, 15, 17, 19–25, 36–38, 47, 49, 50, etc.
Mucosal lesions		
Condylomata acuminate	6,11	40, 42–44, 54, 61, 70, 72, 81
High-grade intraepithelial neoplasias (including cervical condylomata plana, Bowenoid papulosis, erythroplasia of Queyrat) and invasive cancer	16	18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 62, 66, 68, 73, 82
Buschke–Löwenstein tumor	6,11	
Recurrent respiratory papillomatosis, conjunctival papillomas	6,11	
Heck disease (focal epithelial hyperplasia)	13,32	

On the palms, soles, and lateral parts of the hands and feet, palmar and plantar warts occur as dense, endophytic papules. Other types include mosaic warts, flat warts, Butcher's warts, etc.

Condylomata acuminata or anogenital warts usually present over the external genitalia and the perineum, which may extend into contiguous areas such as the inguinal fold and mons pubis. Lesions may spread to the vagina, urethra, or anal canal. Typical lesion is discreet, sessile with exophytic papillomas and may be skin-colored, brown or whitish (if macerated) (Fig. 27.6). They may also present as peduncu-

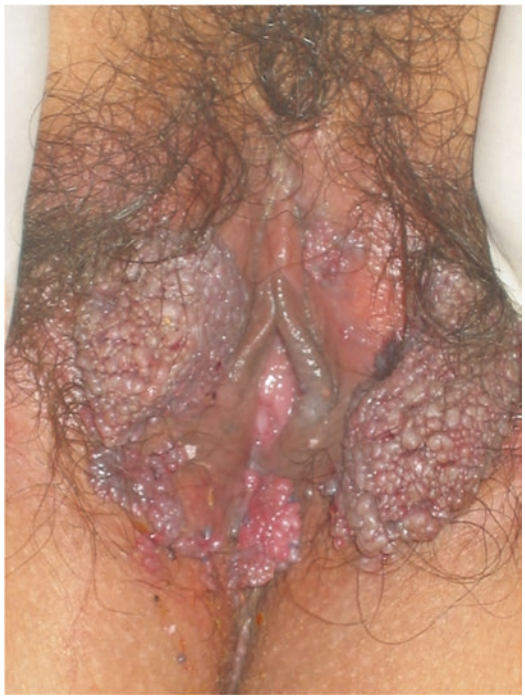

Fig. 27.6 Genital warts in pregnancy—Multiple, exophytic lesions over the vulva in the third trimester of pregnancy

lated or broad-based papillomas up to several centimeters in size.

27.2.5.4 Special Considerations and Complications During Pregnancy

- Due to the reduced cellular immunity and increased vascularity of the female reproductive tract during pregnancy, the size as well as number of warts increases rapidly. Such a growth is seen especially during 12 and 14 weeks of gestation.
- Further, increased friability leads to episodes of bleeding and irritation.
- In some cases, the size of warts may increase to such an extent that it may lead to obstruction of the external genitalia, and the woman may subsequently need a cesarean section.
- HPV transmission to the neonate may occur during delivery and the perinatal period. It may lead to anogenital, oral, or conjunctival lesions in the neonate.

Table 27.5 Complications of HPV infection during pregnancy

Maternal	Fetal
Increase in size and friability	Juvenile laryngeal papillomatosis
Obstruction of the birth passage	Anogenital, oral, or conjunctival lesions
Transmission to neonate	
Excessive risk of bleeding after vaginal delivery	
Bacterial trapping—chorioamnionitis and fetal infection	
Premature rupture of the membranes	
Preterm birth and Placental abnormalities	

- Perinatal transmission of HPV types 6 and 11 may lead to juvenile laryngeal papillomatosis [4]. Whether cesarean section averts respiratory papillomatosis in infants and children is uncertain. Consequently, CDC does not recommend a cesarean section for the only purpose to prevent transmission of HPV to the child. It is indicated for massive warts causing pelvic outlet obstruction or if there is the excessive risk of bleeding after vaginal delivery [4].
- Another major risk is bacterial trapping, which can lead to chorioamnionitis and fetal infection in-utero, as well as premature rupture of membranes by ascending infection. Certain HPV types have been recently associated with preterm birth and placental abnormalities [14]. (Table 27.5)

27.2.5.5 Diagnosis

On most occasions, clinical diagnosis is fairly accurate.

Biopsy: Biopsy is required at times to confirm the diagnosis. Classical features on HPE include papillomatosis, hyperkeratosis, parakeratosis, and acanthotic epidermis with characteristic features of koilocytosis in the middle and superficial epidermis. Koilocytes are large keratinocytes that have an eccentric, pyknotic nucleus with a perinuclear halo. HPV infected cells can have minute eosinophilic granules and diffuse clumps of basophilic keratohyalin granules.

Immunohistochemistry with antibodies directed against cross-reacting epitopes of papillomavirus capsid proteins allows the detection of virions in common warts but is not as accurate in mucosal/genital lesions. Molecular methods for detection of HPV DNA such as nucleic acid hybridization can identify low-risk versus high-risk mucosal HPV types in clinical samples with high sensitivity and specificity. PCR-based techniques can also detect a broad range of genital and skin HPV types.

Detection of subclinical genital HPV infection is aided by inundating with 5% acetic acid for 3–5 min; this leads to whitening *("aceto-whitening")* of lesions and use of a colposcope for magnification will further augment diagnostic accuracy. However, aceto-whitening is not specific for HPV-induced lesions and is also observed in infectious or inflammatory conditions such as Candida vulvitis or balanoposthitis, psoriasis, lichen planus, and eczematous dermatitis.

27.2.5.6 Differential Diagnosis

- Condylomata lata of secondary syphilis; which can be differentiated by serologic testing for syphilis.
- Vestibular papillomatosis—They are tiny, uniformly shaped, finger-like projections at the introitus and on the labia minora; they may occasionally resemble genital warts.
- Others—Molluscum contagiosum, epidermoid cysts and steatocystomas.

27.2.5.7 Management

Management of genital warts during pregnancy can be surgical or non-surgical. Table 27.6 summarizes the recommended treatment options with the level of evidence.

While removal of warts during pregnancy can be contemplated, resolution might be deficient or poor till pregnancy is complete. Surgical modalities including electrocautery, tangential excision with scalpel, cryotherapy, and CO_2 LASER are considered safe during pregnancy and often preferred over non-surgical modalities. Adequate analgesia is essential during such procedures especially nearer to term as excessive pain may precipitate early labor.

Physician applied modalities include the application of TCA in varying concentrations and Podophyllin resin. TCA is considered safe in pregnancy, but the efficacy is poor. Podophyllin resin is a known teratogen (Category X) that may cause ear, heart, and extremities malformation. The active ingredient in Podophyllin resin is Podophtllotoxin which is an anti-mitotic agent

Table 27.6 Management of genital warts during pregnancy

Patient applied therapy		
Modality	Level of recommendation	Pregnancy status
Imiquimod 3.75% or 5% cream	I	US FDA category C
Podophyllotoxin 0.5% soln or gel	I	*Unsafe*. US FDA cat C (Podophyllin resin is category X and teratogen)
Sinecatechins 10% or 15% ointment	I	Unknown/ should be avoided
Provider Administered Therapy		
Modality		**Level of recommendation**
Cryotherapy with liquid nitrogen or cryoprobe		I
Surgical excision: Tangential scissor excision or shave excision, Curettage		I
Electrosurgical excision		I
Surgical excision		III
Trichloroacetic acid (TCA) 80–90% solution		I
Laser vaporization (CO 2, PDL, Nd:YAG)		II

Key to evidence-based data: (I) prospective and controlled clinical trial; (II) retrospective study or large case series; (III) small case series or individual case report [15]

and is also considered unsafe during pregnancy (Category C). Patient applied modalities include Imiquimod 5% cream, Podophyllotoxin, and Sinecatechins. Imiquimod is systemically absorbed in small amounts, but adverse pregnancy outcomes have not been reported. However, due to inadequate studies, its use in pregnancy should be avoided.

As warts tend to regress in size or even spontaneously resolve after delivery, an acceptable option for those who present late in pregnancy can be conservative management.

27.2.6 Molluscum Contagiosum

27.2.6.1 Introduction

Molluscum contagiosum (MC) is a common, benign, cutaneous infection that occurs due to the molluscum contagiosum virus (MCV) of the Poxvirus family. The virus has three genotypes, but the MCV genotype 1 is responsible for most cases of MC. It is a self-limited condition in children but is usually sexually transmitted in adults. Transmission occurs via skin-to-skin contact and, less commonly, fomites.

27.2.6.2 Clinical Features

It usually presents as small, dome-shaped bumps on the skin with dimpling in center (Fig. 27.7). Multiple lesions may occur in clusters associated with itching and tenderness and may last from several weeks to months. Genitals, abdomen, and inner thighs are the common sites. MC genotype MCV 2 has been detected in vaginal lesion specimens. Further, traumatic auto-inoculation of viral particles may occur while itching or rubbing, which leads to linear lesions referred to as *pseudo Koebner* response. There may be an associated molluscum dermatitis in peri-lesional area. Inflammation of MC lesions characterized by the development of a pustule signals the initiation of a host immune response and impending resolution.

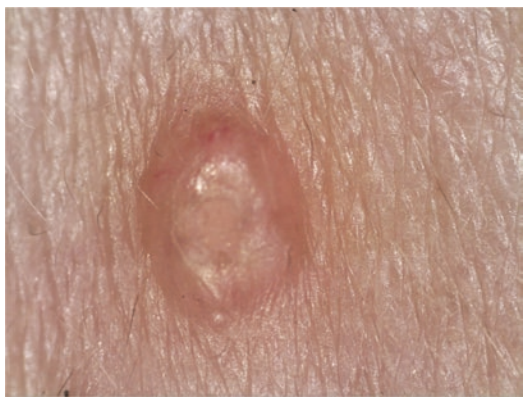

Fig. 27.7 Molluscum contagiosum—Single, skin colored dome-shaped papule with dimpling at center

Mother-to-child transmission is thought to occur during vaginal delivery. So far, there have been few cases of congenital MC reported in the literature where lesions appeared at different postnatal periods ranging from 1 week to 3 months. In all cases, mother's MC was confirmed, indicating the possibility of congenital MC. Morphology of MC lesion in infants is the same as in adults.

27.2.6.3 Diagnosis

The diagnosis is fairly straightforward based on classic clinical features and lesion morphology. In case of uncertainty, crush preparations stained with Giemsa stain reveal classic histopathological feature, i.e., Henderson Patterson bodies.

27.2.6.4 Differential Diagnosis

Differential diagnosis of MC includes adnexal tumors, verrucae, condylomata acuminata, basal cell carcinoma, juvenile xanthogranuloma, melanocytic nevi, papular granuloma annulare, and pyogenic granuloma. In immunocompromised hosts, viral infections such as cryptococcosis or histoplasmosis can mimic MC.

27.2.6.5 Management

In immunocompetent women, MC lesions usually go away without treatment within 6 months to 2 years. In immunocompromised people, the lesions usually persist and spread indefinitely, and hence treatment may be specifically indicated. Treatment options include the application of cauterizing agents such as Trichloroacetic acid, Potassium hydroxide, cryotherapy, curettage, and laser surgery (Fig. 27.8; Table 27.7).

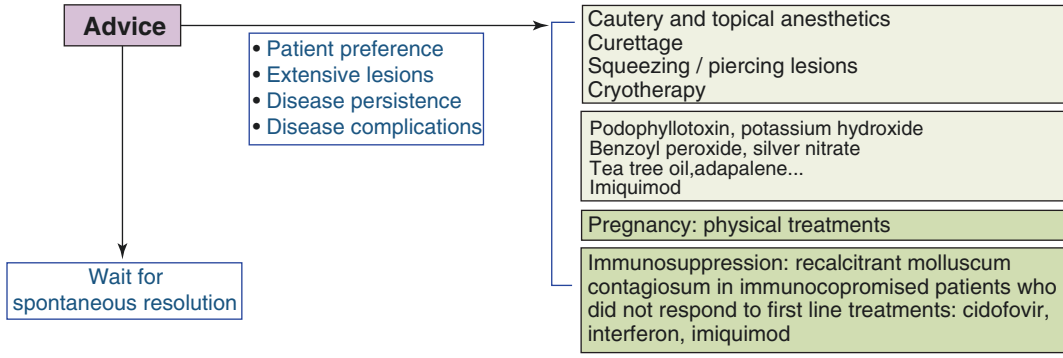

Fig. 27.8 Management plan of molluscum contagiosum patient [16]

Table 27.7 Therapeutic modalities for the management of Molluscum contagiosum [16]

Procedure	Modality	Recommendation and quality of evidence	Pregnancy status
Wait for spontaneous resolution		Grade 2, A	Safe
Physical treatments	Cautery	Grade 1, D	Preferred modality for treatment during pregnancy
	Curettage	Grade 1, C	
	Squeezing/piercing	Weak recommendation	
	Cryotherapy	Grade 1, C	
Topical chemical and other treatments	Podophyllotoxin	Grade 1, C	*Teratogenic*- Not preferred during pregnancy (imiquimod or podophyllotoxin is not advised in pregnancy)
	Potassium hydroxide	Grade 2, D	
	Benzoyl peroxide, silver nitrate	Grade 2, D	
	Tea tree oil, adapalene	Grade 2, D	
	Imiquimod	Grade 1, B	

Key to Table: strength of the recommendations: Grade 1 = strong recommendation (benefits clearly outweigh risks); Grade 2 = weaker or conditional recommendation (risks and benefits are more closely balanced or are more uncertain) Quality of evidence: Grade A = high-quality evidence- randomized controlled trials (RCTs); Grade B = moderate-quality evidence- RCTs with flaws, observational studies; Grade C = low-quality evidence- Trials/observational studies with severe limitations; Grade D = case studies, expert judgment

27.3 Bacterial Infections

27.3.1 Gram-Positive Bacterial Infections

27.3.1.1 Mycobacterial Infections

Leprosy

Introduction

Leprosy or Hansen disease is caused by *Mycobacterium leprae,* which has a predilection for cooler body parts like peripheral nerves, skin, and eyes. It does spread to other organs in its highly bacillated form, i.e., Lepromatous leprosy.

Clinical Features

1. A case of leprosy is identified by the WHO as a person who has not completed the treatment course and has *one or more* of the three cardinal signs: Hypopigmented or erythematous skin lesion(s) with definite loss/impairment of sensation (Fig. 27.9).
2. Definite thickening of a peripheral nerve with sensory impairment.
3. Skin smear positive for acid-fast bacilli (AFB).

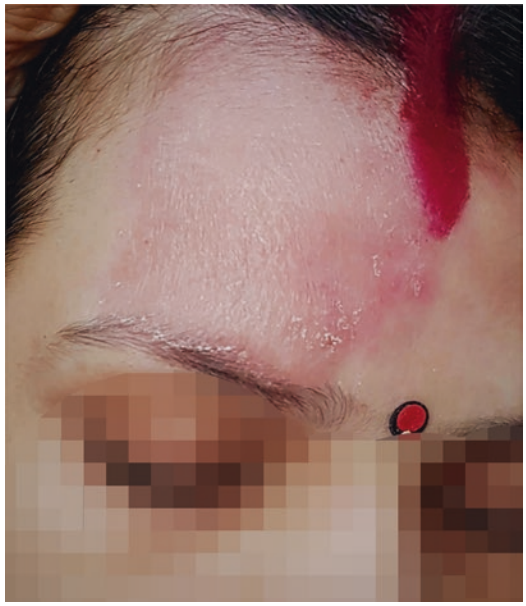

Fig. 27.9 Borderline Tuberculoid (BT) Hansen disease—Single, annular, erythematous plaque with central clearing on the forehead in a pregnant female

Table 27.8 summarizes the Ridley-Jopling classification for the spectrum of leprosy.

Considerations During Pregnancy

There are certain important considerations regarding pregnant patients with leprosy. Pregnancy is associated with downregulation of Th1 response resulting in decreased production of both Th1-associated [interleukin-1 (IL-1), IL-2 and interferon gamma] and other proinflammatory [tumor necrosis factor-alpha and (IL-12)] cytokines and an increased production of Th2-associated (IL-4 and IL-10) cytokines. Due to a shift to Th2 type immune response and depressed CMI, pregnant women are more susceptible to infections such as leprosy. Further, changes in nutritional status and increased levels of physiological steroids also impact the course of disease during pregnancy.

Around 20–30% women may elicit signs and symptoms of leprosy for the first time in preg-

Table 27.8 Ridley-Jopling classification

Characteristics of Ridley-Jopling classification					
Observation	TT	BT	BB	BL	LL
Number of lesions	Usually single (up to 3)	Few (up to 10)	Several (10–30)	Many, asymmetrical (>30)	Innumerable, symmetrical
Size of lesions	Variable, usually large	Variable, some large	Variable	Small, some large	Small
Surface	Excessively dry, scaly, lesions appear turgid	Dry, scaly, lesions appear bright and infiltrated	Dull or slightly shiny	Shiny	Shiny
Sensations in lesions	Absent	Markedly decreased	Moderately decreased	Slightly decreased	Minimally/ not affected
Hair in lesions	Absent	Markedly reduced	Moderately reduced	Slightly reduced	Not affected initially
AFB in lesions	Nil	Nil or scanty	Moderate in number	Many	Innumerable cluster/globi
Lepromin reactivity	Strongly positive (+++)	Weakly positive (+ or ++)	Negative/weakly Positive	Negative	Negative

Key—Abbreviations: TT, tuberculoid; BT, borderline tuberculoid; BB, borderline borderline; BL, borderline lepromatous; LL, lepromatous; AFB, acid-fast bacilli

nancy (due to depression of CMI and resultant multiplication of *M. leprae*) or shortly thereafter (due to recovery of CMI, resulting in reversal reaction) [17]. Further, leprosy aggravates or downgrades in pregnancy and upgrades during lactation.

Transplacental transmission has been suggested to occur due to the presence of IgA (in 30%) and IgM (in 50%) antibodies to *M. leprae* in the cord blood of babies born to mothers with Lepromatous disease. However, such a transmission is tenuous and needs to be validated. Babies born to mothers with LL weigh significantly less at birth than babies born to mothers with tuberculoid leprosy as well as normal healthy controls. Intrauterine growth retardation has been attributed to fetoplacental inadequacy in pregnant women with LL based on lower mean estrogen excretion.

Type 1 reaction, also known as RR, pathogenically due to improvement in CMI, are less frequent during pregnancy (due to decreased CMI) and more frequent in lactation (due to improved CMI). When RRs occur in pregnancy and early postpartum period, cutaneous manifestations are more frequent and conspicuous than the neuritis due to varied antigenic expression of *M. leprae* due to fluctuations in the host CMI. However, Unlike T1R, T2Rs do not have a clear temporal association with pregnancy and lactation.

Neuropathy during the pregnant state may progress faster due to the immunosuppressed state.

Management

With regard to the treatment, Dapsone and Clofazimine both are FDA pregnancy category C drugs, while data on Rifampicin is inadequate. However, *WHO recommends, all pregnant leprosy patients need to be started on MDT irrespective of the trimester.* MDT is to be continued during pregnancy and lactation.

Systemic corticosteroids form the first-line therapy during reactions of leprosy in pregnancy. Anti-reactional drugs like thalidomide, methotrexate, cyclosporine, azathioprine are contraindicated in pregnancy. Breast feeding must be continued even with the ongoing MDT.

Leprosy in pregnancy is discussed in detail in the next chapter.

Cutaneous Tuberculosis

Introduction

Cutaneous tuberculosis (CTB), caused by *Mycobacterium tuberculosis* (*M.tb),* comprises only a small proportion of all cases of TB. However, considering the high prevalence of TB in India, the numbers become significant.

Clinical Features

The clinical spectrum of CTB differs depending on the route of infection (endogenous or exogenous), immune status of patient and prior sensitization of patient with tuberculosis. Primary cutaneous inoculation, usually after trauma, in the non-immune host leads to *tubercular chancre,* whereas, in case of immune host, it develops into verrucous lesions of *Tuberculosis verrucosa cutis* (prosecutor's wart). *Lupus vulgaris* is a chronic, progressive, paucibacillary form of cutaneous TB occurring in previously sensitized individuals (Fig. 27.10). The specific lesion is a plaque, composed of soft, reddish brown papules, which appears like apple jelly on diascopy. *Scrofuloderma* results from the direct invasion of *M.tb* into the skin from an underlying tuberculous focus in bone or lymphnode. Typically, the lesion begins as asymptomatic, bluish-red swelling that breaks down to form ulcer with bluish undermined margin and granulating tissue at the base. Lesions heal with a distinctive puckered scarring mark at the site of the infection.

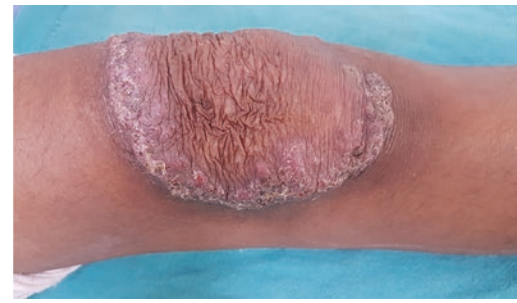

Fig. 27.10 Lupus Vulgaris—Single, annular plaque with central clearing and scarring

Other rare forms of CTB include orificial TB, acute cutaneous miliary tuberculosis and metastatic tubercular abscess. Certain forms of cutaneous TB occur as a hypersensitivity response to mycobacterial antigen and not directly due to M. tb. These are referred to as *Tuberculid* and include *Lichen scrofulosorum*, papulonecrotic tuberculid, and erythema induratum of Bazin.

Diagnosis

In patients with clinical suspicion, a *skin biopsy* is suggested, which shows characteristic tuberculoid granuloma and caseation necrosis. Demonstration of *M. tb* in either *tissue culture* from skin biopsy specimen or cytological smear or the detection of mycobacterial DNA by *PCR* is confirmatory but often difficult esp in paucibacillary TB cases. Ancillary testing such as *Tuberculin test* and evaluation for other foci of systemic TB is important as per clinical suspicion.

Differential diagnosis: Box 27.3 summarizes the differentials.

Box 27.3 Differential diagnosis of cutaneous tuberculosis

- Atypical Mycobacterial infections
- Subcutaneous fungal infections such as sporotrichosis, Phaeohyphomycosis
- Leishmaniasis
- Sarcoidosis
- Verruca vulgaris
- Verrucous carcinoma
- Suppurative lymphadenitis
- Granulomatous rosacea
- Secondary syphilis
- Pyoderma gangrenosum

Management

Treatment of cutaneous TB in pregnancy is standard anti-tubercular therapy consisting of rifampicin, isoniazid, ethambutol, pyrazinamide, and streptomycin. The usual duration of therapy is 6 months but may have to be prolonged in case of partial response.

27.3.1.2 Lymes Disease

Introduction

Lymes disease (LD) is a multisystem disease caused by *Borrelia burgdorferi* spirochetes and transmitted via *Ixodes* tick. It can occur during pregnancy, although less frequently than in non-pregnant patients. There is no proof that Borrelia can be transmitted to the neonate through breastfeeding.

Clinical Features

The principal cutaneous manifestation of Lymes disease is Erythema migrans (EM) which presents typically, within 7–15 days (range, 3–30 days) after tick detachment, as an erythematous, expanding, circular or annular plaque that may have a lighter-colored central area or a bull's-eye appearance. It may occur in any trimester. The eventual diameter is usually at least 5 cm, and the center may become darker red to violaceous in color, crusted, or even vesicular. Untreated, the lesions usually last less than 6 weeks. Erythema migrans is seen in 60–90% of patients diagnosed with LD.

Special Considerations During Pregnancy

Transplacental transmission of *Borrelia burgdorferi* has been reported in animals and also in humans by immunohistochemistry (IHC) studies. Further, adverse pregnancy outcomes such as intrauterine fetal death, prematurity, cardiovascular abnormalities, syndactyly, cortical blindness and hydrocephalus have been reported. However, studies of more than 3500 pregnant women and 1500 offsprings, have not demonstrated a higher risk of organ malformations, prematurity, intrauterine death, or reduced birth weight in patients with Lymes disease [18].

Diagnosis

Mainstay of diagnosis is serological, e.g., ELISA, indirect immunofluorescence and western blot.

PCR is now frequently used for diagnosis. Histopathological features are often not specific, but *Warthin starry stain* may demonstrate the spirochetes from the advancing edge.

Management

The management of Lymes disease during pregnancy remains similar to that of a non-pregnant patient. However, one major exception is Doxycycline which is contraindicated during pregnancy. Tetracyclines can adversely affect fetal bone growth and lead to permanent teeth discoloration. In pregnant patients, such agents can induce fatty liver and hepatic necrosis with fatal effects. Amoxicillin (500 mg thrice a day), cefuroxime axetil (500 mg twice a day) for 2–3 weeks, azithromycin, or ceftriaxone (all FDA pregnancy Category B) are the recommended drugs in the pregnant patient.

27.3.1.3 Sexually Transmitted Disorders

The various sexually transmitted disorders in pregnancy have been discussed in other chapters. Summary of sexually transmitted infections and their associated complications in pregnancy is enumerated in Tables 27.9, 27.10, and 27.11 (Fig. 27.11).

27.4 Fungal Infections

27.4.1 Non-Dermatophytic Infections

27.4.1.1 Vulvovaginal Candidiasis (VVC)

Introduction

Candidal vulvovaginitis may affect up to 50% of pregnant women and is an important cause for consultation during antenatal visits. The enhanced risk is due to increased glycogen content and lower pH value (<5), increased adherence of yeast cells to the vaginal mucosa, and suppression of protective resident bacteria, which enhances fungal development. The risk increases with length of gestation and gravidity. At least 80% of candida vulvovaginitis cases are caused by *Candida albicans*, but non-albicans candida infections, such as C*andida tropicalis*, *Candida glabrata*, and *Candida parapsilosis*, are becoming increasingly common.

Clinical Features

Women are frequently asymptomatic with non-albicans candida infection and early pregnancy. Preterm delivery and low birth weight have been associated with candida vaginitis or persistent asymptomatic vaginal colonization with candida in early pregnancy. The Symptoms of VVC may be more severe during pregnancy, especially during late gestation. Candida can even be passed on to the neonate. Up to half of newborns born to infected mothers may have *C albicans* isolate. Neonatal candidiasis typically occurs from vertical transmission through the contaminated birth canal during transit. It is generally restricted to the skin and mucosa; however, it may result in disseminated infection in low birth weight or immunocompromised neonates. An ascending in-utero infection can result in congenital candidiasis, characterized by generalized skin lesions, pneumonia, and occasionally sepsis, which occur shortly after birth. Box 27.4 lists the maternal and fetal complications

Box 27.4 Maternal and fetal complications of candida infection

Maternal	Fetal
• Preterm delivery • Low birth weight • Increased severity of episode and recurrences • Transmission to offspring	• Neonatal candidiasis • Congenital candidiasis • Disseminated infection with systemic involvement

Diagnosis

The diagnosis can be established by the presence of budding yeast and pseudohyphae on 10% potassium hydroxide (KOH) mount examination and by a positive fungal culture for candida.

Management

For management, CDC [4] recommends the use of only topical azole agents, applied for 7 days during pregnancy. The clinical and mycologic cure rates achieved with topical azole monotherapy can reach 80–90%. As the response is gradual

Table 27.9 Sexually transmitted infections in pregnancy—bacterial

STI–Agents	STI—disease or syndrome	Incubation period	Clinical features	Investigation—key feature	Recommended treatment in pregnancy	Alternatives	Other considerations
Bacterial Neisseria gonorrheae	Gonorrhea—Urethritis, bartholinitis, cervicitis, endometritis, salpingitis, ocular infection	2–5 days	Mucoid/ mucopurulent, or purulent vaginal discharge, burning micturition, Bartholin gland abscess, lower abdomen pain	Leukorrhea (>10 WBC per hpf on microscopy), Culture and NAAT from endocervical swab	Inj. Ceftriaxone 250 mg IM Stat AND T. Azithromycin 1 g Stat	Cefixime 400 mg STAT and Azithromycin Spectinomycin	Usually treatment in required for both gonorrhea and chlamydia
Chlamydia trachomatis D-K	Chlamydial—Urethritis, bartholinitis, cervicitis, endometritis, salpingitis	30 days	Mucoid/ mucopurulent, or purulent vaginal discharge, burning micturition, Bartholin gland abscess, lower abdomen pain	Leukorrhea, Culture and NAAT from first-catch urine or swab from endocervix or vagina	T. Azithromycin 1 g Stat	Amoxicillin 500 mg TDS for 7 days Erythromycin base 500 mg Qid for 7 days	Test-of-cure after 3–4 weeks of treatment is recommended, retesting at 3 months
Chlamydia trachomatis L1,2,3	Lymphogranuloma venereum	3–12 days	Unilateral tender inguinal and/or femoral lymphadenopathy (BUBO), Transient genital ulcer, proctocolitis	Culture, direct immunofluorescence, or nucleic acid detection from lesion swab or bubo aspirate; Chlamydia serology (complement fixation titers ≥1:64)	T. Erythromycin base 500 mg Qid for 21 days	Azithromycin	–
Treponema pallidum	Syphilis	9–90 days	*Primary* syphilis—genital ulcers or chancre *Secondary* syphilis—skin rash, mucocutaneous lesions, and lymphadenopathy *Tertiary* syphilis—cardiac, gummatous lesions, tabes dorsalis, and general paresis	Darkfield examinations, nontreponemal test—VDRL or RPR, treponemal—FTA-ABS, TP-PA, EIA, chemiluminescence immunoassays (fourfold change in Titer is significant in serological tests)	Primary—Inj. Benzathine penicillin G 2.4 million units IM Stat Early Latent Syphilis (<1 year)—Inj. Benzathine penicillin G 2.4 million units IM Stat Late Latent Syphilis—Inj. Benzathine penicillin G 2.4 million units IM once a week for 3 weeks	None in pregnancy Desensitization is recommended for Benzathine penicillin G if allergic	Jarisch–Herxheimer reaction may occur after first 24 h of therapy. (might induce early labor or cause fetal Distress)

(continued)

Table 27.9 (continued)

STI–Agents	STI—disease or syndrome	Incubation period	Clinical features	Investigation—key feature	Recommended treatment in pregnancy	Alternatives	Other considerations
Haemophilus duceyi	Chancroid	1–14 days	painful genital ulcer and tender suppurative inguinal adenopathy	identification of *H. ducreyi* on special culture media	T. Azithromycin 1 g stat	Inj. Ceftriaxone 250 mg IM in a single dose T. Erythromycin base 500 mg TDS for 7 days	No adverse effects of chancroid on pregnancy outcomes have been reported
Klebsiella granulomatis	Donovanosis	3 days to 3 months	Beefy red genital ulcers with subcutaneous granulomas (pseudobuboes)	Demonstration of Donovan bodies on tissue crush preparation or biopsy	T. Azithromycin 1 g orally once per week for 3 weeks OR 500 mg OD for 3 weeks	T. Erythromycin base 500 mg Qid for 3 weeks	–
Mycoplasma, Ureaplasma	Nongonococcal urethritis, cervicitis, salpingitis	1–4 weeks	Burning micturition, discharge	Negative NAATs for chlamydia and gonorrhea, NAAT testing of urine, urethral, vaginal, and cervical swabs	T. Azithromycin 1 g stat (Increased resistance is emerging)	–	–
Gardnerella vaginalis, Prevotella, and others	Bacterial vaginosis	–	homogeneous, thin, white discharge	Clue cells (e.g., vaginal epithelial cells studded with adherent coccobacilli; pH of vaginal fluid >4.5; fishy odor on KOH mount; DNA hybridization probe, PCR	T. Metronidazole 500 mg BD for 7 days OR Metronidazole gel 0.75%, 5 g intravaginally, OD for 5 days	–	Treatment is recommended for all symptomatic pregnant women

Venereal Disease Research Laboratory [VDRL] or Rapid Plasma Reagin [RPR]) and a treponemal test (i.e., fluorescent treponemal antibody absorbed [FTA-ABS] tests, the T. pallidum passive particle agglutination [TP-PA] assay, various enzyme immunoassays [EIAs]

Table 27.10 Sexually transmitted infections in pregnancy—parasitic

STI—agents	STI—disease or syndrome	Incubation period	Clinical features	Investigation—key feature	Recommended treatment in pregnancy	Alternatives	Other Considerations
T. vaginalis	Trichomoniasis	4–28 days	Copious, greenish, foul smelling vaginal discharge, strawberry cervix	Wet mount of vaginal discharge; NAAT from vaginal, endocervical, or urine specimens; Culture from vaginal secretions	T. Metronidazole 2 g stat OR 500 mg BD for 7 days (Avoid any products contacting alcohol for 24 h after taking metronidazole)	Tinidazole should be avoided in pregnant women	a/w premature rupture of membranes, preterm delivery, and delivery of a low birthweight infant
Pthirus pubis	Pediculosis Pubis	1–4 weeks	pruritus in the pubic region, nits at the base of hair shafts, erythema around hair follicles, excoriations, Macula caerulea	Direct identification of crab lice and/or their nits	Permethrin 1% cream rinse applied to affected areas and washed off after 10 min	Pyrethrins with piperonyl butoxide applied to the affected area and washed off after 10 min	–

Table 27.11 Complications of bacterial sexually transmitted infections during pregnancy

Clinical event	Associated STD agents
• Ectopic pregnancy	Prior *C. trachomatis* infection
• Spontaneous abortion	*N. gonorrheae*, bacterial vaginosis
• Post therapeutic abortion-pelvic inflammatory disease	*C. trachomatis*, *N. gonorrheae*, bacterial vaginosis
• Premature delivery, premature and prolonged rupture of membranes	*C. trachomatis*, *N. gonorrheae*, bacterial vaginosis, *M. hominis*, *U. urealycticum*, *T. pallidum*, *Trichomonas vaginalis*
• Amniotic fluid infection	Bacterial vaginosis, *N. gonorrheae*, *Ureaplasma urealyticum*
• Congenital abnormalities	*T. pallidum*
• Intrauterine growth restriction	*T. pallidum*
• Puerperal endomyometritis • Neonatal death, neonatal infection	Bacterial vaginosis, *Strep. agalactiae*, *U. urealyticum, M. hominis*, *T. vaginalis*
• Perinatal	
– Stillbirth – Neonatal death, neonatal infection	• *T. pallidum*, *C. trachomatis* • *N. gonorrheae*, *C. trachomatis*, *T. pallidum*

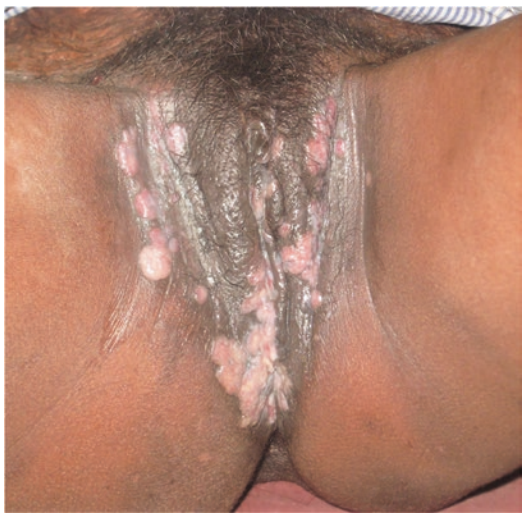

Fig. 27.11 Secondary Syphilis in pregnancy—Multiple, flat, moist papules in the intertriginous area (Condylomata lata)

and recurrences are more frequent during pregnancy, 7–14 days course is suitable. Although any azole may be used, but clotrimazole (1% cream or 100 mg / 200 mg suppositories) and miconazole (2% cream) are favored due to more data and experience. Clotrimazole absorption from skin epithelia and vaginal mucosa is negligible and has no known associated congenital defects.

Nystatin (as cream or vaginal tablets 100,000 units) is used as a second-line therapy. Non-albicans infections, particularly vaginitis, are usually recalcitrant to the conventional antifungals. In such cases, not responding to traditional regimes, the use of amphotericin B vaginal suppositories is an another option. The absorption after topical use is negligible.

Treatment with oral azole is recommended only for serious primary infections with marked inflammation. Fluconazole use during the first trimester has been associated with miscarriages, and its use must be *avoided* during the first trimester. Another therapeutic option is oral itraconazole (200–400 mg once or 200 mg/day for 2–7 days). In prospective research, including several hundred women, the short-term administration of itraconazole in pregnancy was examined and no evidence of teratogenicity was identified [19, 20].

Box 27.5 Management of vulvovaginal candidiasis during pregnancy

Uncomplicated VVC	Complicated VVC—Recurrent, Severe or Non-albicans in immunocompromised
Topicalazoletherapies— Clotrimazole 1% cream 5 g intravaginally daily for 7–14 days Clotrimazole 2% cream 5 g intravaginally daily for 3 days Miconazole 2% cream 5 g intravaginally daily for 7 days Miconazole 4% cream 5 g intravaginally daily for 3 days.	Longer duration of initial therapy (e.g., 7–14 days of topical therapy is required Maintenance therapy with topical agents can be considered in recurrent VVC

27.4.2 Dermatophytic Infections

27.4.2.1 Introduction

Dermatophytes are moulds belonging to the arthrodermataceae family and are a major cause of superficial fungal infections worldwide. They are divided into the three genera—*Epidermophyton, Microsporum,* and *Trichophyton.* Among these*, Trichophyton species,* namely *T. rubrum* and *T. interdigitale*, represent the most common species isolated. They can lead to a spectrum of clinical infections, which include Tinea cruris, barbae, corporis, unguium, capitis, and manuum based on the anatomic region involved. Further, they also cause onychomycosis and *Majocchi's* granuloma.

Recent spurt in number of cases and etiological shifts have led to frequent antenatal consultations for the same. The mode of transmission is usually via direct contact with infected skin or hair retained in clothing, combs, caps, socks, and towels or with animals and soil.

27.4.2.2 Clinical Features

The classic presentation is that of an annular ("ringworm" like) or serpiginous plaque with prominent scaly erythematous border often studded with vesicles that advance centrifugally and central clearing (Fig. 27.12). Concentric erythematous/vesicular rings suggest tinea incognito/ tinea imbricata (often caused by *T. mentagrophytes*), which is secondary to potent steroid application and is very resistant to treatment. Lesion morphology may show minor changes depending on the area of involvement, e.g., macerated lesion with diffuse lesions in flexural areas. *T. rubrum* infections may present as large, confluent, polycyclic, or psoriasiform plaques, especially in immunosuppressed individuals. The clinical presentation of dermatophytic infections does not differ from the non-pregnant state.

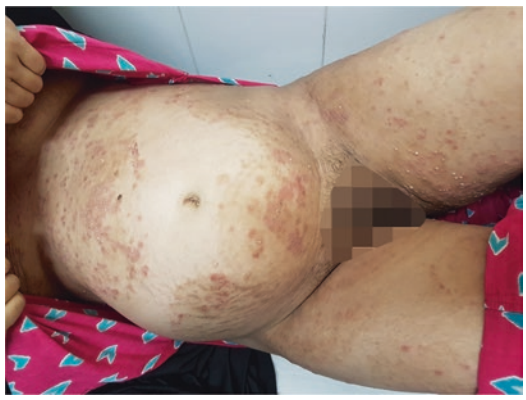

Fig. 27.12 Tinea cruris in pregnancy—Multiple, annular, erythematous plaques with scaling and pustulation

27.4.2.3 Diagnosis

The diagnosis can be confirmed by direct microscopy of potassium hydroxide (10% KOH) mount from the scales from advancing border, subungual debris, or affected hair. It will demonstrate long, septated, and branching hyphae.

Box 27.6 Differential diagnosis

- Erythema annulare centrifugum,
- Nummular eczema
- Psoriasis
- Pityriasis versicolor
- Subacute cutaneous lupus erythematosus
- Cutaneous candidiasis
- Contact dermatitis
- Atopic dermatitis
- Ptyriasis rosea
- Seborrheic dermatitis

27.4.2.4 Management

The diagnosis of tinea is mainly clinical. However, management decisions which maximize benefit and minimize harm to the mother and child are important. The dictum remains to treat it early before it becomes chronic and extensive.

27.4.3 General Measures

As therapeutic choices are limited, the patient should be counseled regarding general measures, including

- Avoiding sharing of contaminated towels and clothing articles, close fitting and synthetic clothing, and excessive sweating.
- Absorbent antifungal dusting powders may be used after taking care of the active infection.
- OM may be treated after lactation is stopped as it mostly requires prolonged antifungal use.

Topical Antifungals: First-line treatment for uncomplicated, localized cutaneous dermatophyte infections such as tinea corporis, tinea cruris, and tinea pedis include:

- Miconazole (2%) and clotrimazole (1%) are safe in pregnancy.
- The data on topical terbinafine and ciclopirox are more limited (Box 27.7).

Topical antifungals are used twice daily, 2 cm beyond the lesion margin, till the lesions reduce and are continued for up to 2 more weeks.

Box 27.7 US FDA Pregnancy categorization of topical antifungals

Topical drug (US FDA category)	
Clotrimazole (B)	Naftifine (B)
Miconazole (C)	Oxiconazole (B)
Nystatin Topical (C) Vaginal (A)	Ketoconazole
Terbinafine (B)	Amphotericin B (B)
Ciclopirox (B)	Luliconazole (C)

In infections involving large body surface areas, tinea manuum, capitis, and unguium, systemic agents are usually required. However, systemic antifungal therapy, although effective, is associated with both maternal and fetal risks, including potentially severe adverse reactions (Box 27.8).

Box 27.8 Pregnancy categorization of systemic antifungals

Systemic drug (US FDA category)
Griseofulvin (C)
Fluconazole (C/D)
Ketoconazole (C)
Itraconazole (C)
Terbinafine (B)

27.4.4 Antifungals

27.4.4.1 Terbinafine

Oral reproduction studies revealed no evidence of any embryo—fetotoxicity in rabbits and rats when administered up to 23 times the maximum recommended human dose. It is not discerned whether terbinafine can cross the human placenta due to limited data on human exposure. A follow-up on 54 women gestationally exposed to terbinafine (26 oral and 23 topical), with 24 exposures occurring during the first trimester and with a mean duration of exposure being 32 ± 9 days, reported no increased risk for major malformations [21]. Though it has been classified as pregnancy category B drug, oral prescription should preferably be postponed until after delivery.

27.4.4.2 Itraconazole

It has been shown that itraconazole is *embryotoxic* and *teratogenic* in rodents, causing craniofacial and rib defects. However, a longitudinal study involving 229 women exposed to itraconazole(198 in 1st trimester) failed to detect any elevated risk of fetal malformations [19].

One more study on 206 women exposed during the first trimester also failed to find any increased risk of malformations (mean daily dose of 182 + 63 mg for a mean of 6.9 + 6.4 days) [20]. An increase in the early fetal loss was however reported. Based on the available data, the drug should *be avoided in pregnancy, especially during the first trimester.*

27.4.4.3 Fluconazole

Fluconazole readily crosses the placenta and has shown *teratogenic* and *embryotoxic* effects at high doses in animals [22]. Oral fluconazole therapy was associated with a distinct history of birth defects in five mothers who were treated with 400–800 mg daily with serious fungal infections during the first trimester of pregnancy. The US FDA released a consumer safety announcement in 2011 about the potential teratogenic effects of long-term, high-dose fluconazole therapy. As a result, the FDA pregnancy category for fluconazole was updated from C (adverse fetal effects in animals and no adequate human data) to D (evidence of human fetal risk, but benefits may warrant use), with the exception for the use of fluconazole at a single dose of 150 mg, for the treatment of vaginal candidiasis.

27.4.4.4 Griseofulvin

Griseofulvin is *carcinogenic, embryotoxic,* and *teratogenic* in rodents at 3–45 times the human dose. A retrospective study compared 38,151 normal pregnancies and 22,843 pregnancies with birth defects in relation to their exposure to griseofulvin (reported in 7 and 21 cases, respectively) and did not find association with any birth defect or with any excess of conjoined twins, as reported previously. But human data are still limited to allow its use in pregnancy, especially in the first trimester.

Box 27.9 Summary of treatment approach to dermatophytosis in pregnancy

Treatment approach to dermatophytosis in pregnancy	
Topicals	*First line*: Clotrimazole, miconazole *Second line*: Terbinafine For *Onychomycosis*: Ciclopirox, Amorolfine
Systemic	• Avoid all systemic antifungals in the first trimester • Terbinafine is category B but very limited human safety data to recommend its use

27.5 Parasitic

27.5.1 Scabies

27.5.1.1 Introduction

Scabies, caused by *Sarcoptes scabiei* mite, accounts for 2–6% of all skin diseases in pregnant patients [23]. The most common means of transmission of the mite is close person-to-person contact. It can also spread by sharing sheets, bedding, or clothes, because the mites can live outside the host for 24–36 h. The female mite can be fertilized by the male once on a human host, and then after impregnation, it burrows into the stratum corneum and lays eggs. After 3–5 days, the eggs hatch, releasing larvae that develop into mature mites in 1–3 weeks.

27.5.1.2 Clinical Features

Two to six weeks after the initial infestation, an infected individual typically presents with excess pruritis which is worse with heat (e.g., hot baths) and at night, when the female is more active. The clinical features include discrete excoriated papules and erosions located in classical sites—interdigital, wrists, axilla, breasts, and periumbilical. "S" shaped furrows are present in the interdigital spaces. Scabies is not usually associated with adverse pregnancy outcomes.

27.5.1.3 Diagnosis

Scrapings from the lesion, especially from furrows in KOH reveal mite, eggs, or fecal pellets. Dermatoscopy shows the jetliner-with-contrail sign at the site of infestation. Multiple household members with itch should raise suspicion.

27.5.1.4 Differential Diagnosis

Its clinical presentation resembles other pregnancy-specific dermatosis like polymorphic eruption of pregnancy, intrahepatic cholestasis of pregnancy which may carry adverse maternal and fetal outcomes. Hence, the differentiation between them is important (Box 27.10).

Box 27.10 Differential diagnosis of scabies in pregnancy

- Atopic eruption of pregnancy
- Intrahepatic cholestasis of pregnancy
- Polymorphic eruption of pregnancy
- Drug reactions
- Viral exanthem
- Dyshidrotic eczema/ Id reaction
- Folliculitis

27.5.1.5 Management

With regards to management, the pyrethroid, *Permethrin 5% cream* is safe and the treatment of choice during pregnancy (*level of evidence III; grade B recommendation)* [24]. No event of teratogenicity has been observed in animal studies and it has <2% systemic absorption. Although Permethrin crosses the placenta, the ingested amount is small and is quickly metabolized, so the risk of fetal exposure is low, *Precipitated sulfur 8%* and *benzyl benzoate 25%* lotion are second-line treatments; however, they are less effective than permethrin. However, the Sulfur application is often messy and associated with foul odor as well as staining and no longer preferred.

Crotamiton and *malathion* are third-line treatment options. Crotamiton 10% ointment (Category C) is not as effective as permethrin, and there is dearth of studies for its use in pregnancy. Malathion 0.5% (Category B) has a percutaneous absorption rate that depends on the formulation and may reach 8% (ace tone vehicle).

Lindane should never be used in pregnancy. When used on abraded tissue, it has the ability to produce maternal neurotoxicity and aplastic anemia. An increased risk of hypospadias can be associated with it when used during the first trimester. Further, neural tube defects and behavioral retardation have also been linked with it.

Ivermectin (Category C) can only be used in the event of a significant infestation, i.e., crusted scabies. Ivermectin has been found teratogenic (oral clefts, clubbed forepaws) at high doses. But, increased risks for miscarriage, stillbirth, congenital malformations or child health disorders have not been reported by mass care services for onchocerciasis.

27.5.2 Cutaneous Leishmaniasis

27.5.2.1 Introduction

Cutaneous Leishmaniasis (CL) is caused by a parasite from the genus Leishmania infection and is transmitted to humans by the bite of female sand flies. The altered of cell-mediated immune response and an increased susceptibility to many infectious agents during pregnancy leads to atypical cutaneous presentation.

27.5.2.2 Clinical Features

The clinical features of cutaneous leishmaniasis (CL) may vary in terms of type and extension, ranging from single, chronic ulcerative lesions to disseminated nodular ones; however, several unusual and atypical clinical features of the disease have been reported in the literature. In contrast to the typical presentation of a well-demarcated ulcer with raised borders, CL during pregnancy is characterized by larger lesions with a highly atypical, exophytic appearance (Fig. 27.13).

27.5.2.3 Management

The management of CL during pregnancy remains controversial as there is no description of congenital infection, and many antileishmanial drugs, such as pentavalent antimony or miltefosine, are teratogenic. Many clinical reports suggest that topical therapy represents a safe, efficient, less toxic and well-tolerated therapeutic alternative, especially for individuals with contraindications for the use of systemic therapy (pregnancy, children). The topical application of 15% paromomycin sulfate produces protozoal clearance in 76–85.3% of patients with cutaneous leishmaniasis caused by *L. major*. Other effective approaches include local infiltration with pentavalent antimony or physical methods, including cryotherapy, cauterization, excision, and the application of local heat.

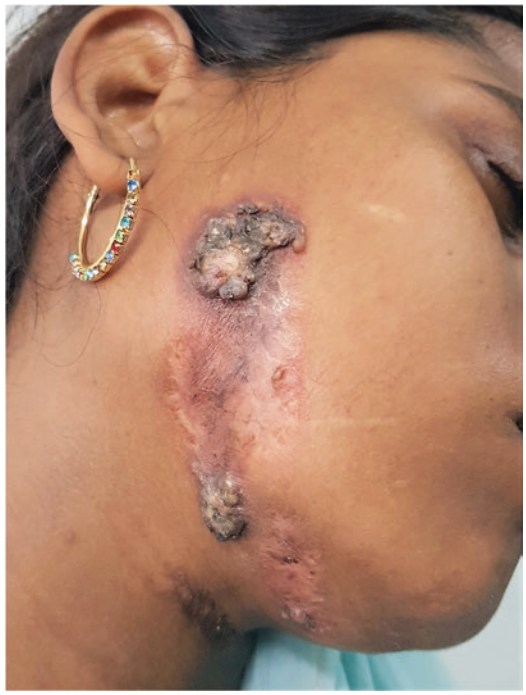

Fig. 27.13 Cutaneous Leishmaniasis in pregnancy—Atypical, exophytic lesion during pregnancy

Alternative therapies such as Amphotericin B should be considered as the drug of choice for all patients diagnosed with atypical CL. As spontaneous healing has been reported to occur after the delivery, several groups avoid the use of specific treatments and follow the patients by using local heating and/or antibiotic ointments to control lesion development and secondary infections.

Table 27.12 gives a comprehensive account of various dermatologic infections during pregnancy and their complications.

27.6 Conclusion

Skin infections are a frequent occurrence during pregnancy. These infections and their management may require altered approach because of the pregnant state and altered maternal immune response. Rarely, skin infections may lead to adverse maternal and fetal outcomes such as congenital malformations.

Table 27.12 Key infections in pregnancy and complications

Infection	Maternal risks
Bacterial infections	
Cellulitis, fasciitis	Life- and limb-threatening complications (rare)
Community-acquired methicillin-resistant Staphylococcus aureus (MRSA) infections	Involvement of gluteal and vulvovaginal region
Gonorrhea	Disseminated infection, including arthritis and perihepatitis
Mycobacterial infections—Leprosy	Exacerbation of leprosy and leprosy reactions, Transplacental transmission (rare)
Fungal infections	
Coccidiomycosis, Blastomycosis, cryptococcosis	Dissemination (meninges, skin, bone) with increased mortality, transmission to neonate at delivery
Parasitic infections	
Leishmaniasis	More exophytic/vegetative and larger lesions

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28 Evaluation and Management of Leprosy in Pregnancy

Cynthia Ruth Butlin

28.1 Introduction

Global reports from 160 countries revealed that during 2019, there were 202,185 people newly-diagnosed with leprosy with huge regional/national variations in the annual case detection rate (Table 28.1). The number of cases has been slowly falling over the past decade. Worldwide, 39% of the new cases detected in 2019 were female [1]. The proportion varied from one region to another being lowest in the African region (at 30%) but 40% in Southeast Asia where most cases are found.

Only 20 years ago, the number of new cases reported in 1999 was 678,758 (70% in India) but the female proportion was not given (Data submitted to WHO was not disaggregated by gender until 2004, when global female proportion was 31%. All WHO reports divide cases into adults (over 15 years of age) or child, with no further age breakdown). During the period 1985–2000, global new case detection was about 500,000–600,000 per annum and has fallen only slowly since then [2]. Most of those women diagnosed with leprosy over the past 35 years are still alive and many will be in child-bearing age groups

Table 28.1 Total leprosy cases reported in 2019 [1]

	Number registered cases at year-end, 31.12.19	Number of new cases detected in year ending 31.12.19	Number of new cases who were female	% of new cases who were female (%)
Regional total				
Africa	22,695	20,205	5983	29.6
Americas	35,231	29,936	13,185	44.0
Eastern Mediterranean	4894	4211	1715	40.7
Europe	18	42	17	40.5
South East Asia	109,956	143,787	56,403	39.2
Western Pacific	4381	4004	1322	33.0
Global total	177,175	202,185	78,625	38.9

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(ages 20–45) including some who were diagnosed as children (and some with permanent leprosy-related disability). There are not adequately-detailed data available to estimate the number of leprosy-affected women now at risk of pregnancy.

About 10% of new cases occur in children under 15 years of age, but in every country, the majority of leprosy cases are adult when diagnosed. According to the WHO definition [3], a person is "a case of leprosy" only when having signs of leprosy and not yet completed a course of chemotherapy, and the registered prevalence figures only reflect number of cases still registered to receive chemotherapy (normally 6 months for paucibacillary cases and 12 months for multibacillary cases). Yet a large number of people already have permanent impairment before completing their chemotherapy, and more develop new impairments later as a result of immune-mediated inflammatory episodes (Leprosy reactions), or suffer deterioration (secondary traumatic damage to sensory-impaired limbs) and these people need long-term support to manage their physical impairments.

Amongst leprosy-affected women, four categories may present at an obstetric clinic:

1. New cases with previously undiagnosed leprosy as an incidental co-existent condition
2. Women with a known past history of leprosy who are still at risk of reactional episodes which might complicate obstetric care
3. Women who had a leprosy infection successfully treated in the past but have residual impairment which needs to be considered in relation to their own self-care and future child care
4. Women who had leprosy treatment in the past and now show signs suggestive of relapse.

These categories will be dealt with in turn, considering how they present and how they can best be managed. (Fig. 28.1: algorithm) After due consideration of the women themselves, a section will follow on those aspects of leprosy which directly affect the child to be born.

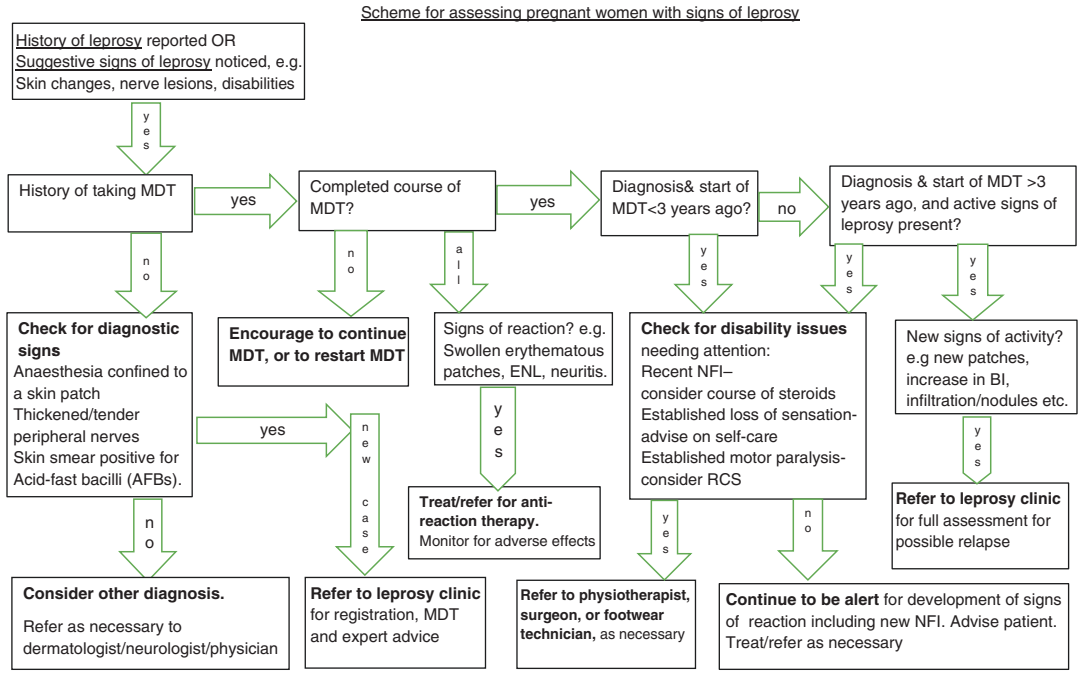

Fig. 28.1 Algorithm: scheme for assessing leprosy-affected women

28.2 New Case Detection in a Maternity Unit or Antenatal Clinic

Passive surveillance (by health workers at all levels) is an important mode of case detection in most national leprosy control programmes, especially where the programme is integrated into the general health services [4].

In some endemic countries, the main reason for any woman of child-bearing age seeking health care may be pregnancy-related issues. An alert health professional (whether a female community health volunteer or a consultant obstetrician) might notice any signs and symptoms of untreated leprosy, for which the woman had not previously sought medical attention since early manifestations of leprosy tend to be inconspicuous and easily ignored. Sometimes the aggravation of symptoms when "leprosy reaction" (see below) occurs during pregnancy leads to the diagnosis of leprosy being made in an ante-natal clinic [5, 6].

Generally, when staff suspects that a woman attending an antenatal clinic has untreated leprosy, the best course of action (after a considerate explanation of the reason) would be a referral to a local leprosy clinic for full assessment.

28.2.1 Diagnosis of Leprosy

The commonest early signs of leprosy are skin changes: either single or multiple, hypopigmented or erythematous non-itching patches, which may show impaired sensation confined to the patch, or a diffuse thickening and shininess of the skin which may appear erythematous and is often associated with madarosis. In some cases, nerve lesions occur early, causing peripheral nerve function impairments (often without pain). Mucosal lesions in nasal passages and the oropharynx can cause nasal stuffiness, mild epistaxis and hoarseness of voice. [7, 8] (Box 28.1)

Box 28.1: Diagnostic criteria for leprosy

Diagnostic signs of leprosy [7]

The diagnosis of leprosy in endemic countries is based on the presence of at least one of three cardinal signs:

1. Definite loss of sensation in a pale (hypopigmented) or reddish skin patch
2. Thickened or enlarged peripheral nerve with loss of sensation and/or weakness of the muscles supplied by that nerve
3. Presence of acid-fast bacilli in a slit-skin smear

In doubtful cases, histology of a skin lesion may be helpful

Leprosy can often be confirmed or excluded on the spot through simple physical examination without the need for sophisticated investigations. Besides the standard "systems examination" used by clinicians for any patient, two additional techniques should be included: testing touch sensation on patches, and palpating peripheral nerves for enlargement and tenderness at a site of predilection. Unless the diagnosis is already clear, a slit skin smear [9] should be employed. If there is still doubt, the choice is to proceed to biopsy or to wait, observing the patient untreated for 2–3 months. Other investigations such as PCR and ELISA antibody tests, and ultrasound measurement of nerve thickness, are at present only research tools and not proven of sufficient sensitivity & specificity to be recommended for clinical diagnosis [10].

28.2.2 Differential Diagnosis

Leprosy is not a "diagnosis of exclusion" but there are a myriad manifestations that can mimic other diseases. A full treatment of differential diagnosis is not appropriate here, and leprosy textbooks can be consulted (see recommended reading). In each country the list of other diseases to be considered will differ to some extent. However, certain common conditions which are easily mistaken for leprosy by untrained staff or lay people may be quickly ruled out: for example

birth marks, fungal infections of skin, post-inflammatory hypopigmentation, peripheral nerve function impairment from traumatic injury, plantar anaesthesia due to spinal lesions or diabetes mellitus, and nutritional neuropathy.

28.2.3 Management of Suspected New Cases

As with any leprosy suspect, the pregnant woman with signs suggestive of leprosy needs a full assessment of skin lesions, peripheral nerves, eyes and limb disability. If the case is confirmed, she will need to be registered for chemotherapy wherever the service is provided in her area: in some countries this would be at the Primary health center, elsewhere it might be a dermatology clinic or an infectious disease unit [4]. A discrete explanation from the obstetrician regarding onwards referral for further assessment of the lesions noticed, maybe all the woman needs to ensure she receives correct and timely chemotherapy. Taking into account her known social circumstances, the obstetrician may feel he should speak to her spouse to gain his cooperation for the referral. The leprosy clinic will register the case in the national health information system [3] and also be able to offer household contact examinations, especially important if there are other children in the household. When the newly-detected leprosy case next attends antenatal clinic or needs admission to a ward (after starting her chemotherapy) there is no need for segregation in the waiting area, nor for staff to use Personal Protective Equipment, as she will not present a public health risk. It is an opportunity for staff to demonstrate inclusive culture. If she appears to be afraid of disclosing her diagnosis to others, one may need to discretely speak to her husband or in-laws to avert risk of rejection and ensure support.

28.2.4 Classification for Chemotherapy Purposes

Leprosy manifests clinically in a spectrum of different ways according to the person's innate immunity—this is reflected in the Ridley Jopling classification (see below) which helps to predict complications of leprosy—but for purposes of chemotherapy, only two groups have to be distinguished [7, 11]. Paucibacillary (PB) cases are thought to have a low bacterial load; they are recognised by more localised forms of the disease (for example, fewer more well-defined patches, asymmetrical nerve involvement) and no mucosal lesions, whereas multibacillary (MB) cases have more widespread disease (symmetrically distributed) and can harbour huge quantities of bacteria (Table 28.2). Untreated MB cases may discharge *M leprae* from oral/nasal mucosa. This latter group is thought to be mainly responsible for transmission of disease, and they tend to have a worse prognosis.

Table 28.2 Classification (PB/MB criteria) for chemotherapy

The case definitions of PB and MB leprosy [3, 7]		
A case of leprosy	Paucibacillary (PB) case	Multibacillary (MB) case
Is a person with signs & symptoms of leprosy, who has not yet completed a course of multidrug therapy	A case of leprosy with 1–5 skin lesions, without demonstrated presence of bacilli in a skin smear	A case of leprosy with more than five skin lesions; or with nerve involvement (pure neuritic, or any number of skin lesions and neuritis); or with the demonstrated presence of bacilli in a slit-skin smear, irrespective of the number of skin lesions

28.2.5 Anti-leprosy Chemotherapy

As leprosy is a chronic infection requiring prolonged chemotherapy, it should never be treated with monotherapy, for fear of drug resistance. Since 1982, two standard regimens of multi-drug therapy (MDT) have been in use [4, 7]: for PB leprosy in an adult it is dapsone 100 mg daily and rifampicin (preferably as a supervised dose) 600 mg monthly; for MB leprosy in an adult it is dapsone 100 mg daily, clofazimine 50 mg daily,

and monthly (preferably supervised) rifampicin 600 mg plus clofazimine 300 mg. Originally the PB regimen was recommended for 6 months and the MB regimen for at least 24 months. More recently the MB regimen has been given as a fixed duration course of 12 months (on recommendation of WHO) [11]. Whilst these are still the usual regimens in 2020, it has been suggested [7] that PB patients might benefit from triple therapy (addition of clofazimine to existing PB regimen) for 6 months, although the evidence in its favour is weak. The suggestion that MB patients might be given only 6 months of triple therapy, is not yet supported by sufficient evidence for its widespread adoption [7]. Monthly supervision by a health worker of the rifampicin dose is not always convenient, but as far as possible patients should be supported to adhere to the regimen, and an accompanying person (such as a parent or spouse) may be asked to undertake supervision of the domiciliary multi-drug therapy. This is referred to as "accompanied MDT" (A-MDT) [4].

The MDT regimen is robust and usually well-tolerated. Adverse effects of MDT, however, include the life-threatening dapsone hypersensitivity syndrome (DHS) [12] which tends to present at about 2 months after initiating MDT. One systematic review found it occurred in 1.4% of patients treated with dapsone (71% of whom were given it for leprosy). Fatality rate for DHS approaches 10%, so it should be treated actively with steroids and supportive care, preferably in a hospital. Recent research reveals its association with a genetic marker [13], which might be used in future to identify women who should not be given dapsone. Because of the risk of DHS, it is wise to see the patient personally at least at the time of dispensing the second monthly MDT pack, to remind her about the risk of DHS and to check for any signs of it. Dapsone frequently causes anaemia, particularly in women with inherited disorders such as haemoglobinopathies and G6PD deficiency. The consequences of sudden onset of severe anaemia being worse during pregnancy than at other times of life, the woman's hemoglobin should be checked before starting dapsone and within the first month. If the hemoglobin is already low when leprosy is diagnosed, MDT can be started without dapsone, which will be introduced once the anaemia is corrected. Folic acid supplementation during pregnancy is particularly important when taking dapsone as it is a folate inhibitor.

Other rare adverse effects of dapsone include hepatitis, fixed drug eruption, psychosis, bone marrow suppression, and peripheral neuropathy related to folic acid deficiency [14] (Table 28.3). Rifampicin causes red colouration of urine, which can be alarming to a patient who does not expect it. Rifampicin in monthly doses rarely causes serious adverse effects; occasional cases are seen with "flu-like syndrome" or thrombocytopenia or jaundice (although other causes of jaundice—such as infectious hepatitis—should be excluded before it is attributed to rifampicin). The monthly dose probably causes very little enzyme induction, so interactions with other drugs are less of a problem than with daily rifampicin as given for Tuberculosis. Clofazimine in doses used for MDT rarely causes troublesome adverse effects other than temporary skin discolouration.

Depending on her circumstances, there may be difficulties for the woman to attend her usual leprosy clinic near the time of delivery, so she might be offered A-MDT [4, 14] for 1–2 months, provided she has already had more than 2 months MDT without adverse effects & her condition is stable. The immediate post-partum period is thought to be a time of high risk for reaction (see below) so it is wise to plan a review within 1 month of delivery.

The potential teratogenic risk of standard MDT is considered extremely low, so there is no need to withhold or alter it during pregnancy [14], although some extra attention should be paid to certain other effects. Clofazimine is considered safe in pregnancy but—like the mother, the fetus is likely to have some colour change, which gradually fades after delivery unless the mother continues to take clofazimine while breast-feeding. A small increase in congenital abnormalities after pregnant women consumed daily rifampicin has been reported, but the causation was not certain [15].

Table 28.3 Adverse effects of MDT reported in adult patients

	Dapsone	Rifampicin	Clofazimine
Recommended precautions	Check haemoglobin Avoid if previous allergy to sulphur- containing drugs	Check liver function (especially in elderly), renal function (especially if history of liver damage or of alcohol abuse) and platelets	Avoid in patients with pre-existing chronic intestinal disorders Preferably give after food
Major or common adverse effects	Haemolysis, anaemia (often associated with haemoglobinopathies, or G6PD deficiency)	Thrombocytopenia (More common with intermittent administration)	Severe abdominal pain (more common with high dose, very rare with dosage used in MDT)
	Dapsone hypersensitivity syndrome (dermatitis, fever, anaemia, jaundice, systemic symptoms)	Hepatitis (dose-related), jaundice with Gilberts syndrome	
	Psychosis	'Flu-like syndrome' (More common with intermittent administration)	QT prolongation
	Folic acid deficiency (anaemia, neurological deficit)	Renal failure	
	Bone marrow suppression (rare)		
	Hepatitis		
Minor & rare adverse effects	Fixed drug eruption, Other rashes	Red colouration of urine, tears, saliva, sputum (harmless) May permanently stain contact lenses	Reversible change in colour of skin & cornea, colouration of secretions such as, tears, sputum, milk, and of faeces
	Parasthesiae	Enzyme induction affecting metabolism of other drugs	Dose-related nausea, indigestion, loose motions
	Blurred vision		Ichthyosis on sun-exposed areas of skin

Table 28.4 Reports of neonatal problems tentatively attributed to MDT

	Dapsone	Rifampicin	Clofazimine
Fetal development	Not reported with dosages used for leprosy	Small increase in incidence of various congenital malformations noted after daily rifampicin	Not reported in humans
Perinatal problems	Occasional cases of haemolysis in neonate	Occasional cases of haemolytic disease of new-born infant (vitamin K prophylaxis recommended)	Coloration of skin due to clofazimine deposition (as in mother)—harmless
	Occasionally hyperbilirubinaemia in neonate		
Breast-fed infant	Haemolytic anaemia in infant of mother taking dapsone (rare)	None reported	Coloration of skin due to clofazimine deposition (as in mother)- harmless

Occasional instances of fetal adverse drug events related to MDT occurring around the time of delivery have been published. Hemorrhagic diseases of new-born is occasionally seen after the mother took daily rifampicin for tuberculosis [15, 16], but the risk may be less with the monthly does of rifampicin used in leprosy. Vitamin K prophylaxis is recommended for the neonate. Haemolysis in neonates as a result of maternal consumption of dapsone is theoretically possible (Table 28.4).

28.2.6 Second Line Anti-leprosy Drugs

Only rarely, in presence of severe adverse effects or contra-indications with first-line drugs or in presence of proven drug resistance, would a woman need second-line drugs such as minocycline, clarithromycin, or fluoroquinolones. Any use of the alternative regimen should be only on specialist advice [10, 17] and might need to be deferred until after delivery in view of possible adverse effects.

28.2.7 Public Health Concerns

Does a woman in labour, or a recently-delivered woman, with leprosy present an infection risk to her own or any other neonate? Not if she has started (or completed) her MDT. There is no justification in modern times for refusing admission to a maternity unit on grounds of a mother having leprosy, nor for separating mother and child at birth! If a woman needs admission for postpartum leprosy reaction or for post-natal obstetric care, she should take her child with her into the hospital; if a neonate needs admission for special care his/her leprosy-affected mother (who is taking or has taken a course of MDT) should not be excluded from attendance on her infant.

28.2.8 Epidemiology

Unanswered questions include: Are pregnant women at higher risk of developing overt leprosy than other women of similar age in that population? Some old publications suggest it might be so, but these were either individual case reports or related to cohorts identified at leprosaria with inappropriate controls. A systematic review [18] found no high-quality evidence, applicable to the present day, that pregnancy increases the risk of developing leprosy but noted that the decrease in T cell-based immunity observed during pregnancy which might theoretically increase susceptibility to leprosy infection [19].

28.3 Recognition of Reactional Episodes in Leprosy-Affected Women

28.3.1 Immunological Basis and Manifestations

Leprosy-affected individuals are prone to develop immune-mediated inflammatory episodes referred to as "Leprosy reaction". These predominantly occur before MDT is given, or during the first 2–3 years after starting MDT. Type 1 reaction (often referred to as reversal reaction) is a cell-mediated immune response to mycobacterial antigens, which typically presents as acute inflammation in skin patches or peripheral nerves. Type 2 reaction is a systemic disorder akin to immune complex deposition syndrome, characterised by high fever, crops of transient painful subcutaneous nodules (erythema nodosum leprosum or ENL), acute neuritis and extracutaneous organ inflammation (such as iridocyclitis, orchitis, nephritis and arthritis) [20] (Table 28.5).

Neuritis may occur as part of type 1 or type 2 reaction, but also occurs in isolation. Peripheral nerve function impairment (NFI) leads directly or indirectly to most of the permanent & progressive limb and eye disabilities seen in leprosy-affected people (Table 28.6).

The Ridley-Jopling classification [21] is based on the concept that clinical manifestations of leprosy reflect the patient's place on a spectrum ranging from "polar tuberculoid" cases which have strong cell-mediated immunity (CMI), with granulomatous histological responses and low bacterial numbers, to "polar lepromatous" cases which have very little CMI (but exhibit a serological non-protective response to *M leprae* antigens) and may have very heavy bacterial load. Between these extremes lie Borderline cases (with a mixed clinical picture) whose immune level tends to fluctuate, making them prone to type I reaction (Table 28.7).

Table 28.5 Diagnosis of reactional episodes

	Reversal reaction / Type 1 reaction	ENL reaction / Type 2 reaction	Lucio phenomenon
Systemic symptoms	Usually mild: low fever, slight malaise	May be severe: High fever, malaise, anorexia, insomnia.	Usually absent
Edema	Edema of patches; peripheral edema may be severe (feet, hands and face)	Peripheral Oedema often seen	Usually absent
Cutaneous lesions	Inflammation of existing patches: erythema, swelling, warmth, discomfort, spontaneous ulceration New patches may appear	Erythema nodosum leprosum (ENL): few or many transient erythematous tender subcutaneous nodular lesions, appearing in crops; may subside leaving a bruise-like mark, or may become necrotic and ulcerate; sometimes atypical ENL lesions occur resembling erythema multiforme	Multiple tender, painful red patches, becoming purpuric, centre becomes necrotic, eschar develops and falls off, leaving ulcer or scar. Process takes about 15 days.
Nerve lesions	Inflammation shown by thickening, tenderness, spontaneous pain, or acute abscess formation New loss of function shown by sensory impairment in skin supplied by the nerve or motor impairment seen as paralysis of muscles supplied by the nerve	Inflammation shown by thickening, tenderness, spontaneous pain, at times micro-abscess formation New loss of function shown by sensory impairment in skin supplied by the nerve, or motor impairment seen as paralysis of muscles supplied	Usually no associated neuritis
Other organs clinically affected	Usually not affected	Inflammation widespread, but variable severity; there may be inflammation of: lymph nodes (lymphandenitis) eye (iridocyclitis) testes (orchitis) joints (arthritis) bone (typically dactylitis, or periostitis of lower tibia)	Usually not affected
Routine Laboratory investigations	Usually not abnormal	Proteinuria (common) Blood and casts in urine may be detected Commonly high white cell count with neutrophilia & “left shift”	No typical abnormalities

28.3.2 Clinical Recognition & Management

Type 1/Reversal reaction: It generally occurs in patients with BT, BB or BL type of disease and rarely in TT cases. There is sudden onset of swelling, redness and pain in existing skin lesions, sometimes associated with acute neuritis at sites of predilection leading to loss of nerve function [5]. Often there will be peripheral edema but generally not much systemic disturbance. Untreated type 1 reaction may lead to permanent disability. First-line medical therapy for all but the mildest cases is oral corticosteroids [22].

Table 28.6 Characteristic peripheral nerve damage in leprosy

Nerve	Site of predilection for nerve damage and of palpable thickening	Results of nerve damage—sensory	Results of nerve damage—motor
Trigeminal	At exit from skull	Loss of corneal sensation	Not seen in leprosy
Facial	At edge of zygomatic arch	Not clinically important	Lagophthalmos, +/− Lower facial palsy
Radial	As it bends around humerus near insertion of deltoid muscle	Not clinically important (innervates a small area on back of hand)	Wrist drop, loss of full extension of fingers
Ulnar	Above olecranon groove, at medial side of upper arm.	Loss of sensation over ulnar side of hand, palm and 3 fingers	Weakness of intrinsic muscles of hand (lumbricals, interossei) and of abduction of 5th finger
Median	Just above distal wrist crease, on volar aspect of wrist	Loss of sensation over thumb, index finger & part of middle finger	Weakness of thumb opposition & abduction
Lateral popliteal (common peroneal)	Near head of fibula	Loss of sensation over lateral side of ankle & foot	Foot drop
Posterior tibial	Below/behind medial malleolus, beside posterior tibial artery	Loss of sensation over sole	Weakness of intrinsic muscles of foot, claw toes

Table 28.7 Ridley Jopling classification (main clinical features): useful for assessing risk of reaction [21]

	TT	BT	BB	BL	LL
Skin lesions	Single or few, well-defined patch(es), with dry surface, usually with hair loss & markedly impaired sensation, asymmetrical distribution	Variable number of patches, usually dry with hair loss, and impaired sensation, asymmetrically distributed May be satellite lesions	Typically mixture of patches, sometimes with mildly impaired sensation, often have a "punched out" centre, often irregular or annular shaped	Many patches, often ill-defined, may be small, shiny, without sensory impairment, tendency to symmetrical distribution.	Diffuse infiltration (shiny smooth erythematous appearance of skin), symmetrical distribution; bilateral madarosis; firm non-tender nodules.
Nerves	May be single nerve trunk affected, often cutaneous nerve thickening adjacent to patch	May be several nerve trunks affected, often close to visible skin lesions; asymmetrical Typically early nerve function impairment	May be many nerve trunks affected, symmetrical distribution	May be many nerve trunks affected, symmetrical distribution.	Usually many nerve trunks thickened, symmetrical distribution. Nerve function impairment may be absent in early stage; later glove & stocking type anaesthesia.
Mucous membranes	Not affected	Not affected	Not usually affected	May be affected	Mucous membranes of nose, oropharynx affected, may be epistaxis, nasal congestion, hoarse voice, rarely palatal perforation.

(continued)

Table 28.7 (continued)

	TT	BT	BB	BL	LL
Other organs	Not affected	Not affected	Not affected	Eyes and testes often affected	Eyes and testes usually affected
Skin smear	Negative	Negative	May be positive some sites	Positive	Positive
Reaction Risk	Rarely type 1 reaction	Type 1 reaction common	May have type 1 reaction or type 2 reaction	May have type 1 or type 2 reaction	Type 2 reaction common

Table 28.8 Recommended prednisolone courses (for adult with body weight over 40 kg)

	Standard regimen (safe for field use) [11, 14]	Prolonged course, lower dose (for type 1 reaction/ neuritis) [23]	Prolonged course, higher dose (for type 1 reaction/ neuritis) [23]	Prolonged course (recommended for severe ENL reaction)
Tapering dosage	40 mg od for 14 days, 30 mg od for 14 days, 20 mg od for 14 days, 15 mg od for 14 days, 10 mg od for 14 days, 05 mg od for 14 days.	30 mg od for 14 days, 25 mg od for 14 days, 20 mg od for 56 days, 10 mg od for 28 days, 05 mg od for 28 days.	60 mg for 14 days, 50 mg for 14 days, 40 mg for 14 days, 30 mg for 14 days, 20 mg for 28 days, 10 mg for 28 days, 05 mg for 28 days.	40 mg od for 14 days, 35 mg od for 14 days, 30 mg od for 14 days, 25 mg od for 14 days, 20 mg od for 28 days, 15 mg od for 28 days, 10 mg od for 14 days, 05 mg od for 14 days.
Total dose	1.68 gm	2.31 gm	3.5 gm	3.01 gm
Duration	12 weeks	20 weeks	20 weeks	20 weeks

Note: Oral prednisolone is usually given as single in morning, after food

Courses of 12 weeks or more are needed; it is common practice to commence with prednisolone at a starting dose of 40 mg daily in an adult (or up to 1 mg/kg body weight) after which the patient usually begins to respond within a few days. The daily dose can then be tapered weekly or fortnightly, preferably to a maintenance dose of 20 mg/day or less at which side effects of prednisolone are less troublesome (Table 28.8). One randomised controlled trial found that a 20 week course may be more effective (than a shorter course) for type 1 reaction, [23], but there are few high-quality trials directly comparing courses of different lengths. These patients with type 1 reaction need to be carefully assessed and monitored for nerve function impairment (NFI). They can benefit from physiotherapy (splinting and supportive care, as well as passive exercises in the acute phase). Early active management of NFI is likely to result in recovery in at least 70% cases [24, 25]. Severe cases of type 1 reaction unresponsive to oral corticosteroids may sometimes be treated with immune-modulating agents such as azathioprine, as steroid-sparing agents; however, such drugs are contra-indicated during pregnancy (see Box 28.2 case scenario A).

Type 2/ENL reaction: It is seen only in MB cases (BB, BL or LL types) with a positive slit skin smear. It can occur long after completion of MB MDT, while the bacteriological index is still positive, indicating a pool of *M leprae* antigens that remain in the body. Its main features are fever and pain. Patients with ENL reaction are systemically ill with malaise, anorexia, and apathy. They often need admission for nursing care and close medical attention. When untreated, ENL reaction results in great suffering with consequent weight loss, depression and permanent

Box 28.2 Case scenario

Patient A lived in a rural area where she was treated at a peripheral leprosy clinic run by a specialist NGO, which had no in-patient facilities of its own.
She had recently completed MB MDT for BL leprosy when her father-in-law came to the clinic saying she had delivered her first baby at home 1 week before, and now was ill with swollen red patches, oedema of hands and feet, pain in 2 nerves and new weakness of hand muscles.
A paramedical worker did a home visit to assess the situation and reported to the NGO medical officer who advised the family to take her to the nearest government medical college (1 h drive away). He gave a referral letter addressed to the dermatology department, detailing her past leprosy treatment, saying she now needs management of post-partum type 1 reaction, and recommending admission. He suggested that a female relative should accompany her in the ward to take care of the infant, without separating the child from its mother.
The patient was admitted in dermatology ward and treated with prednisolone. A midwife from the obstetric unit came to the ward to check mother's post-partum condition and baby's health.

Box 28.3 Case scenario

Patient B was newly married and in early pregnancy when she was diagnosed with lepromatous leprosy and started MBMDT. After 6 months she presented for follow-up at to a primary health centre's antenatal clinic with high fever, red eyes, and many painful red nodules on her skin.
The midwife suspected acute type 2 reaction (ENL) and asked a physician with an interest in leprosy to assess her.
He prescribed prednisolone, starting at 40 mg daily after food, the dose to be reviewed after 2 weeks. He felt the small risk of adverse effects (to mother or to foetus) from prednisolone was justified by the severity of her reaction, and the risk of future disability if the reaction was untreated. He asked the midwife to monitor the patient for hypertension, hyperglycaemia and other adverse effects of prednisolone. He arranged for a trained paramedical worker to do a nerve function assessment.
If she did not improve satisfactorily, he planned at next visit to offer her a 12-week course of high dose clofazimine (to suppress recurrence of ENL, and as a steroid-sparing agent), starting at 100 mg tds, if she agreed to this plan after hearing about the likely change in skin colour (which would be temporary) and other possible adverse effects.

disability (such as nerve function impairment, visual loss, testicular failure and secondary disability such as contractures). In many parts of the world first-line therapy is oral corticosteroids [26], but (if it is available) thalidomide is very effective and relatively safe (for men). In some countries, regulations allow use of thalidomide in post-menopausal women but it should not be given at any stage during pregnancy (nor to other women of childbearing potential, except with the strictest precautions if permitted under national rules) because of its known propensity to cause severe fetal damage such as phocomelia. Long courses of clofazimine (which is safe in pregnancy) in high doses is thought to reduce severity of ENL and to reduce recurrence, but evidence is conflicting [27]. Other second-line drugs which have been tried for ENL include cyclosporin and methotrexate, which are also contraindicated in pregnancy [17, 26] (Box 28.3 case scenario B).

Isolated nerve function impairment (ie without other signs of reaction), if recognised within 3–6 months of onset, is treated with physiotherapy and oral corticosteroids, for at least 12 weeks [14, 17, 28] (Tables 28.5 and 28.7). Some clinicians suggest that a longer course is desirable to improve recovery rates, but a randomised controlled trial did not find greater benefit (compared with 20 weeks) if the course was extended to 32 weeks. [24]. Unless regular monitoring of nerve function is undertaken, new impairments may be overlooked until it is too late to expect recovery. For high-risk cases, such as MB patients with pre-existing nerve function impairment at diagnosis, monthly nerve function assessment is desirable (covering the cranial & peripheral nerves commonly affected by leprosy) [28]. Some patients can learn to do a simple assessment by themselves at home (Box 28.4 case scenario C).

Box 28.4 Case scenario

Patient C arrived at the leprosy clinic of a district general hospital as a new case of BT leprosy with a history of 1-month duration loss of function in her left median nerve, without pain or other signs of type 1 reaction. She was prescribed PB MDT.
The doctor was considering a course of prednisolone for her recent nerve function impairment, but she had said she thought she was 6–8 weeks pregnant. In first trimester, he knew, there is a small risk to the fetus from prednisolone. However, if a steroid course is given within 3–6 months of new impairment, there is still a good chance of recovery of function.
After explaining this to her, they decided to defer steroid therapy and review her progress after another 4 weeks. He asked the physiotherapist to give her a supportive splint (to reduce wrist movement) and to teach her about prevention of injury to the insensitive area of skin. She was also shown how to do passive exercises of the affected hand to prevent contracture from developing.
At her next visit, the impairment was not worse, she had just been to antenatal clinic where they confirmed a 12-week healthy pregnancy. In discussion with the patient and her husband, it was decided to start a 12-week steroid course, with fortnightly monitoring for adverse effects.

Lucio phenomenon is a very rare syndrome first observed in central/south America, which presents as necrotic skin lesions with minimal systemic disturbance, and responds well to steroids [6].

Special considerations: Diagnosis and first-line treatment of reactional episodes in pregnant women is the same as for other patients, but management needs more care as the principal anti-reaction drugs have adverse effects which may be more troublesome in pregnancy. As the management of a pregnant woman with severe leprosy reaction is complex there is a need for agreed shared care arrangements. If admission is required it is probably better to admit in the obstetrics unit and request a leprosy specialist to visit rather than the reverse: a maternity hospital might not have a physiotherapy department available, whilst a leprosy unit may not have a trained midwife on the staff.

28.3.3 Anti-reaction Drugs

Corticosteroids—At the doses commonly used in treating type 1 or type 2 leprosy reaction, prednisolone may cause hypertension or hyperglycaemia. Both of these problems can also occur during pregnancy uncomplicated by steroid therapy, and careful monitoring is necessary. A prednisolone course should be preceded in most endemic countries by presumptive deworming, as occasionally strongyloides hyperinfestation occurs as a complication of steroid therapy. The mild immunosuppression accompanying steroid therapy is often manifested with fungal skin infections; it may sometimes precipitate reactivation of latent tuberculosis. Adrenal suppression occurs easily within 3–6 months raising the risks of adrenal shock if the exogenous corticosteroid is suddenly withdrawn, so a warning card should be supplied giving the prescription and indication. There is little evidence that prednisolone directly causes damage to the unborn baby [29] and the risk may be confined to first-trimester exposure. On the other hand, whilst the adverse effects of corticosteroids may compromise the mother's health, this risk may be preferable to the alternative of enduring uncontrolled leprosy reaction with the suffering and risk of permanent impairments it entails. A skilled clinician, in discussion with the patient, will be able to balance the risks of keeping the steroid dose as low as possible, and the course as short as possible [14].

High dose Clofazimine can be prescribed for recurrent ENL reaction to reduce further episodes, or as a steroid-sparing agent in chronic ENL reaction, but its onset of action being after only 3–4 weeks, it is never used alone as first line anti-reaction therapy. For 1–3 months 300 mg per day in divided doses with food can be given, to an adult patient of over 40 kg body weight, after which the dose is tapered to a maintenance level of 100 mg/day for upto 6 months. The drug being lipid-soluble accumulates in the body, causing pigmentation of skin and subcutaneous fat (including of unborn baby), tears and of breast milk, as well as ichthyosis on sun-exposed areas of skin. These adverse effects occur in all cases

and are not physically harmful (though they may be embarrassing). More serious adverse effects are related to the gastrointestinal tract (nausea, diarrhoea) and very rarely there is acute severe abdominal pain, mimicking a surgical emergency. This latter appears to be due to crystal deposition occurring when the patient is overloaded with clofazimine; for such cases, the drug must be immediately stopped and supportive measures applied. It is occasionally fatal. Clofazimine may cause QT prolongation, so caution should be exercised if the patient has any cardiac disease; co-prescribing of other drugs with this tendency should be avoided. The drug has not been found to cause damage to the human fetus [30].

28.3.4 Epidemiology

Important unanswered questions include the following: are women at higher risk of reaction when pregnant than at other times in their life? or at higher risk than other women similarly affected by leprosy who are not pregnant? Do reactions in pregnant women respond as well to anti-reaction therapy? In particular, does recovery of NFI occur at the same rate on standard steroid courses?

Given the known changes in the immune system during pregnancy (a relative suppression of immune response with a shift from cell-mediated towards humoral response, especially in the third trimester) and the rapid recovery of cell-mediated responsiveness post-partum, one might expect that the incidence & severity of immune-mediated reactions during leprosy would be impacted [19]. A systematic review [18] concluded that there is evidence of ENL reaction occurring throughout pregnancy and the postpartum period (in perhaps one-third of BL/LL cases), some evidence for an increase in Type 1 (reversal) reaction during the post-partum period (compared with its incidence during pregnancy), and some evidence for a high incidence of neuritis (including silent neuritis) during pregnancy and especially in the post-partum period. However, these deductions rely on studies that were all from Africa and conducted 40–50 years ago, hence may not be applicable in other countries, in the different epidemiological situations prevailing nowadays, and with women living in different socio-economic conditions. There is insufficient evidence on which to predict an individual's risk of developing reaction or neuritis during and soon after her pregnancy; to date, there is no evidence whether her response to treatment would be different from the response of non-pregnant women.

28.4 Mitigating Effects of Disability in Leprosy Affected Women (During or After MDT)

28.4.1 Common Disabilities in Leprosy

Most of the common disabilities seen in leprosy stem from nerve function impairment, leaving the patient with sensory, autonomic and motor loss in the skin areas and muscles supplied by the nerve (Table 28.5) [4, 28, 31]. Immune-mediated inflammatory damage (which may be sudden or gradual) occurs at sites of predilection, such as the ulnar nerve near the elbow, the median nerve at the wrist and the lateral popliteal nerve near the knee. An insidious symmetrical loss of sensation in the extremities (glove and stocking pattern) can also occur in late lepromatous cases as a direct result of infiltration of peripheral nerves by *M leprae*. The primary neural impairments (which may be reversed by prompt use of corticosteroids) may first occur before, during or soon after MDT, whereas secondary impairments can progressively develop and worsen long after completion of chemotherapy.

Loss of sensation in limbs or eyes means that the woman loses protective reflexes, which normally prevent people from injuring themselves during activities of daily living (including walking), so she becomes prone to unfelt injuries on hands and feet or of the cornea. These injuries may be mild, superficial wounds at first but easily become chronic open sores and may be infected by environmental bacteria. Such wounds do not

contain viable leprosy bacteria. The risk of injury is greater if the person also has dry skin (from autonomic nerve damage) and if the limb is being used in an abnormal manner on account of motor weakness (eg increased pressure on forefoot in a person with footdrop due to lateral popliteal nerve damage). Dense anaesthesia in a foot sometimes results in neuropathic disintegration of bone (akin to the condition of Charcot joint); without an external visible wound, the early stage of this condition is easily overlooked.

28.4.2 Management Options

28.4.2.1 Self-care

Management of sensory-impaired limbs is largely by training and empowering the patient to avoid injury and to manage effectively, while they are small and shallow, any new wounds which occur [32] (Table 28.9). If the patient understands that any new wound which is cleaned and covered, then protected from any pressure will usually heal quickly, she can take responsibility for her

Table 28.9 Common impairments in leprosy-affected women: first line of management

	Self-care, physiotherapy	Medication	Other intervention
Primary impairments			
Loss of sensation in patch	If on trauma-prone area, advise on daily inspection & protection from trauma	Sensation may slowly recover after MDT	
Loss of sensation in hand	Advise on protection during activities of daily living and work Advise on adapting tools, eg handles for cooking pots	If recent, consider steroid course	
Loss of sensation in foot	Advise on protection during standing, squatting & walking Advise on footwear	If recent, consider steroid course	
Loss of sensation in cornea	Advise on protection of eye from smoke, dust, insects, trauma; offer lubricant drops	If recent, consider steroid course	Offer simple spectacles (plain lens)
Mobile claw hand, loss of opposition of thumb	Advise on passive and active exercises	If recent, consider steroid course	If not responded to steroid course or too late, consider referral for reconstructive surgery
Wrist drop	Advise on passive and active exercises Provide cock-up splint	If recent, consider steroid course	If not responded to steroid course or too late, consider referral for reconstructive surgery
Foot drop	Advise on passive and active exercises Offer toe spring/ other orthosis to maintain dorsiflexion	If recent, consider steroid course	If not responded to steroid course or too late, consider referral for reconstructive surgery
Lagophthalmos	Advise on protection of eye from smoke, dust, insects, trauma Offer protective spectacles/ goggles. Offer lubricant drops	If recent, consider steroid course	If not responded to steroid course or too late, consider urgent referral for lateral tarsorraphy or reconstructive surgery
Visual loss from iridocyclitis	Advise avoid sunshine, wear dark glasses	Treat associated ENL reaction, give atropine drops, consider topical steroids	If acute inflammation not improving, refer urgently to ophthalmologist Exclude associated cataract in chronic cases

Table 28.9 (continued)

	Self-care, physiotherapy	Medication	Other intervention
Secondary Impairments			
Trophic ulceration of hand or foot	If simple: advise cleaning & covering wound, resting the part until healed. Elevate ulcerated hand in sling Offer crutches if one foot is ulcerated Bedrest if both feet ulcerated. After healing, review footwear	If signs of systemic infection, consider antibiotics Treat exacerbating conditions (anaemia, diabetes, etc.) Consider whether need for debridement	Consider admission to hospital If not healing with simple measures, refer to surgeon or leprosy specialist
Corneal ulceration or exposure keratitis	Protection of eye, lubrication	May need antibiotic drops and atropine drops for corneal ulcer	Consider ophthalmic referral, or surgical referral if lagophthalmos present
Neuropathic disintegration of bone (suspected)	Stop weight bearing, give splint	Treat associated osteoporosis if present	Urgent referral to orthopaedic or leprosy specialist For a non-pregnant woman, arrange X-ray
Contractures of fingers or of tendon achilles	Advise on massage & exercises		Refer to physiotherapist

own foot/hand/eye care. Self-care routines must become habitual as they are needed life-long. Appropriate footwear is essential when there is plantar anaesthesia, but custom-made shoes are only indicated if there is any deformity. One must be pro-active about early wound care, insisting on rest for the injured limb. If allowed to persist, a wound might become infected; however, one should be wary of unnecessarily using antibiotics (often cleaning and debridement is sufficient to control secondary infection). Some common antibiotics are contraindicated in pregnancy. Routine tetanus vaccination given during pregnancy will prevent tetanus arising in presence of any deep sinus associated with trophic ulceration. One should be alert for neuropathic bone disintegration (swollen feet are easily wrongly attributed to pregnancy). Risk of this, as of trophic ulceration, may be increased by change in body weight and in gait during pregnancy, but otherwise, the risks and management are the same as in non-pregnant women with nerve function impairment from any cause.

Motor weakness (eg in small muscles of hand following ulnar nerve palsy) should be treated with passive and active exercises to retain flexibility and delay development of contractures. A physiotherapist or nurse will be able to demonstrate to the patient simple exercises to do at home. Since leprosy leads to paralysis of only selected muscles, tendon transfer surgery can often restore useful function by use of muscles that retain good innervation e.g. tibialis posterior transfer for foot drop (Table 28.9).

28.4.2.2 Surgery

Clinicians should consider referral for reconstructive surgery (RCS) if they find established motor impairment (too late for a course of corticosteroids to be recommended) [31] but RCS will only be effective if the post-operative re-education period is sufficient (meaning an admission of 4–6 weeks). For most cases, it may be best to defer surgical procedures until after delivery; however, surgical correction of lagophthalmos (either a temporalis muscle transfer or a simple tarsorrhaphy) may be urgent to prevent sight-threatening corneal damage and can be safely done during pregnancy. Similarly, it may be desirable to correct certain severe disabilities

like wrist-drop which are likely to hinder child-care; it might warrant surgical correction early in pregnancy (since no general anaesthesia is needed, RCS is relatively safe for the pregnant woman).

Very rarely, below-knee amputation is required for life-threatening infection in an ulcerated lower limb; this can be safely done under spinal anaesthesia even during pregnancy. A prosthesis should be given as early as possible to allow the mother to be mobile without crutches before delivery, otherwise carrying her infant is difficult.

28.4.2.3 Epidemiology

Evidence on frequency of trophic ulcers or neuropathic disintegration of bone during pregnancy, compared with at other times of a woman's life, is lacking.

28.5 Detection of Relapse in Women with Previously Completed Course of MDT

28.5.1 Recognition

Relapse after a full course of chemotherapy is extremely rare; although few large scale long term active follow-up studies have been done following standard MDT, the relapse rates for both PB & MB cases are thought to be very low according to WHO (in the region of 1% treated cases) [11, 33]. As they lack the ability to mount an effective CMI response, polar lepromatous cases are not apparently immune to reinfection after completing a course of chemotherapy. Some may harbor "persister" organisms which can later cause endogenous relapse. This is comparable to reactivation of latent tuberculosis.

It is normal practice to review past medical history at antenatal clinic, paying particular attention to any chronic disorder. Pregnancy is said to be a risk factor for relapse, so if there is any history of chemotherapy for leprosy, even many years before, then it is wise to check for active signs such as new skin lesions (if necessary do a slit skin smear) (Fig. 28.1. algorithm). If relapse was suspected, one would need to refer to a leprosy specialist for assessment and consideration of drug resistance testing. For any confirmed relapse, repeat household contacts examination is an urgent requirement as well as restarting chemotherapy. Acute symptoms of leprosy within a few years of diagnosis are more likely to be due to late type 1 or type 2 reaction [33].

28.5.2 Epidemiology

There is no good quality epidemiological evidence from community-based studies to answer the question of whether pregnancy does increase risk of relapse [18] but there are theoretical grounds to cause concern. The general depression of cell-mediated immunity might be expected to increase the risk of exogenous infection or of endogenous *M leprae* multiplying. To date most relapses after MDT involve *M leprae* which are sensitive to the same drugs used before, but (in any smear-positive relapse) samples should be collected for drug-resistance testing.

28.6 Consequences for the Child of Maternal Leprosy During Pregnancy

There is only weak evidence of increased fetal loss (miscarriage or stillbirth) and low birth weight as a result of leprosy in the mother [34]. Some of the studies concerned leprosy-affected women living in leprosaria/slum colonies being compared with non-leprosy-affected women from the general population, who might have had better living conditions & nutrition.

It is extremely rare to see clinical signs of leprosy in an infant. A few case reports of leprosy in children under 2 years of age have been published. Some early studies done in the pre-MDT era when dapsone resistance was common seemed to suggest a possibility of congenital infection but it is impossible to exclude postnatal airborne infection of the infant. The demonstration of *M leprae* in the placental tissue or pres-

ence of antibodies to *M leprae* in cord blood does not prove prenatal infection of the fetus [34]. There is very little evidence for early post-natal infection from mother *if she has already been treated* with MDT, hence the importance of recognising any undiagnosed leprosy case during the antenatal period, and promptly instigating chemotherapy.

Risks to the fetus from drugs given to the mother during pregnancy must be considered. The minimal risk from anti-leprosy chemotherapy or anti-reaction drugs has been dealt with above (Table 28.3). Drug prescribing for incidental illness or complications of leprosy (eg antibiotics for infected ulcer, analgesics for neuritis) should also be carefully considered. As far as possible, as in any pregnant woman, non-pharmacological measures should be preferred to drug administration for mild illness (eg thorough cleaning of wounds, tepid sponging for fever, splinting of painful limbs).

Risks to the welfare of the baby from its mother's illness/ disability/social circumstances interfering with access to medical services or hindering childcare might be addressed through counseling and practical advice. A diagnosis of leprosy should never be cited as a justification for discrimination against a woman needing medical/social assistance [4].

28.7 The Leprosy-affected Woman After Delivery and Her Family

28.7.1 Post-partum Review: Breast-feeding

M leprae may be discharged through the airways of a mother who is an MB case (and may be inhaled by the infant during nursing) but if the woman is on chemotherapy it is unlikely the bacteria will be viable. The same applies if the father/ other carer is a leprosy case. Simple hygiene should be advised.

Lactation advice for a leprosy-affected woman should be the same as for other women in her community: breast milk, which is the best nutrition for a neonate, is also clean and economical. In most leprosy-endemic situations, the alternatives to breast milk are much more hazardous. Breast-feeding may provide some level of immunity against common infections. A woman might worry about transmitting leprosy infection to the child through her milk but there is no conclusive evidence that this ever occurs. The presence of *M leprae* has been demonstrated in breast milk of lepromatous mothers [34], but infection through the gastrointestinal tract is not an established route. The presence of anti-leprosy drugs in milk might partly counter any small risk of infection. Rifampicin and clofazimine are detectable in breast milk but not in quantities harmful to the infant [30, 34] whereas dapsone in the milk might occasionally cause haemolysis in a susceptible infant [35]. Anti-reaction drugs such as prednisolone may also be excreted in very small quantities in breast milk, unlikely to be harmful to the infant: if the woman has a severe reaction, the balance of risk is probably in favour of their use.

28.7.2 Risk of Reactions and Disability

One must observe the woman for reversal reaction/neuritis during the first few weeks and months after delivery, and warn the new mother of this risk. It seems to be highest in women who are within 3 years of starting MDT. Management of severe post-partum reaction is difficult and should be agreed upon between obstetrician and leprosy specialist; family members might be called on for practical and emotional support to the new mother.

Disability care advice should be reiterated for any woman with nerve function impairment or eye impairment, since her natural preoccupation with the infant may cause her to neglect her self-care. Should she need admission (e.g. for management of trophic ulcers) it is desirable for the infant to be admitted with her to continue breast-feeding; an attendant who can assist in child care might accompany the woman, and hospital staff should be able to keep the infant safe.

28.7.3 Protection for Children

Reassurance of her baby's future low risk of contracting leprosy is important to the new mother. Although household contacts of known cases have a higher incidence of leprosy than the general population, it is still very low (below 5% over a period of up to 20 years) [36]. If she is a recently diagnosed case, her family should be screened with all household contacts being examined for signs of leprosy. Some programmes keep household contacts under active surveillance for 2–5 years. In some countries single dose rifampicin is offered to healthy contacts of recently diagnosed leprosy cases, but is not recommended for children under 2 years of age [10, 37]. These small children are partially protected—if other household members received the "post exposure chemoprophylaxis"—by the reduced risk of leprosy occurring within the household where they live. In addition, if the infant is given soon after birth the BCG vaccination, under the Tuberculosis control programme, some degree of immunity to leprosy is also elicited [10, 11].

28.7.4 Prospect of Future Pregnancies

Contraceptive advice should be offered to any leprosy-affected woman (and her spouse) if she has active disease, particularly if she has already had reaction at least once. For her own welfare, it is desirable to delay a subsequent pregnancy until her risk of reaction has reduced (as well as for the infant to receive adequate care within its early life). This may mean 2–3 years of family planning. Oral or injectable or depot hormonal contraceptives are not incompatible with MDT. Since rifampicin in MDT is given only monthly it causes less enzyme induction than daily rifampicin (as used in anti-tuberculosis therapy), so is unlikely to interfere with the pharmacological activity of hormonal contraceptives (other than the lowest dose preparations).

Whilst offering advice regarding contraception may be necessary for every woman who is still within 3 years of diagnosis, any severely-disabled woman also might need to consider family planning to limit the burden of child care to that with which she can expect to cope.

Leprosy gives no adverse effect on fertility of women but a leprosy-affected husband may have hypogonadism resulting in infertility [38]. This issue may need to be addressed tactfully, since the damage to testes that occurs in MB leprosy is not well known to the public.

28.8 Conclusion

A woman affected by leprosy may require special attention in the antenatal clinic/ward, but the risks are mainly to her (the chance of new impairments occurring during reaction or of incurring further secondary damage to sensory-impaired limbs) and not to the fetus. In most cases, the pregnancy is likely to proceed undisturbed by the sequelae of leprosy infection, to a live birth of a healthy infant. Shared care with a leprosy specialist should be possible to mitigate the woman's risk of increased disability impairing her capacity to undertake good childcare when the baby arrives.

Key Points

1. Leprosy or consequences of leprosy may be an incidental finding in a woman being assessed for pregnancy. Antenatal staff should be alert for signs of leprosy. Such women should be referred to an appropriate clinic for further management of leprosy.
2. Once started on multidrug therapy women with leprosy quickly become non-infectious. There is no need to isolate leprosy-affected women from other patients at the clinic/hospital.
3. Congenital leprosy infection does not occur and anti-leprosy drugs are not harmful to the fetus or neonate.
4. Since pregnancy and parturition may exacerbate health problems for a leprosy-affected woman by increasing

risk from leprosy reaction, contraceptive advice should be offered to newly-diagnosed or recently treated cases.
5. Management of leprosy reaction follows the same principles during pregnancy as at other times, but requires shared care between a leprosy specialist and an obstetrician, with special attention to adverse effects of steroid therapy.
6. Post-partum women are at high risk of reactions, and these should be managed at a leprosy clinic.
7. Management of leprosy-related impairments, in a woman who is taking or has already completed chemotherapy, should not be neglected during pregnancy.
8. Very little is known about epidemiology of leprosy (incidence/case detection rate, reaction rate or relapse rate) in relation to pregnancy in the present day, so individual risk prediction is impossible.
9. Social circumstances assessment may be important for a leprosy-affected pregnant woman, since indirect effects of the disease may impair her ability to access services or to undertake childcare.

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29 Common Surgical Conditions Encountered During Pregnancy

Vivek Agrawal and Chiranjeet Singh Khurana

29.1 Acute Appendicitis

29.1.1 Relevant Anatomy

Appendix which is a true diverticulum arises most commonly from the posteromedial border of the cecum. The base of the appendix can be reliably located at the point where all three taeniae converge on the surface of cecum. The length of the appendix ranges from 5 to 35 cm with the average length being 9 cm [1]. The function of the appendix has traditionally been a topic of debate with none agreeing on one purpose.

The location of the appendicular orifice is consistent, i.e. at the base of the cecum but the position of its tip is not. The most common position of tip of appendix is retrocecal. The various positions of tip of appendix include retrocecal (reaching far into the hepatorenal recess in some cases), subcecal, pre-ileal and post-ileal, and pelvic (Fig. 29.1). The location of appendix also depends on factors such as posture, respiration, and distention of adjacent bowel which leads to variable clinical presentations of its diseases, especially causing inaccuracies in diagnosing appendicitis. Agenesis of the appendix as well as its duplication or triplication has rarely been described in the literature [2, 3]. With advancing pregnancy, the cecum is pushed cephalad by the enlarging uterus, displacing the appendix along with it; so much so that, by the end of the third trimester the pain of appendicitis may be perceived in the right upper quadrant of abdomen. This entails difficulty in differentiating it from the diseases of other organs placed in this region.

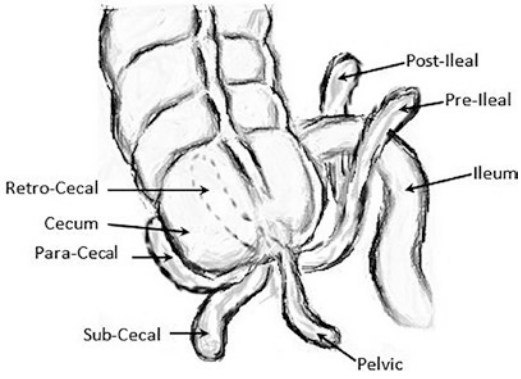

Fig. 29.1 Different positions of appendix. (Courtesy Sahil Juneja)

Appendicular artery, the terminal branch of the ileocecal artery, supplies the appendix. Ileocecal artery arises from superior mesenteric artery that nourishes the midgut. Lymphatic drainage from both the appendix and cecum reaches the ileocolic group of lymph nodes. The lymphatic fluid from the cecum drains via several

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intermediate mesenteric lymph nodes whereas the appendix drains via a single intermediate node. From the ileocolic lymph nodes, the lymph is directed to the superior mesenteric lymph nodes [4].

The sympathetic (autonomic) innervation of appendix arises from the superior mesenteric plexus. Afferent sensory fibers from the appendix are carried along the sympathetic plexus to enter the spinal cord at T10, which corresponds to the umbilical dermatome—thereby explaining the reason for periumbilical initiation of pain in acute appendicitis.

29.1.2 Introduction

Appendicitis is the most common nonobstetric general surgical emergency ailment encountered during pregnancy. Various challenges can be faced in its diagnosis due to non-classical presentation, displaced location of appendix by gravid uterus, occurrence of physiological leukocytosis of pregnancy and surgeon's bent to not to perform surgery upon a pregnant lady. These lead to increased risk of development of complications which can adversely affect the fetal outcome. Acute appendicitis is an important differential diagnosis in any pregnant lady presenting with sudden abdominal discomfort and the prompt management of the condition can definitely reduce the morbidity in both, the mother and the baby.

29.1.3 Incidence

The incidence of appendicitis during pregnancy varies between 1 in 800 and 1 in 1500 pregnancies [5]. The condition is more commonly seen during the second trimester but complications like perforation are more commonly seen during the third trimester, mostly due to delayed diagnosis.

Appendicectomy causes higher morbidity and mortality to the fetus than the mother. Fetal loss occurs in about 2% of uncomplicated appendectomies but the rate goes up to 36% in case it perforates [6]. On the other hand, there is no significant difference in morbidity and mortality following appendicectomy in pregnant and non-pregnant women. However, there is increased incidence of onset of preterm labor (10.6 vs. 5.9% in comparison group) [7].

29.1.4 Etio-Pathophysiology

It is same as in non-pregnant female. Most commonly appendicitis results from obstruction of appendicular lumen due to fecoliths, fruit and vegetable material, parasites, etc. followed by distension due to increased mucus secretion and gas production by bacterial fermentation. This leads to increase in luminal pressure that causes venous stasis followed by arterial insufficiency precipitating mucosal ischemia which progresses to involve the entire thickness of appendix wall and ultimately leading to gangrene and perforation of the affected appendix wall.

Distention of the appendix is responsible for the initial visceral and vague periumbilical abdominal pain stated by the affected patient. The pain does not typically localize over the right lower abdomen area, where the appendix is normally located, until the appendicular tip becomes inflamed—which then irritates the adjacent parietal peritoneum or perforates itself leading to localized peritonitis.

29.1.5 Clinical Presentation

Appendicitis can have both classical and non-classical presentation during pregnancy. Non-classical presentation becomes more common as the pregnancy advances. Classical presentation includes occurrence of periumbilical pain which is followed by nausea, vomiting, and occasionally fever. Non-classical presentation includes diarrhea, constipation, flatulence, heartburn, dysuria, etc.

The pain of appendicitis starts in the periumbilical region which then shifts to McBurney's point [junction of lateral 1/3rd and medial 2/3rd of an imaginary line joining umbilicus and anterior superior iliac spine (ASIS)]. This is evident

in early stages of pregnancy but later on, as the gravid uterus pushes the appendix cephalad, pain occurs in right flank and upper abdomen. Apart from this, the gravid uterus also distances the contact between anterior abdominal wall's parietal peritoneum and inflamed appendix; hence, often there is lack of tenderness and rebound tenderness in pregnancy, masking the true clinical picture of appendicitis leading to difficulty in diagnosis. Several other signs, Rovsing sign (presence of right lower quadrant pain on palpation of the left lower quadrant), the Obturator sign (right lower quadrant pain on internal rotation of the ipsilateral hip), and the Psoas sign (pain with extension of the ipsilateral hip) may be present during early pregnancy and depending on the location of appendix.

Various scores are used to improve accuracy of the diagnosis of appendicitis. These include Alvarado (Table 29.1), Eskelinen, Ohmann, AIR, RIPASA (Table 29.2), Tzanakis, Lintula, Fenyo-Lindberg, and Karaman systems. Although the most commonly used score among all is Alvarado score, its use in pregnancy has not demonstrated high accuracy as it has shown in non-pregnant women; but when Alvarado score is combined with CRP and RIPASA scores, it has yielded higher specificity to diagnose appendicitis in pregnant females, as confirmed in various studies [8].

Table 29.1 Alvarado score

	Features	Score
Symptoms	Migratory Pain	1
	Anorexia	1
	Nausea	1
Signs	Tenderness in right lower abdomen	2
	Rebound Tenderness	1
	Elevated Temperature	1
Laboratory Findings	Leukocytosis	2
	Shift of white blood cell count to left	1
	Total	10

Score 1–4: Acute appendicitis, very unlikely, keep under observation
Score 5–6: Acute appendicitis, may be, for regular observation
Score 7–8: Acute appendicitis, probable, operate
Score 9–10: Acute appendicitis, definite, operate

Table 29.2 RIPASA score

	Parameters	Score
Patients	Female	0.5
	Male	1
	Age <39.9 years	1
	Age >40 years	0.5
Symptoms	RIF Pain	0.5
	Pain Migration to RIF	0.5
	Anorexia	1
	Nausea & Vomiting	1
	Duration of Symptoms <48 h	1
	Duration of Symptoms >48 h	0.5
Signs	RIF Tenderness	1
	Guarding	2
	Rebound Tenderness	1
	Rovsing Sign	2
	Fever >37 °C < 39 °C	1
Investigation	Raised WBC	1
	Negative Urine Analysis	1
Additional Score	Non –Asian	1
Total score		17.5

Score < 5: Probability of acute appendicitis is unlikely
Score 5–7: Low probability of acute appendicitis
Score 7.5–11.5: Probability of acute appendicitis is high
Score > \ = 12: Definite acute appendicitis

29.1.6 Diagnosis

Accurate diagnosis is the most important step in managing appendicitis because negative appendectomy can be associated with a high risk of fetal loss and premature birth [5].

Leukocytosis: Physiological leukocytosis of pregnancy with neutrophils predominance, where counts as high as 16,000 cells/mm^3 seen during pregnancy may mask the leukocytosis due to the disease.

Ultrasonography: Its easy availability, low cost, and lack of ionizing radiation make it a good initial radiological investigation to diagnose appendicitis. However, presence of gravid uterus and displacement of appendix from its normal right lower abdomen location may lead to its non-visualization in 88–97% of the cases; USG has overall sensitivity between 20–40% and specificity 95–100% [9]. Thus, relying on USG may result in delaying diagnosis which increases the risk of complications.

Computed Tomography: The teratogenic effect of this diagnostic modality has to be weighed against its diagnostic accuracy. This risk is reduced during the later stages of pregnancy because organogenesis is already complete by that time. Incase we need to use CT scan in inconclusive cases, we should image a limited area to decrease radiation exposure; according to ALARA (as low as reasonably achievable) principle and also contrast should not be used. It has been found that radiation exposure less than 500 mGy has no teratogenic effect but there is 0.1% increased risk of childhood cancer following exposure to 100 mGy radiation [10].

Magnetic Resonance Imaging: It is a safer option as compared to CT scan as it has less teratogenic potential. It is more accurate than ultrasonography to visualize the appendix (50–60%) [10]. There is better characterization of pathologic tissue by MRI and it has the capability of direct multiplanar cross-sectional imaging. The reported sensitivity in pregnancy is 80–100% and specificity is 93–100% for diagnosing appendicitis. Various studies have shown MRI reduces the rate of negative appendectomies by 50% [10]. Its inconsistent availability in peripheral centers limits its use. Where MRI is not readily available and the potential risks of radiation to the fetal growth and development are outweighed by serious immediate complications that could result from a missed diagnosis, a CT scan should be considered to increase the pre-operative accuracy of the diagnosis.

29.1.7 Complications

If untreated, acute appendicitis can progress to severe complications with high morbidity. Appendicular perforation is one of the dreaded complications which can either lead to free peritonitis or contained/localized "walled-off" peritonitis.

Perforations cause dissemination of pus and fecal matter into the peritoneal cavity, which subsequently leads to sepsis and increases risk of preterm labor or fetal loss. Contained or walled-off perforations can cause intraperitoneal abscess or phlegmon; that forms around a burst appendix and requires extended antibiotic treatment and often a surgical drainage.

Complications of the surgery itself can be extensive and include infections (postoperative peritonitis, intraperitoneal abscess, surgical site infections, UTIs, pneumonia, etc.), bleeding, and damage to adjacent structures.

29.1.8 Treatment

Appendectomy remains the treatment of choice for all cases diagnosed as appendicitis in pregnancy.

Anesthesia: Appendectomy requires anesthesia and general anesthesia carries 17 times higher risk in pregnancy as compared to non-pregnant women [11]. Obese pregnant women have neck shortening which in association with edema and breast engorgement can result in difficult intubation. There is higher risk of aspiration of gastric contents (Mendelson's syndrome) and hypoxia. Also, pregnant women desaturate much quicker than non-pregnant counterpart (3 min as opposed to 9 min), especially if body mass index is high. All anesthetic induction and maintenance agents cross the placenta but effects are transient and if the neonate is born during general anesthesia, then ventilatory support is required to sustain the neonate until the effects of drugs wear off. So, regional anesthesia is preferred over general anesthesia, only risk being hypotension secondary to sympathetic blockade. Opiate analgesia is sufficient to control perioperative pain and use of NSAIDS should be avoided as they cause premature closure of ductus arteriosus, especially after 32 weeks.

Surgical Management: For appendicectomy, two main approaches are available—open and laparoscopic. Either may be adopted based on patient's preference, gestational age, and expertise of the surgeon. However, the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) guidelines advocate the use of laparoscopic appendectomy as the standard of care in pregnant patients owing to higher safety profile [12].

Some modifications are recommended while performing laparoscopic surgery in a pregnant lady which includes slight left lateral positioning of the patient (especially during the second half of pregnancy) to prevent aortocaval compression, the use of an open port access (Hasson technique) for initial trocar placement to avoid injury to the gravid uterus, limiting intra-abdominal insufflation pressure to less than 12 mmHg, and adjustment of port position commensurate to uterine fundal height [13].. While performing open surgery, mark the point of maximal tenderness and give incision on it and not necessarily at the McBurney's point. If a surgeon is not sure of the diagnosis, a lower midline vertical incision may be preferred as it helps to explore other organs whose affection can result in appendicitis like picture. All cases should be given broad spectrum good antibiotic coverage for gram-positive and gram-negative bacteria as well as anaerobes.

Management of complications: If the surgery is not performed within 24 h, there is increased risk of perforation. Perforation can be either free or contained. Free perforation is the one where there is spillage of contents into the peritoneal cavity causing generalized peritonitis resulting in a sick looking patient and adding to the risk of fetal loss. It is managed with urgent exploratory laparotomy, appendectomy, and drainage of peritoneal cavity. In case the perforation is walled off, resulting in abscess formation, then management is conservative with IV antibiotics, bowel rest, and IV fluids with close monitoring and minimal access or open surgical drainage. However, there is lack of sufficient data on conservative management of walled-off perforation in pregnant females. Pregnancy being a hypercoagulable state, a decision should be made to give thromboprophylaxis with low molecular weight heparin.

Fetal Monitoring: After the period of viability of fetus, i.e. 24 weeks is attained, fetal monitoring should be done both pre-operatively and post-operatively. If the fetal heart is not reassuring, continuous fetal monitoring may be required [14]. Inhalational agents which contain cardiodepressants and decreased sympathetic tone seen during pregnancy can cause maternal vasodilation leading to lowering of blood pressure with a resultant drop in uterine perfusion. Cardiotocography (CTG) changes consistent with fetal compromise can usually be reversed by maximizing maternal oxygenation, correcting hypovolemia and hypotension, and ensuring a left lateral tilt.

Obstetric Management: If the patient is critically ill and surgery is needed urgently, it should be done regardless of gestation, as maternal welfare is always a priority over and above the fetus. Appendicitis may cause irritation to the uterus and potentiates the risk of preterm labor. If the gestation is above 34 weeks, labor should be allowed to proceed. Antenatal steroids should be given between 24 and 34 weeks. Steroids should not be used in severe maternal sepsis as it may interfere with maternal immune responses. There is no risk of rupture of appendectomy scar during labor. C-section is for obstetric indications only and performed along with appendectomy if the gestation is 37 weeks or more. Fetal heart rate abnormalities are common and adequate analgesia should control it in most of the cases. Persistent abnormalities on CTG during planned appendectomy may warrant the need of C-section. Thus, simultaneous delivery is attempted only in case of severe fetal or maternal compromise and preferably as close to term as possible.

29.1.9 Differential Diagnosis

Other conditions, both surgical and gyneco-obstetric, should be considered in differential diagnosis. Common surgical conditions that may mimic appendicitis are cecal diverticulitis, Meckel diverticulitis, acute ileitis, inflammatory bowel disease (Crohn and ulcerative colitis), renal colic, and urinary tract infections. Gynecological conditions like tubo-ovarian abscess, pelvic inflammatory disease, ruptured ovarian cyst, ovarian, round ligament syndrome, and fallopian tube torsion are the differential diagnosis which should always be kept in mind. Obstetric conditions with similar presentation include placental abruption, uterine rupture, pre-eclampsia, HELLP (hemolysis, elevated liver

function tests, low platelets) syndrome. During early pregnancy, ectopic pregnancy is a very important differential diagnosis which needs to be excluded.

29.1.10 Prognosis

Appendectomy in pregnancy has similar morbidity and mortality as that in non-pregnant females. The greater risk is for the fetus inside the womb.

Risk of fetal loss in appendicitis and related conditions is as follows [6, 7]:

- In uncomplicated appendectomy—2%
- In case of generalized peritonitis and abscess—6%
- In negative appendectomy—4%

Risk of preterm labor due to appendectomy is as follows [6, 7]:

- In uncomplicated—4%
- In cases with complications—11%
- In negative appendectomy—10%

29.1.11 Conclusion

Appendicitis may pose a diagnostic dilemma during pregnancy. It is a double-edged sword with increased risk of fetal loss, both when diagnosis is either delayed resulting in perforation or inaccurate resulting in negative appendectomy. A multidisciplinary approach involving a general surgeon, an obstetrician, an anesthetist, and a radiologist is required for accurate pre-operative diagnosis of the condition so as to ensure maximum safety to both the mother and the baby.

29.2 Acute Cholecystitis

29.2.1 Relevant Anatomy of Gallbladder

The gallbladder is a piriform (pear-shaped) organ that occupies the undersurface of segments IVB and V of the liver. The cystic plate separates the gallbladder from the liver parenchyma. Small bile ducts may drain from liver parenchyma directly to the gallbladder through the cystic plate (ducts of Luschka). Fundus of the gallbladder projects beyond the margin and undersurface of right lobe of the liver, it continues into the main body of the gallbladder that lies in a fossa on the undersurface of the liver. Infundibulum is the narrow part of GB that is the continuation of body and it leads through the neck to form the cystic duct which unites with the common hepatic duct to continue as common bile duct (CBD).

The cystic duct has "valves" of Heister which are spiral folds of the mucosa lining the duct. The Hartmann pouch is an inferior outpouching of the gallbladder infundibulum or neck and is present sometimes. The cystohepatic triangle (Fig. 29.2) is formed by the cystic duct on the right, common hepatic duct (CHD) on the left, and undersurface of the liver above. The cystic artery and cystic lymph node of Lund form the contents of this triangle.

The peritoneal fold runs as lesser omentum from the inferior surface of the liver (between the porta hepatis and the umbilical fissure) till the lesser curvature of the stomach and the first part of the duodenum. The free right edge of the lesser omentum is known as the hepatoduodenal ligament.

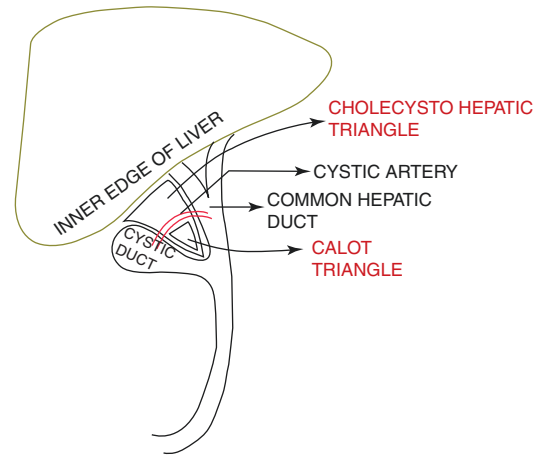

Fig. 29.2 Cystohepatic and Calot's triangle

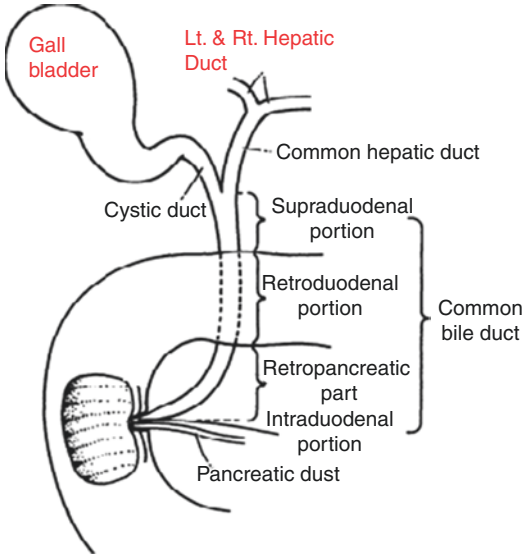

Fig. 29.3 Extrahepatic biliary system showing different parts of CBD

The common bile duct has four parts (Fig. 29.3), namely a supraduodenal, a retroduodenal (behind the first part of the duodenum), an infra-duodenal or retropancreatic (in a groove or sulcus behind or a tunnel through the upper half of the head of the pancreas), and an intraduodenal (intramural) part.

A common channel formed by the terminal parts of CBD and the pancreatic duct runs through the duodenal wall and opens as a nipple like projection on the medial wall of the second part of the duodenum as major papilla.

Sphincter of Oddi, a smooth muscle sphincter, is present around the common channel of the CBD and the main pancreatic duct and prevents reflux of duodenal juice into the two ducts. Two other smooth muscle sphincters, one present around the terminal part of the CBD (sphincter of Boyden) and the other in the terminal part of main pancreatic duct, prevent reflux of pancreatic fluid into the CBD and of biliary secretions into the main pancreatic duct.

Arterial supply: The celiac trunk arises from the anterior surface of the aorta at the level of T12–L1 and divides into the common hepatic artery (CHA), the splenic artery, and the left gastric artery. The CHA gives off the gastroduodenal artery (GDA) and continues as the proper hepatic artery within the hepatoduodenal ligament lying to the right side of the CBD and in front of the portal vein.

The cystic artery is a branch of the right hepatic artery. It divides into an anterior and a posterior branch that supply the gallbladder. Blood supply comes to the gallbladder from the liver via the gallbladder bed also.

There is no named cystic vein but multiple small veins drain the gallbladder into the intrahepatic branches of the portal vein in the liver (segments IV and V); and hence explains the occurrence of bilobar liver metastases.

The lymphatic drainage of gallbladder is via cystic lymph node of Lund along the cystic artery, between the cystic duct and the CHD. Subserosal gallbladder lymphatics also drain into subcapsular lymphatics in liver.

Gallbladder cancer can spread directly to the lymph nodes in the porta hepatis or the hepatoduodenal ligament, without involving the cystic group of lymph nodes therefore refuting the theory of it being the sentinel lymph node.

The gallbladder receives parasympathetic nerve supply from the right vagus through its hepatic branch and sympathetic supply comes from T7 to T9 through the celiac plexus.

Normally gallbladder has a capacity of 30–50 mL but since it acts as a reservoir, its size changes from time to time depending on the volume of bile present in it.

29.2.2 Introduction

Acute cholecystitis is the second most common nonobstetric surgical emergency in pregnancy after acute appendicitis. Pregnancy is associated with increased incidence of gallstone disease due to hormonal changes in estrogen and progesterone. Estrogen causes cholesterol crystal aggregation while progesterone causes bile stasis leading to increased biliary sludge precipitation and gallstone formation. It takes several months after pregnancy to return to normalcy. In addition, obesity and high pre-pregnancy body mass index

are strongly associated with risk of gallstone formation. Like in appendicitis, diagnosis may be delayed due to non-specific signs and symptoms, thereby increasing the risk of complications.

29.2.3 Incidence

Biliary sludge formation (precursor of gallstone) occurs in 30% of pregnancies and gallstone formation occurs in 3% of all pregnancies. Prevalence of gallstone disease is 12.2% in multiparous females versus 1.3% in nulliparous females [15]. Despite predilection for biliary sludge and gallstone formation, acute cholecystitis occurs only in 0.1% of the total pregnancies [16].

29.2.4 Clinical Presentation

Symptoms of acute cholecystitis are usually similar to those that occur in the non-pregnant state and include the classic colicky or stabbing pain in the right upper abdominal quadrant, which can radiate to the inferior angle of right scapula and/or right shoulder. Other symptoms, that may be present, include anorexia, nausea, vomiting, dyspnea, low-grade fever, and fatty food intolerance. Pain usually exacerbates after fatty meal due to the gallbladder contraction which increases the intraluminal pressure secondary to ductal obstruction. Persistence of right upper abdominal pain with low grade fever and vomiting should alarm the treating obstetrician of the possibility of acute cholecystitis.

Physical examination of a patient with acute cholecystitis reveals tenderness in the right upper quadrant of abdomen and a positive Murphy's sign (increase in pain and catch in breath upon abdominal palpation during deep inspiration). Fever and tachycardia suggest an underlying infection. The presence of peritoneal inflammatory signs is extremely ominous, which may reflect either pus formation (empyema) or rupture of the gallbladder.

29.2.5 Pathophysiology

Bacterial invasion is not the primary cause of acute cholecystitis which mainly occurs when the cystic or common bile ducts are obstructed by gallstones. It is the inflammation, hyperemia, and edema of the gallbladder that follow the obstruction and subsequently lead to venous and lymphatic obstruction culminating finally in ischemia. It is only after this secondary ischemia, the bacterial invasion and infection commonly occur [17].

Bactibilia has been reported in up to 65% of women with acute cholecystitis. Conversely, bactibilia is found in 20–30% of patients with biliary concrements that have minimal or no signs of obstruction. E. coli accounts for 75% of all bacterial strains recovered from patients with acute cholecystitis [17].

29.2.6 Diagnosis

Laboratory evaluation may provide assistance in diagnosing the condition but it is clear that management plan will be dictated by the clinical course. Laboratory studies include blood leukocyte count, evaluation of hepatic function, serum bilirubin, amylase, lipase, and alkaline phosphatase. There are numerous alterations in several of these laboratory parameters during pregnancy and this can limit their usefulness. In pregnancy the blood leukocyte count varies from 5000 to 16,000/ml and these values may rise significantly at labor. The liver function tests may not be very helpful in pregnancy as normally also alkaline phosphatase activity (increases two fold during normal pregnancy) and postprandial plasma levels of total bile acids progressively increase during pregnancy. Therefore, laboratory evaluation will only provide clues of affection of biliary tract disease during pregnancy. Common bile duct stones should be suspected if bilirubin remains elevated with persistent jaundice and if there is associated significant leukocytosis, then an underlying infectious process should be considered.

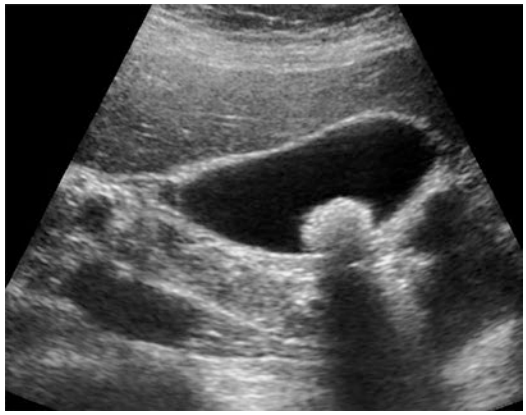

Fig. 29.4 USG showing gallstone with thickened gallbladder wall

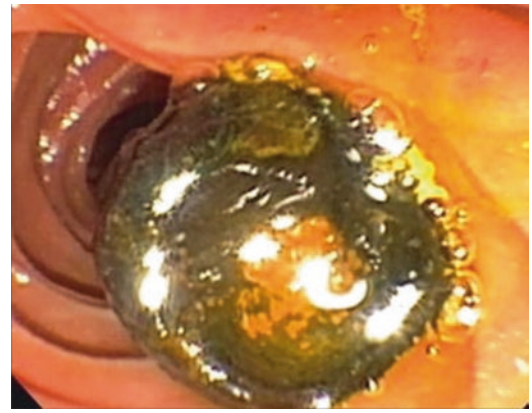

Fig. 29.5 ERCP showing stone in CBD

Ultrasonography: It is the best investigation to diagnose acute cholecystitis in pregnancy as it is cost-effective and non-invasive; with sensitivity of 85–95% and specificity of 95%. Classical findings of acute cholecystitis seen on USG include a thickened gallbladder wall over 3–5 mm, pericholecystic fluid, calculi (Fig. 29.4), and a sonographic Murphy's sign (focal tenderness under the ultrasound transducer positioned over the gallbladder). Few patients may not have typical gallstone on USG evaluation but may show wall echogenic shadow (WES) which is suggestive of either a large gallstone or multiple small gallstones completely filling the lumen of a contracted gallbladder.

MRI and MRCP (Magnetic Resonance Cholangiopancreatography): Magnetic resonance is an imaging modality that can be relied upon to diagnose different etiologies of abdominal pain in any stage of pregnancy [18]. Contrary to the traditional fears, safety of MRCP in pregnancy is approved [19].

ERCP (Endoscopic Retrograde Cholangiopancreatography): It is a useful method to diagnose small stones as well as stones which are present in the ductal system (Fig. 29.5). It has proven to be both diagnostic and therapeutic. ERCP along with sphincterotomy can be used to extract stones and manage pancreatitis by relieving obstruction in common bile duct. The risk of radiation exposure to the fetus from ERCP (approximately 310 mrad) is only theoretical, and is not of concern when conducted after the first trimester [20].

29.2.7 Differential Diagnosis

These include appendicitis, pancreatitis, peptic ulcer disease, pyelonephritis, HELLP syndrome (syndrome of hemolysis, elevated liver enzymes, and low platelets), acute fatty liver, and hepatitis and can be differentiated through blood chemistry and ultrasonography.

29.2.8 Complications

If left untreated, the most dreaded complication is gangrenous cholecystitis. Other serious complications include empyema gallbladder, localized abscess, perforation, internal or external fistula, gallstone ileus, and emphysematous cholecystitis.

29.2.9 Management

Traditionally, conservative approach was used to manage acute cholecystitis in pregnancy as it was accepted that interventions affected gravid uterus and led to increased fetal morbidity and mortality. With advancements made in the fields of

anesthesia, surgery, and obstetrics, an early cholecystectomy by laparoscopic approach is the preferred modality of treatment. Nonoperative management was found to be associated with recurrent attacks, multiple hospital admissions, and complications of the disease resulting in preterm labor, spontaneous abortions, and overall increased fetal morbidity and mortality. The risk of recurrence of symptoms with conservative management if the initial presentation is in first trimester is 92% followed by 64% in second trimester and 44% in the third trimester [21]. Because of high fetal and maternal complication rates, the management of complicated gallstone diseases in pregnancy needs early treatment. Laparoscopic cholecystectomy can be safely performed in pregnancy so as to lower fetal and maternal complications rates.

29.2.9.1 Nonoperative Management

In managing acute cholecystitis in pregnancy, many physicians advocate initial nonoperative management in an effort to prevent effects of surgical intervention's insult on gravid uterus. It includes discontinuation of oral ingestion, intravenous fluid replacement, analgesia, and administration of antibiotics. As spasm of sphincter of Oddi is caused by morphine and its derivatives, these should be avoided as analgesics in pregnant females. Among commonly used antibiotics, the combination of a penicillin and an aminoglycoside has long been recommended as the initial treatment of choice for these patients. This broad spectrum antibiotic therapy is initiated empirically and is based on the bacterial flora likely to be encountered in the biliary tract. While penicillin offers adequate coverage against gram-positive organisms along with most of the anaerobes and enterococcus species, aminoglycosides act against gram-negative facultative biliary pathogens including Pseudomonas. Due to the rising concern about aminoglycoside-induced nephrotoxicity, especially in patients with jaundice and sepsis, cephalosporins have potentially come in use in place of penicillin plus aminoglycoside. On reviewing the efficacy of cefepime in patients of acute cholecystitis, it was found that its single drug therapy was as effective as combination therapy with mezlocillin and gentamicin [22]. Cefepime requires 12 h dosing to achieve high bile, blood, and gallbladder levels. Piperacillin, an extended spectrum penicillin, has been shown to be effective in patients with acute cholecystitis and it has broad coverage against all organisms commonly found in the biliary tract, with excellent biliary excretion and negligible nephrotoxicity.

29.2.9.2 Minimally Invasive Procedures

In selected high-risk patients where medical management has failed and operative interventions pose serious operative risks, less invasive procedures such as percutaneous transhepatic gallbladder drainage (PTGBD) and ERCP can be performed to combat the acute inflammatory phase, decrease the infectivity, and enable patient to better tolerate any definitive surgery. USG guided PTGBD provides adequate biliary decompression and has been shown to be safe and temporarily effective in treating acalculous cholecystitis [23]. It is recommended that the drainage tube should not be removed until a mature fistulous tract forms around it (around 2 weeks). Major disadvantages associated with this procedure are bile leakage, bile duct injury, and abdominal abscess [24]. When CBD stones are considered to be the offending cause of acute cholecystitis, ERCP and generous sphincterotomy should be performed with an aim of subsequent removal of the stone [25].

29.2.9.3 Surgical Management

All attempts must be made to defer surgical intervention on a patient in her first trimester until the second trimester, and of a patient in the third trimester, try to postpone until after parturition. Fetal organogenesis is complete by the second trimester and the size of the gravid uterus also allows relatively good visualization of operative field. With advances in laparoscopic surgery in pregnancy, it has been safe to use open Hasson trocar method for inserting first port into the abdominal cavity; to prevent injury to the gravid uterus [26]. Pneumoperitoneum should be kept at a maximum pressure of 12 mmHg and fetal well-

being should be monitored continuously with transvaginal ultrasound. Laparoscopic surgery has advantageous end results of a shorter hospital stay, smaller incision, and early ambulation. Patients undergoing open cholecystectomy experience a higher frequency of postoperative premature uterine contractions requiring tocolytic therapy compared to those undergoing laparoscopic cholecystectomy, resulting in lesser need of open intervention [27].

29.2.10 Prognosis

Perinatal outcomes among patients with acute cholecystitis treated conservatively [28] are as follows:

- Preterm delivery—3.4%
- Missed abortion—1.7%
- Low birth weight—5%
- Maternal death—1.7%.

Perinatal outcomes among patients with acute cholecystitis treated surgically [28] are:

- Preterm delivery—3.4%
- Low birth weight—3.4%.

29.2.11 Conclusion

Biliary tract disease in pregnancy is relatively an uncommon occurrence. Progression to acute cholecystitis can be difficult to recognize due to the heterogeneous nature of the disease. Once appropriately diagnosed, the initial management consists of conservative approach which includes institution of antibiotic therapy along with analgesics and IV fluids. Depending on the gestational age at diagnosis, the further management plan may differ. Surgical intervention, when indicated, should not be delayed as this could lead to deleterious effects on both fetus and the mother. A planned intervention done in second trimester appears to offer a better outcome than surgery performed under emergent conditions.

29.3 Intestinal Obstruction

29.3.1 Relevant Anatomy

29.3.1.1 The Small Intestine

The small bowel lies between the stomach and the large intestine. It includes the duodenum, jejunum, ileum, and proximal colon. Embryologically, it develops from midgut, with the superior mesenteric artery (SMA) as its arterial supply. It is during the early stages of development that the midgut communicates with the yolk sac via the vitellointestinal (omphalomesenteric) duct but then subsequently returns to the abdominal cavity to occupy the normal anatomical position after completing its 270° rotation.

29.3.1.2 The Large Intestine

The proximal part of large intestine develops from the midgut (from cecum to proximal 2/3rd transverse colon) whereas the distal part develops from the hindgut (from distal ⅓ transverse colon to dentate line in anorectum), and proctoderm (below the dentate line). It derives its arterial supply from both superior and inferior mesenteric arteries (SMA & IMA).

Variation in anatomy such as malrotation of gut, Ladd's band, persistence or patency of vitellointestinal duct, etc. may predispose a person for development of intestinal obstruction.

29.3.2 Introduction

Intestinal obstruction is a rare but serious surgical condition. Its incidence is reported to be similar in pregnant and non-pregnant females varying between 1 in 1500 pregnancies to 1 in 66,431 pregnancies [29]. It causes high maternal mortality (6–20%) as well as fetal mortality (20–26%) [30]. The commonest cause of intestinal obstruction in pregnancy is adhesions, accounting for around 60% of the cases. Some of the other causes include sigmoid volvulus (25%), intussusception (5%), stricture, hernia, carcinoma, and diverticulitis/diverticulosis [31].

Adhesions account for 6, 27, 44, and 21% of the intestinal obstruction rates seen during the first, second, and third trimester of pregnancy and postpartum respectively.

Delay in diagnosis can lead to intestinal strangulation, further increasing the incidence of maternal morbidity, mortality, premature labor, and fetal loss. Therefore, early recognition of the disorder and prompt initiation of treatment is mandatory [32].

29.3.3 Pathophysiology

Intestinal obstruction can be either dynamic or adynamic. In dynamic type, peristalsis occurs against a mechanical obstruction, e.g. stricture/adhesions whereas in adynamic type, there is no mechanical obstruction but there is absent/decreased peristalsis leading to bowel stasis, e.g. paralytic ileus. Dynamic intestinal obstruction is further classified into small bowel obstruction (high/low) and large bowel obstruction.

One of the hypotheses in favor of intestinal obstruction manifesting in pregnancy is that due to distortion in relationship between various organs as a result of enlarging gravid uterus, previous asymptomatic adhesions may stretch and precipitate compression upon the adjoining intestine.

29.3.4 Clinical Features

The cardinal symptoms of intestinal obstruction in pregnancy include abdominal pain (98%), vomiting (82%), and obstipation (30%). Abdominal tenderness and increased abdominal peristalsis are observed in 71 and 55% of the patients, respectively [33]. The sequence of appearance of symptoms varies according to the site of obstruction. In case of small bowel obstruction, vomiting precedes obstipation whereas in case of large bowel obstruction obstipation along with pain abdomen is the most common presenting complaint. Vomiting, in case of large bowel obstruction, may not be present in patients presenting early in the course of disease. Pregnant females usually have 'morning sickness' in the first trimester of pregnancy, which can be misinterpreted as intestinal obstruction. Nausea in morning sickness is sometimes accompanied by vomiting (non-bilious in nature) and occurs in the morning only whereas any pregnant lady with persistent and progressive bilious vomiting should be evaluated for intestinal obstruction especially when she has had a history of surgery before—as she is more likely to have developed adhesions resulting from that past surgery. Also, increasing abdominal girth in obstruction may be attributed to enlarging uterus due to advancing pregnancy. In addition, stretched anterior abdominal wall becomes less sensitive to parietal peritoneal irritation (which is the cause for pain) & may delay the diagnosis of precipitating complications.

29.3.5 Diagnosis

Blood investigations: TLC is normally elevated in pregnancy due to increased adrenocortical activity. Serial WBC counts are more useful to arrive at a diagnosis in pregnancy. Serum electrolytes and KFT may also predict the cause and effect of obstruction. Hypokalemia and hypocalcemia are very important causes of adynamic obstruction which can be easily ruled out by performing serum electrolyte analysis. Conversely, in small bowel obstruction patients may develop hypokalemia secondary to persistent vomiting.

Arterial blood gas (ABG) is another necessary investigation that helps in diagnosing intestinal strangulation early in the course of disease. It calculates lactate levels which are raised in case of strangulation.

Ultrasonography(USG): It is used as an initial investigation and shows dilated bowel loops with to and fro movement of the dilated loop along with some free fluid in the abdomen suggestive of dynamic bowel obstruction. When there is absence of this to and fro movement but the bowel is dilated, then one must think either of adynamic obstruction or late stage of dynamic

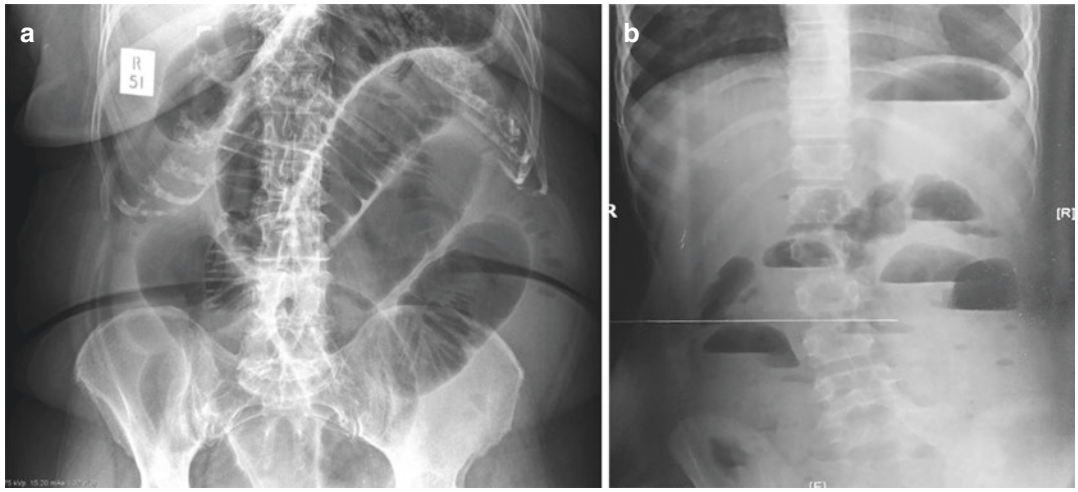

Fig. 29.6 (**a**) Step ladder pattern in case of small intestine obstruction. (**b**) Centrally placed multiple air fluid levels, classical of small intestinal obstruction

obstruction with bowel fatigue. Apart from diagnosing the condition, it also helps to follow the course of a conservative treatment; it will suggest for laparotomy in case a thickened intestinal wall, reflecting an ischemia, is seen. It also eliminates the other causes of ileus, viz. biliary and renal origin. It is the only investigation that specifies fetal or embryonic viability.

X-ray: In case USG is inconclusive, X-ray abdomen may be required to make definitive diagnosis (Fig. 29.6a and b). The United States National Council on Radiation Protection considers exposure of 5 cGy or less to be negligible, in causing harm to the fetus, compared with other risks of pregnancy [34]. If essential, diagnostic abdominal X-ray in the pregnant women can be done with an acceptable risk in the appropriate setting.

Computed tomography (CT): It remains the gold standard for the diagnosis of intestinal obstruction. However, it is contraindicated in phase of organogenesis during pregnancy because of detrimental effects from high doses of irradiation. But recent data suggests that noncontrast CT scan can be safer in diagnosing intestinal obstruction in pregnant females with very little chances of fetal damage, especially when other modalities of diagnosis have failed to give a concrete answer [35].

Magnetic Resonance Imaging: MRI provides large field-of-view images of maternal abnormalities with excellent soft-tissue delineation. It also allows the pancreatic and biliary ducts, blood vessels, and genitourinary tract to be visualized without the intravenous administration of a contrast agent. MRI also does not expose the fetus to ionizing radiation and aids in diagnosis even without the need for the intravenous administration of contrast material. It can be used to evaluate a pregnant lady presenting with abdominal symptoms, to delineate the anatomy and to exclude a variety of patient's pathological processes that may give rise to small bowel obstruction [36].

29.3.6 Management

In the absence of signs of peritonitis, a conservative approach should be tried initially, which includes monitoring vital parameters, abdominal girth monitoring, nasogastric aspiration, supplementation of intravenous fluids, and analgesics. This relieves majority of the patients of their symptoms and prevents unnecessary manipulations that could have detrimental effects on pregnancy. Surgical intervention is indicated when conservative therapy fails even

after 48–72 h of observation and when signs of impending bowel strangulation or symptoms of fetal distress set in. To decrease the risk of premature uterine contractions, tocolytic agents are administered prophylactically, especially when surgery is contemplated or complications occur. In the third trimester, if adequate exposure of intestine cannot be obtained, cesarean section must be performed and laparotomy is continued [37]. The entire bowel must be examined for other areas of obstruction and viability. Segmental resection with anastomosis or exteriorization of proximal segment (as stoma) may be necessary in the presence of gangrenous bowel. In pregnant women having inadequate oral intake, underlying disease states requiring complete bowel rest or severe illness should be treated with intravenous hyperalimentation (TPN). TPN might benefit the fetus by promoting intrauterine growth in cases involving fetal growth retardation due to severe maternal nutritional deprivation.

Although majority of the patients are initially managed conservatively, definitive treatment of conditions causing dynamic obstruction is surgery, which is to be undertaken after proper resuscitation to decrease maternal and fetal morbidity and mortality. Preferably, definitive procedures are generally postponed until after delivery, if possible, or else they are performed under calculated risk after proper informed consent.

29.3.7 Prognosis

Maternal mortality increased from 20 to 31% in 1958 but subsequently it has decreased to 6%, or even zero at present, because of the progress made in resuscitative measures taken at right time [38]. However, fetal mortality remains static between 20 and 30%; prematurity and fetal hypoxia secondary to maternal hypotension being the harbingers [38]. Fetal mortality also varies with respect to age of gestation: none in the first trimester & reaching 36 and 64% in the second and third trimesters, respectively [39].

29.3.8 Conclusion

Onset of intestinal obstruction in pregnancy is rare and distension, which is not differentiated easily, delays the diagnosis. Maternal morbidity and fetal mortality remain high though early diagnosis and prompt treatment improves prognosis. Conservative treatment, besides aiding in relieving the obstruction, helps to prepare the patient to bear the surgical trauma better.

29.4 Hernia in Pregnancy

29.4.1 Introduction

Hernia is one of the rare nonobstetric surgical problems encountered in pregnant females. Primary ventral hernias are usually either umbilical or epigastric. Among groin hernias, inguinal and femoral hernias occur in a ratio of 5:1. Prevalence of primary ventral hernia in pregnancy is unknown but pregnancy is a known risk factor for recurrence of hernia after primary repair. Also, the evidence for surgical strategy in pregnant women with a hernia is limited and is only reported in a limited number of case reports. The data on risk of hernia incarceration or strangulation during pregnancy and planning of subsequent elective repair are also unknown.

29.4.2 Incidence

Incidence of inguinal hernia during pregnancy is reported to be 1:1000–3000. Out of all the inguinal hernias occurring in pregnancy, 75% occur in multipara pregnancies, suggesting that the increased intra-abdominal pressure and related hormonal changes during pregnancy predispose a female to develop inguinal hernia [40].

29.4.3 Classification of Hernia

Hernias are categorized according to the site of origin and the contents present in the hernial sac. (Table 29.3).

Table 29.3 Classification of hernia

According to region	Ventral hernia	Umbilical–paraumbilical Epigastric Incisional Parastomal Spigelian Lumbar Traumatic
	Inguinal hernias	Direct inguinal hernia Indirect inguinal hernia
	Femoral hernia	
	Lumbar hernia	Superior lumbar hernia Inferior lumbar hernia
	Rare external hernias	Perineal hernia Obturator hernia Gluteal and sciatic hernia
	Diaphragmatic hernias	Bochdalek hernia Anterior Morgagni's Hiatus hernia
According to Contents	Omentocele—omentum Enterocele—intestine Cystocele—urinary bladder Litter's hernia—Meckel's diverticulum Maydl's hernia—Sliding hernia Richter's hernia—part of the bowel wall forms the content of hernial sac Amyand hernia—containing appendix as a content in inguinal hernial sac De Garengeot—appendix in femoral hernia sac	

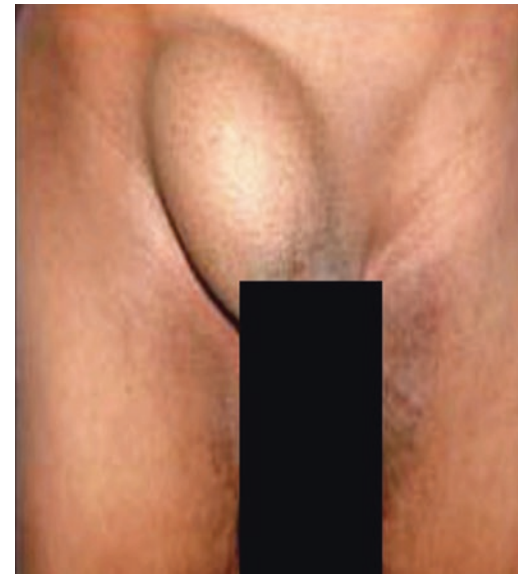

Fig. 29.7 Right indirect inguinal hernia

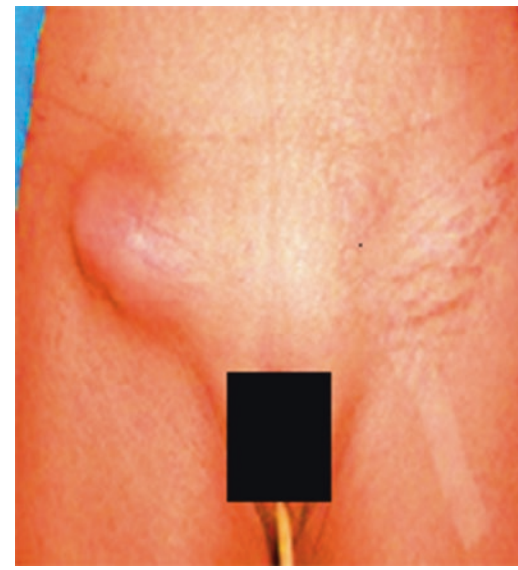

Fig. 29.8 Right femoral hernia

29.4.4 Types of Hernias Common in Pregnancy

29.4.4.1 Groin Hernia

These can be direct inguinal hernia, indirect inguinal hernia (Fig. 29.7), or femoral hernias (Fig. 29.8). The risk factor for development of inguinal hernias are same as for the general population, i.e. family history of inguinal hernia, collagen disorders, smoking, renal failure, chronic lung disease, diabetes mellitus, long-term steroid use, malignancy, malnutrition, cirrhosis, ascites, and obesity. Adding to these factors, increase in intra-abdominal pressure due to an enlarging pregnant uterus has also been postulated to play some role.

Recurrence after hernioplasty can be secondary to deep infection, undue tension on the repair site, or tissue ischemia, leading to wound dehiscence, as is seen in non-pregnant patients. Majority of the cases can be managed by elective surgery. Possible reasons for the high rate of

emergency operations during pregnancy, particularly in femoral hernias, are ignoring the asymptomatic hernias prior to their getting incarcerated and difficulties in diagnosis.

29.4.4.2 Umbilical Hernia

The herniation occurs typically at the umbilicus (Fig. 29.9), but paraumbilical are also frequent; in some cases, it may be either above (supraumbilical) or below umbilicus (infraumbilical). The defect is covered directly by skin without any underlying fat.

Mostly, the cause is attributable to a weakness of the abdominal wall or an increase in abdominal pressure (as occurs in pregnancy), cirrhosis, or obesitiy [41]. These hernias show slow enlargement over a period of years and chances of subsequent strangulation are much more as compared to that occurring in pediatric umbilical hernias. Diagnosis is primarily clinical, based on definitive evidence of dilated umbilical ring, with or without contents in the hernia sac. If incarceration is present, symptoms depend on the organ affected and its duration. Strangulated bowel causes intense pain, vomiting, distension and obstipation; uterine fibroid or greater omentum when strangulated causes only pain and local tenderness. If the bowel present in the hernia sac becomes necrotic or if perforation ensues, the surrounding tissue and the overlying skin of the abdominal wall become erythematous and edematous. Abdominal ultrasound can be used for diagnosis in doubtful cases. Differential diagnosis of strangulated umbilical hernia includes omphalitis and periumbilical abscess. One of the differential diagnoses of umbilical hernia is postoperative hernia after laparoscopic surgery occurring through supra or infraumbilical port site incisions which can easily be differentiated by history taking and evidence of surgical scars. Both suturing and mesh can be used for repair, the latter having a significantly lower recurrence rate [42].

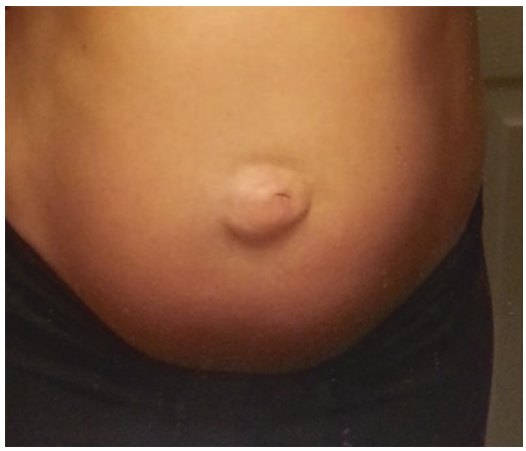

Fig. 29.9 Umbilical hernia in distended abdomen due to pregnancy

29.4.4.3 Incisional Hernia

The overall incidence of postoperative hernia in pregnancy is unknown. Following cesarean section, it is around 3% and is commonly associated with midline incisions, the number of additional operative procedures, occurrence of postoperative abdominal distension, intra-abdominal sepsis, intra-abdominal abscess, wound dehiscence, and postoperative fever [43]. History of previous abdominal surgery, signs and symptoms [bulge at or around the scar (Fig. 29.10), obstruction—abdominal pain, vomiting, non-passage of flatus and stool] and physical examination (abdominal wall scars of previous surgery, with palpable defect in the abdominal wall and distension) are

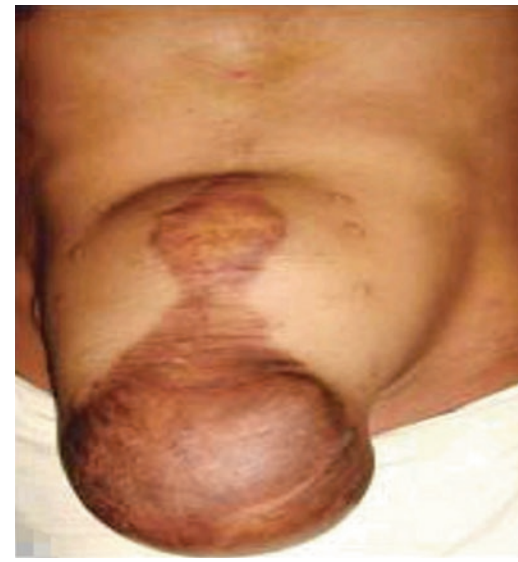

Fig. 29.10 Incisional hernia

sufficient for the diagnosis. If in doubt, ultrasound examination can be done to define hernial sac and its contents. Rarely, a gravid uterus can herniate into anterior abdominal wall through an incisional hernia and lead to serious obstetric consequences including strangulation, abortion, premature labor, accidental hemorrhage, intrauterine death, and rupture of the lower uterine segment [44, 45]. Strict monitoring of affected pregnant woman and her fetus is necessary because the uterus in an abdominal wall hernia can interfere with fetal growth and may cause intrauterine growth restriction. The management in emergent conditions depends mainly on the gestational age at presentation. If the uterus is strangulated early in pregnancy, termination of pregnancy with immediate anatomical repair of the hernial defect should be undertaken. If it occurs at or near term, emergency laparotomy, cesarean section delivery, followed by immediate repair of the hernia is recommended. The best method of repair is mass closure [closure of all the layers of the abdominal wall (except the skin) as one structure] using wide bites with the sutures sufficiently close together so as to comply with Jenkin's rule which declares the need for use of four times the length of suture material as the length of the wound [46]. Mesh closure is better than suturing the defect, if an incisional hernia is operated before planned pregnancy; but development of recurrence is a definite possibility which may be a factor to favor suturing till the family is completed and then repair of hernia can be undertaken by mesh placement.

29.4.4.4 Parastomal Hernia

A parastomal hernia is a type of incisional hernia that is related to an abdominal wall stoma. The principles of diagnosing and treating these hernias are the same as in non-pregnant patients. Ileostomy, urostomy, and colostomy are the three types of ostomies commonly seen in pregnant women with ileostomy being the most frequent. Some degree of parastomal herniation is considered to be almost inevitable. As parastomal hernias frequently obstruct, their diagnosis is difficult to be made in a pregnant patient because the symptoms of nausea, vomiting, and constipation can be seen normally in pregnancy. Examination should be performed both in standing and supine position wherein hernia appears as a bulge around the stoma. Digital examination of the stoma enables assessment of fascial aperture and parastomal tissue and local tissue strength. If history is suggestive of a hernia but it is not evident clinically, then ultrasound or computed tomography (CT) should be advised to detect even subclinical hernias. Surgical options for correcting the condition include peristomal hernia repair and stomal transposition with or without mesh repair.

29.4.5 Diagnosis

Majority of the patients with abdominal wall hernias can be easily diagnosed clinically but few subclinical cases or those presenting with atypical features need additional radiological and biochemical investigations.

29.4.5.1 Blood Investigations

These are necessary to aid in ruling out strangulation or obstruction. Baseline blood investigations along with ABG (arterial blood gases) are the minimum blood investigations required while managing the above conditions.

29.4.5.2 USG

It is a non-invasive imaging modality that does not use radioactive substance and has no harmful effects on fetus. This can be safely used in cases with doubtful diagnosis. Ultrasonography can be included in the diagnostic assessment of a pregnant woman with a bulge in the groin. Round ligament varicosities constitute a differential diagnosis to inguinal and femoral hernia [47, 48].

29.4.5.3 CT Scan

It is not used routinely in diagnosing uncomplicated hernias but has been used, at low radiation dose, in complicated cases without significant effects on fetal health.

29.4.5.4 MRI

MRI as a diagnostic tool in cases of hernias has a limited role. It has been used in cases of interstitial hernias due to their lack of clarity & obvious physical findings. It has also been used in diagnosing atypical cases in the first trimester so as to avoid CT which is known to carry a radiation risk, how so ever small or mere theoretical, on fetal development.

29.4.6 Treatment

Watchful waiting during pregnancy with a plan for repair post-delivery is the ideal treatment modality that is being followed by majority of surgeons. A groin bulge may resolve in several patients after childbirth with less than one-fifth patients needing formal postpartum repair. In a pregnant lady with uncomplicated reducible hernias, it has been found that recommending watchful waiting is safe and cost-effective for both primary ventral and groin hernia, and perform surgical repair if symptoms persist after delivery.

Conservative measures including weight control, the avoidance of heavy weight lifting, stool softeners, and abdominal binders are used in uncomplicated cases.

Abdominal wall hernia repair can be done concomitantly with cesarean section as the current literature suggests no increased risk of severe perioperative complications. Moreover, a combined procedure saves the patient from an additional operative procedure that will need to be performed at a later date.

In case of a hernia in the infraumbilical region, where concomitant hernia repair is being planned, the incision of choice for cesarean section should be Pfannenstiel, due to the low risk of complications such as incisional hernia [49]. Furthermore, repair of hernias with a large cranio-caudal fascial defect should be undertaken through cranio-caudal incision. In case of groin hernias in women, it is generally advised to place a preperitoneal mesh due to the risk of overlooking a femoral hernia [50]. This should also be undertaken for repair concomitant to cesarean section.

Repair of small umbilical or paraumbilical hernias under local anesthesia is feasible and it imposes no anesthetic risk to the fetus. When using regional anesthesia, spinal anesthesia is preferred over epidural or combined spinal-epidural, as it offers the least drug transfer for the degree of anesthesia achieved [51]. The need for sedation or general anesthesia is greater in a pregnant woman because of the tension created by the gravid uterus. Maternal risk with general anesthesia during obstetric delivery is well documented, with a mortality risk ratio 16.7 times that for regional anesthesia [52]. Fetal risk with anesthesia is less clear and there is no clear evidence that any anesthetic agent is a definite human teratogen [52, 53]. The repair of umbilical, inguinal, and ventral hernias during pregnancy is indicated only in the event of an incarceration or strangulation [52].

29.4.7 Pregnancy, Hernia Recurrence, and Recommendations for Repair

Since pregnancy causes an increased risk of abdominal hernia recurrence, the same should be conveyed to the patients who are planning to undergo an elective hernia repair before a subsequent gestation. A mesh repair, though ideal, may restrict the flexibility of the anterior abdominal wall (due to dense fibrosis induced by mesh) and may lead to increased pain during a subsequent pregnancy [54]. Hence suture repair is to be undertaken, when indicated, till the family commitments get completed. Formal mesh herniorrhaphy can then be undertaken, which will avoid the pregnancy stresses to play upon the hernia repair causing it to break down leading to increased chances of recurrences.

Having said about the options and methods of treating different types of hernias, till date there are no clinical or experimental studies that could dictate the adequate time interval between hernia repair and pregnancy. Although a gap of minimum 1 year is advised by most of the surgeons, there is no consensus on whether this 1-year

interval ends after beginning of the pregnancy or after the time of birth. *We would recommend that the patients should be counseled to conceive and proceed on their family way after a period of minimum 1 year following repair of hernia and further delay of couple of years more, if no contradictions are there.*

With all the evidence available, it can be concluded that mesh repair of ventral hernia and inguinal hernias appears to be a safe in pregnant women with no significant impact on pregnancy and labor course [55, 56]. Also, hernia repair with mesh is preferred in women who have not completed their family yet as it has no significant effect on future pregnancy and course of labor. *Yet, we would recommend primary suture repair of small hernias over mesh supplementation; the latter being reserved for larger and recurrent hernias or when the patient has completed her family.*

29.5 Conclusion

Abdominal wall hernias which are rare during pregnancy can present for the first time during pregnancy or become clinically worse during pregnancy. Hernias during pregnancy are usually asymptomatic or have minimal symptoms. Such hernias need to be managed as in non-pregnant females. Conservative measures including weight control, the avoidance of heavy lifting, stool softeners, and abdominal binders are used in uncomplicated cases. Definitive repair should be done deferred till delivery and complete uterine involution so as to prevent possible hernia-related complications during normal daily activities or later pregnancies. If patients present with hernias before a planned pregnancy, then these should be repaired to avoid possible complications during gestation. It is of utmost importance to diagnose emergent situations such as incarceration (obstruction), strangulation, and perforation because these affect both mother and the fetus. There is still no consensus on undertaking repair of irreducible hernia during pregnancy, but potential surgical effects upon pregnancy would favor to undertake an elective operation after pregnancy is over. Also, hernioplasty is recommended during pregnancy, especially in early gestation, to avoid complications that are likely to occur with advancing pregnancy.

Key Points

- Acute appendicitis is the most common nonobstetric surgical condition encountered during pregnancy.
- Physiological changes in pregnancy including uterine growth pose great challenge in timely diagnosis of the condition in pregnant women. Alvarado score combined with CRP and RIPASA score have emerged as very useful tools to diagnose acute appendicitis with good results even in pregnant females.
- Appendicectomy in pregnant females has similar morbidity and mortality as in non-pregnant females; the risk is greater for the fetus.
- Acute cholecystitis is the second most common nonobstetric surgical emergency in pregnant females after acute appendicitis.
- Diagnosis may be delayed due to nonspecific signs and symptoms. History, clinical examination along with noninvasive investigation like ultrasound are still the most common method of diagnosing acute cholecystitis.
- With advancement in the field of anesthesia, surgery, and obstetrics, an early cholecystectomy by laparoscopic approach is the preferred modality of treatment.
- Intestinal obstruction is a rare but serious surgical condition encountered during pregnancy and delay in diagnosis due to overlapping signs and symptoms may lead to increased chances of strangulation which in turn causes higher maternal morbidity and mortality, premature labor, and fetal loss.
- Diagnosis of intestinal obstruction is aided by clinical examination and inves-

tigations like ultrasound, low dose NCCT, and MRI (during the period of organogenesis).
- Management of intestinal obstruction is mainly conservative until there are ominous signs suggestive of failure of conservative therapy or development of complications.
- Incidence of inguinal hernia in pregnancy is reported to be 1:1000–3000 with majority seen in multiparous women.
- Increased intra-abdominal pressure combined with pregnancy related hormonal changes have been postulated to be the etiological factors predisposing a pregnant woman for developing a hernia.
- Diagnosis is predominantly clinical; albeit few exceptions when a non-invasive investigation like ultrasound is used to diagnose the condition in females presenting with atypical features.
- Watchful waiting during pregnancy with a plan for postpartum repair is the ideal treatment modality; definitive repair of hernias is to be done after spontaneous delivery and uterine involution, to prevent possible hernia-related complications.

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Oral Health during Pregnancy

30

Vishal Kumar, Swati Sharma, and Bushra Sheikh

30.1 Introduction

Pregnancy is a physiological period that is accompanied by a series of bodily changes. Every woman deserves a healthy and sound pregnancy which can be achieved by appropriate medical and oral health assistance along with adequate emotional and physical support. It is an age-old saying that "the mother loses a tooth for every baby"; this highlights the fact that dental management of pregnant women is essential and requires marked attention both by the treating obstetrician and the dental care professional. The dental professional may delay any elective procedure so as to prevent detrimental effects on normal organogenesis and maturation of the fetus. At times, when the patient is in need of any prompt dental treatment, the dentist should address the patient's need against the fetal demands. The dentist must educate the patient about the oral changes during pregnancy, the significance of oral health care, and the consequences of not maintaining it.

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Certain dental procedures can be performed in pregnancy depending upon the period of gestation, following all precautionary measures. Dental professionals should also keep in mind the importance of drug safety and teratogenicity while prescribing any medication to pregnant patient. It is the responsibility of the dentist to provide adequate dental counseling and render good treatment which is favorable for oral health, the expecting mother, and the developing fetus.

30.2 Oral Microbiome

The oral cavity is made up of the teeth, tongue, gingival sulci, cheeks, tonsils, soft and hard palate. It forms the natural niche for harboring more than 700 different bacterial species like *Streptococci, Lactobacilli, Staphylococci, Corynebacteria*, etc. [1]. Oral homeostasis is the symbiotic relationship between the resident oral microbiota which guard the oral cavity from infections, tooth decay, and malodor. During pregnancy, there is an alteration in the oral microbiome under the influence of hormones, estrogen and progesterone, which predispose to oral infections. Studies have documented that the number of microorganisms identified in the pregnant women's saliva samples was significantly higher than in the non-pregnant women [2]. Species like Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, *Strep-*

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tococci, Staphylococci, and *Candida species* were significantly higher in pregnant women, especially during the first and second trimesters. Porphyromonas gingivalis has been shown to rise under the influence of rise in prostaglandin level, and is implicated in increased incidence of gingivitis. Both the saliva and *sub-gingival plaque show prominence of* genus *Prevotella, Streptococcus*, *Veillonella,* and *Terrahaemophilus.* The saliva in addition shows prominence of genus Neisseria*, while Fusobacterium was seen to increase in concentration in the sub-gingival* plaque [3, 4]. *It has also been documented that the* Shannon diversity index (which is a measure of species diversity) of the salivary microbiome in pregnant women is significantly higher than in non-pregnant women. This change in the microbiome is responsible for common oral health conditions like gingivitis, periodontitis, dental caries, and perimolysis.

30.3 Physiological Adaptations during Pregnancy Relevant to Oral Health

Physiological adaptations during pregnancy are necessary to create an environment conducive to the healthy growth of the fetus. Some of these changes affect oral health and predispose to dental infections.

30.3.1 Rise in the Circulating Levels of Estrogen/Progesterone

Increase in the secretion of estrogen by 10 fold and progesterone by 30-fold, is important for the normal progression of pregnancy. Most of the physiological alterations witnessed in the oral cavity are a consequence of this [5].

- The increase in the sex-steroid hormones increases capillary permeability leading to tissue edema and increased susceptibility to trauma and bleeding. This is manifested as gingival inflammation and gingival bleeding [6]. Pyogenic granulomas (discussed below) are also seen during pregnancy as a result of increased angiogenesis under the effect of hormones.
- Estrogen-induced mucosal desquamation and increase in crevicular fluid predispose to dental caries [7].

30.3.2 Respiratory System

Increased estrogen levels during pregnancy predispose to engorgement of the nasal capillaries, edema, and congestion [8]. This favors mouth breathing over nasal breathing, snoring, and more mouth opening. Open mouth especially at night can lead to loss of as much as 2 liters of saliva through drooling. Xerostomia or dry mouth develops as a consequence of this, which then causes bad breath and dental decay due to loss of protective saliva.

30.3.3 Gastrointestinal System

- The composition of the saliva is critical for the protection of the tooth enamel against bacteria. The calcium, phosphate, and proteins present in the saliva form a protective layer on the surface of the teeth, which acts as a buffer and is antibacterial. Under the influence of the hormones, the saliva in pregnant women has been found to be more acidic in both the first and third trimester. There is decline in the levels of salivary calcium, increased salivary phosphate level and a progressive decrease in salivary glucose level throughout pregnancy. All these changes predispose to dental caries [9].
- Morning sickness or hyperemesis gravidarum—It is associated with 66% of pregnancies and mainly occurs as a result of increased levels of gonadotropins. Acidic content of the vomitus can destroy the tooth enamel (discussed later). Hyperemesis also predisposes to increased salivation or ptyalism as the preg-

nant woman with excessive nausea is unable to swallow the normal amounts of saliva.

- 30–70% of pregnant women experience an increased intragastric pressure and a reduction in the lower esophageal sphincter tone secondary to inhibition of the production of the motilin peptide hormone(due to a rise in progesterone concentration). A twofold increase in the gastric emptying time is observed in pregnant women. This causes severe gastritis, gastric acid reflux, and heartburn. This also predisposes to tooth decay [10].

30.3.4 Renal System

There is an increase in renal perfusion and glomerular perfusion rate, particularly during the second half of pregnancy. This causes an increased drug excretion in the urine. Drug dosing adjustments are thus commonly required in such patients.

30.3.5 Cardiovascular Changes

Pregnancy is associated with increase in cardiac output, plasma volume, and heart rate. The pregnant woman is also prone to postural hypotension due to vasomotor instability. This change can lead to *Supine Hypotension Syndrome* while positioned on the dental chair during procedures; it has been seen in 8% of women in the third trimester of pregnancy. The increasing size of the gravid uterus causes pressure on the aorta and inferior vena cava. Aortocaval compression can lead to generalized weakness, light headedness, restlessness, sweating, hypotension, syncope, and convulsions [11].

30.3.5.1 Dental Chair Position in Pregnancy

To avoid supine hypotension, the dentist should make the following changes in positioning the pregnant woman on the dental chair (Fig. 30.1)

- Right hip elevation by 10–12 cm by placing a rolled towel
- 5–15% tilt on the left side
- Full left lateral position in case hypotension develops even in the above positions [12].

30.3.6 Tooth Mobility

Changes in the hormonal milieu and oral microbiome during pregnancy result in changes in the lamina dura or the attachment apparatus (periodontal ligament) of the tooth. This increases tooth mobility which resolves postpartum [11]. Vitamin C deficiency contributes to this problem, so the patient should be advised accordingly. The condition generally is not severe enough to cause tooth fall.

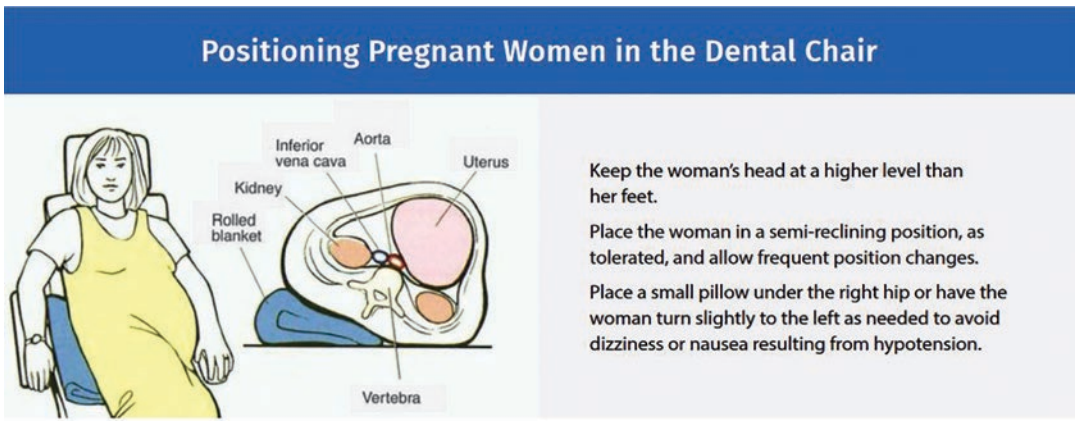

Fig. 30.1 Positioning of pregnant woman on dental chair

30.4 Oral Manifestations during Pregnancy

30.4.1 Gingivitis

An increase in the prevalence and severity of gingival inflammation during pregnancy without plaque accumulation has been reported since the early 1960s. Pregnancy gingivitis commonly occurs in 60–75% of women [6]. A plaque-free environment at the initiation of pregnancy and sustained throughout the gestation prevents the condition. It is commonly known that the gingiva during pregnancy, similar to other keratinized mucous membranes of the body becomes soft. An increased estrogen level during pregnancy results in increased capillary permeability predisposing the pregnant woman to hyperplasia of gums. Marginal gingiva and interdental papillae are generally affected. The collagen production in gingiva is also altered due to increased levels of progesterone in the blood which in turn decreases the body's potentiality to repair which is further accentuated by a deficiency of folic acid occurring due to high levels of sex hormones.

30.4.1.1 Pathogenesis

At first, the gingiva bleeds easily when traumatized by toothbrush and the bleeding tendency is increased if the gums were not in a healthy state prior to the onset of pregnancy. Subsequently, the marginal gingiva gets inflamed and becomes dull red in appearance. There is profuse bleeding on probing and this condition is called as the "Raspberry red gum" and is more commonly observed in anterior region [13] (Fig. 30.2).

In the next phase, there is generalized hypertrophy of the oral tissues with swollen gums which are often bright red in color (Fig. 30.3). The interdental papillae become hypertrophied and may enlarge to cover the tooth itself. Gingival bleeding is predominantly seen but gums are seldom painful, the condition being called the "Hypertrophic gingivitis of pregnancy", although it is a cellular infiltration and inflammatory hyperplasia rather than a true hypertrophy.

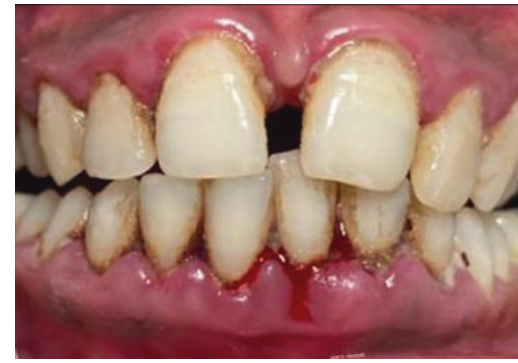

Fig. 30.2 Pregnancy gingivitis with inflamed gums which are prone to bleeding even on slight probing

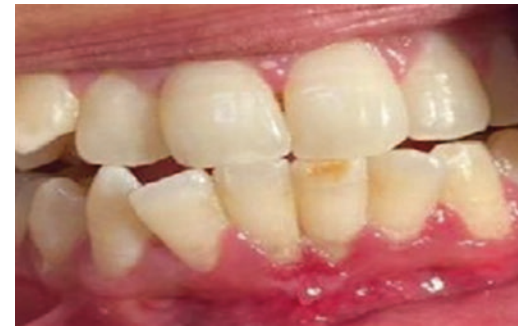

Fig. 30.3 Inflamed gingiva in relation to mandibular anterior teeth

In a study by J.E Raber et al., experimental gingivitis was induced during pregnancy and the postpartum period and the hormonal levels were monitored during the study [14]. The authors concluded that the bleeding and inflammation of the gums was increased markedly during pregnancy and there was increased prevalence of Prevotella intermedia. Another study by B Rai et al. inferred a high prevalence of Porphyromonas gingivitis along with Tannerella forsythensis and T. denticola and marked risk of periodontitis in pregnant females [15].

30.4.1.2 Clinical Features

- Swollen or puffy gums
- Tender gums
- Gums that are more red than usual
- Unusual bad breath
- Receding gums

30.4.1.3 Treatment

The influence of estrogen and progesterone on the gingival tissue and sub-gingival micro-biota can be minimized by maintaining good plaque control and oral prophylaxis.

- *Mild disease*—To maintain good oral hygiene is the first and best defense against pregnancy gingivitis. Pregnant women must try to brush twice and floss daily.
  - *Salt water rinse*—Salt is a natural disinfectant and reduces gum edema by osmosis. It is recommended to perform once or twice daily saltwater rinse for 30 seconds till symptoms subside. Saltwater is prepared by mixing half teaspoon of salt in one glass of water.
  - *Mouth wash*—Alcohol-free mouth wash rinse once a day helps to destroy disease-causing microorganisms. A rinse with baking soda solution after an episode of vomiting in hyperemesis gravidarum helps to reduce the acidic damage to the gums and teeth which are already inflamed.
- *Severe disease*—In case of severe pain, extremely bad breath, severely bleeding gums, or swollen gums, the patient should consult a dentist who will clean the teeth and remove the plaque and calculus which aggravate the condition.

30.4.2 Periodontitis

Periodontitis is the infection of the supporting structures of the tooth. Approximately 40% of pregnant women are affected with some form of periodontal disease during pregnancy [16]. The modifiable risk factors associated with periodontitis during pregnancy include low socioeconomic status, smoking, presence of visible plaque prior to pregnancy, obesity, and specific hormonal alterations during pregnancy [17, 18]. The non-modifiable risk factors are genetic factors, age, ethnicity, and systemic diseases, especially diabetes and AIDS. During pregnancy, there is a rise in circulating level of both progesterone and estrogen. These alter the oral microbiome and increase the percentage of anaerobic bacteria, especially *Prevotella intermedia* and *Porphyromonas gingivalis* which serve as pathogenic organisms.

30.4.2.1 Pathogenesis

Hyperemia and edema due to associated gingivitis cause formation of periodontal pockets which serve as reservoirs for these organisms. The periodontal disease causes inflammation of all the tissues that support the teeth, including the gingiva (gum tissue), cementum (outer layer of the roots of teeth), periodontal ligament (connective tissue fibers between the cementum and the alveolar bone), and alveolar bone (sockets into which the teeth are anchored). The main alterations evidenced are gingivitis, alveolar bone absorption, and disappearance of the fibers connecting the bone to the tooth. Gingivitis is a precursor to chronic periodontitis.

30.4.2.2 Clinical Features

Acute Periodontitis: (Fig. 30.4)

- Swollen, bright red gums
- Gums that are tender to touch
- Spaces developing between teeth causing periodontal pockets to form
- A buildup of pus between teeth and gums
- Bad breath or a bad taste in the mouth
- Loose teeth that do not fit together during a bite

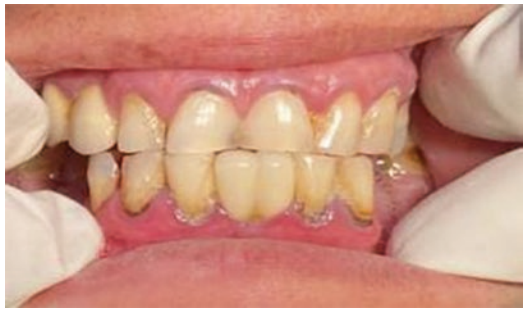

Fig. 30.4 Acute Periodontitis

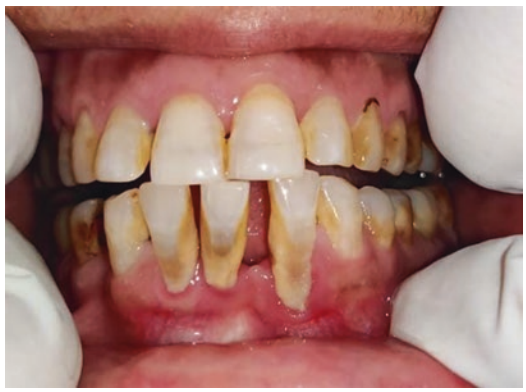

Fig. 30.5 Severe receding gums in chronic periodontitis

Chronic Periodontitis:

- Chronic bad breath
- Swollen and bleeding gums
- Severe receding gums (Fig. 30.5)
- Deep periodontal pockets
- Teeth that are loose
- Misaligned teeth (Fig. 30.6)

30.4.2.3 Treatment

- Pre-pregnancy treatment of periodontitis with antimicrobials, cleaning of periodontal pockets and scaling of teeth helps to reduce their incidence during pregnancy.
- Pregnant women are advised to brush their teeth twice a day and floss regularly.
- If there is evidence of bacterial infection, treatment with safe antibiotics is recommended.
- Removal of plaque by scaling and root planing should be undertaken between 14–20 weeks of gestation.

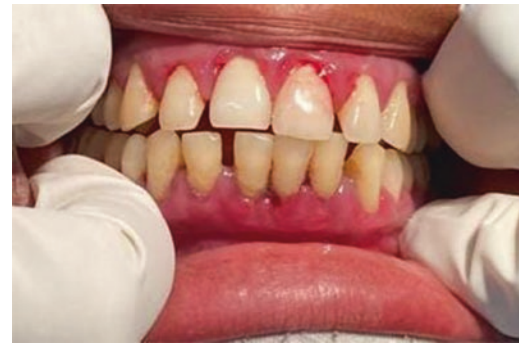

Fig. 30.6 Misaligned teeth in chronic periodontitis

30.4.3 Pyogenic Granuloma (Granuloma Gravidarum)

It is a hyperplastic, inflammatory response to local irritation or trauma which develops under the vascular effects of hormones during adolescence, pregnancy, and menopause. It is also known as the "pregnancy tumor" and usually develops during the second or third trimester of pregnancy. It was first described by Poncet & Dor in 1897 as a vascular mass termed as "human botryomycosis" [19]. Later Hartzell (1904), suggested the term "pyogenic granuloma" for this vascular growth, but both these terms are a misnomer as it neither contains any pus nor represents a true granuloma [20]. The prevalence of pyogenic granuloma in pregnant females is about 1–5% [21].

30.4.3.1 Pathogenesis

During pregnancy, an increase in angiogenesis under the effect of hormones concomitant with gingival irritation caused by local factors such as plaque, calculus, and foreign body are believed to be responsible for genesis of pyogenic granuloma [22]. They are histologically characterized by hyperplastic stratified squamous epithelium with an underlying fibrovascular stroma. There is presence of multiple endothelium-lined vascular spaces in this fibrillary matrix. Chronic inflammatory exudate with polymorphonuclear leukocytosis is found in most cases. These tumors of pregnancy are histologically indistinguishable from an oral pyogenic granuloma in males and in non-pregnant females [23–25].

30.4.3.2 Clinical Features

Clinically these tumors are asymptomatic. Characteristically they present as localized, smooth, lobulated, exophytic lesions with sessile or exophytic base arising from the gingival tissue (Fig. 30.7). In 35% of the cases, extragingival sites are involved which includes the tongue, lips, buccal mucosa and palate. They are pink/red to purple in color and bleed with minimal trauma. Ulceration is seen in some granulomas. Due to its bleeding tendency they may make brushing and regular oral care difficult. Radiological examination of the tumor may show erosion of the underlying bone. They have a recurrence rate of 5% [26].

30.4.3.3 Treatment

In most cases, the tumor subsides after parturition which is attributed to the regression of the capillaries; thus giving it the name of "vanishing tumor." In case the tumor is disturbing, it can be excised under local anesthesia during pregnancy or 4 weeks post delivery [11]. The patient is advised regarding oral health and chlorhexidine rinses post excision. Laser can be used for excision of the granuloma.

30.4.4 Perimolysis or Acidic Erosion of Teeth

Perimolysis is the chemical dissolution of the dental hard tissue by endogenous factors.

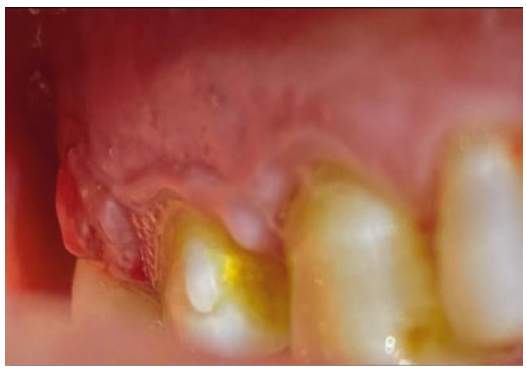

Fig. 30.7 Pyogenic granuloma in relation to a maxillary molar tooth

Perimolysis is associated with morning sickness or severe gastroesophageal reflux in which the acidic contents of the vomitus erode the enamel.

30.4.4.1 Pathogenesis

During pregnancy, about 30–70% of women report an increase in acid reflux. This is a consequence of the rise in progesterone levels that lowers the tone of the esophageal sphincter and decreases the gastric and intestinal motility. Also, during pregnancy, the stomach is displaced superiorly to the uterus and the increasing size of the gravid uterus increases the intragastric pressure and facilitates reflux. The acid is responsible for change in the microbiome as well as destruction of the protective enamel, especially of the front teeth. The erosion of the tooth enamel by the gastric acids occurs mainly on the palatal and lingual aspects of teeth in anterior region. Exogenous acids (such as consumption of sodas which have citric acid and phosphoric acid or having acidic foods such as citric fruits) as well as endogenous acids, both are associated with enamel erosion.

30.4.4.2 Clinical Features

The condition presents as linear erosive lesions on the teeth commonly involving the cutting edge of the incisor teeth. The acid erosion begins initially in the enamel, causing it to become thin and making the edge appear transparent. The erosion subsequently progresses to the dentin. Once the enamel has been completely eroded, the yellow dentin is revealed and the teeth appear to have a yellow tint. Severe erosions may present as dentin hypersensitivity. A change of shape of the teeth is noticed with the edges becoming rounded and increase in the gaps between the teeth which can lead to malocclusion of teeth.

30.4.4.3 Treatment

Tooth erosion can simply be controlled by asking the patients to thoroughly rinse their mouths after vomiting with a solution containing sodium bicarbonate as it will help to neutralize the pH of oral cavity. Viscous varnishes (resin-based) and fluoride pastes (casein-based) act as artificial biofilms and help in remineralization.

In this context, pregnant women having an increased vomiting tendency should not be given dental appointments in the morning. During dental treatment, the dental chair must be kept upright to relieve intra-abdominal pressure.

30.4.5 Dental Caries

Dental caries is defined as an irreversible microbial disease of the calcified tissues of the teeth, characterized by demineralization of the inorganic portion and destruction of the organic substance of the tooth, which often leads to cavitation [27]. This results when the dietary carbohydrate is fermented into acid. It has been classified as an infectious disease caused by Streptococcus mutans and few other species of Lactobacillus.

30.4.5.1 Risk Factors

Pregnancy increases the incidence of caries by:

- Increase in the circulating estrogen levels—Estrogen increases the desquamation of mucosal cells of oral cavity in combination with an increase in sub-gingival crevicular fluid level. The desquamating cells provide nutrition for bacterial growth leading to high risk of dental caries.
- The salivary changes during pregnancy may dispose the expecting mother to dental caries.
- Increase in gastric reflux causes damage to the enamel.
- Food craving during pregnancy with erratic hours of food intake with high carbohydrate content.
- Poor dental hygiene.

30.4.5.2 Pathogenesis

The high carbohydrate intake during pregnancy initiates the development of dental plaque. The presence of plaques or calculus on the teeth prior to pregnancy precipitate caries. The calculi create a shield for the bacteria and allow them to proliferate in the crevicular fluid. The acidic environment erodes the enamel and exposes the soft dentine. The dentine has fine tubular network that communicate with the nerves. The bacteria invade through the nerves and blood vessels to reach the pulp of the tooth causing pulpitis. Inflammation of the pulp causes it to swell and compress the nerve roots causing excruciating pain. Intraoral sinus formation can also occur as a sequel of pulpitis (Fig. 30.8).

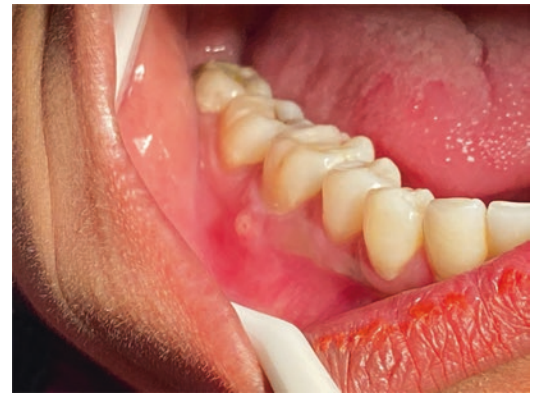

Fig. 30.8 Intraoral sinus (Sequel of pulpitis)

30.4.5.3 Clinical Features

Patient presents with various symptoms depending on the extent of involvement. Initially, the patient may notice surface discoloration of the concerned tooth which could be white or brown and she may give history of food getting lodged in the area. If caries has progressed to the pulp, the patient would present with sensitivity to thermal changes and mild to moderate pain in the tooth concerned.

Careful examination reveals brownish deposits on the pits and fissures, opacity beneath the pits and fissures, or frank cavitation of the tooth surface (Fig. 30.9). Caries examination requires dental radiography to evaluate involvement of the root. The dental surgeon should consider the period of gestation before undertaking the radiography.

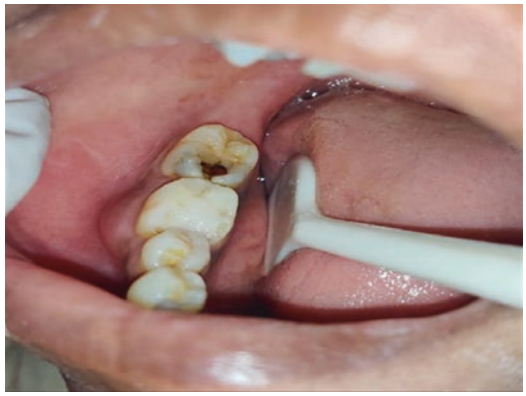

Fig. 30.9 Carious lesion on the mesio-occlusal surface of crown of mandibular right second molar

30.4.5.4 Treatment

Caries removal and restoring the tooth is the standard treatment and is never contraindicated during pregnancy. The procedure is not an emergency and can be planned during pregnancy though it is preferable to postpone the procedure till delivery.

Pregnant patients should decrease their risk of caries by brushing twice daily with fluoride toothpaste and limiting sugary foods. Patients with untreated caries and associated complications should be referred to a dentist for definitive treatment.

30.5 Effect of Periodontal Diseases on Pregnancy

Maternal periodontal disease has been studied extensively in relation to adverse pregnancy outcomes, including preterm delivery, pre-eclampsia, and low birth weight infants. Reports suggest that hematogenous transport of bacteria and/or pro-inflammatory mediators (cytokines) such as tumor necrosis factor-alpha, interleukin-1-beta, and interleukin-6, from the highly vascularized and inflamed periodontal tissues into the placenta, fetal membranes, and amniotic cavity cause damage to the vascular endothelial tissue which subsequently leads to these adverse outcomes [28].

Studies have also reported association of periodontal disease with cardiovascular disease, diabetes mellitus, respiratory infections and Alzheimer's disease. Based on these associations, theories of placental infection leading to placental dysfunction, pre-eclampsia, prematurity, and low birth weight infants have been researched extensively [29–32].

Offenbacher et al. in 1996 first documented the association of periodontal disease and low birth weight [33]. Thereafter, various studies have been conducted to prove the biologically plausible association of periodontal disease with adverse pregnancy outcomes. But the criteria used to define the exposure of periodontal disease and the exposure times are inconsistent in these studies. Moore et al. (2004) published one of the largest study conducted in the United Kingdom including 4000 pregnant women. Periodontal infection was evaluated in all participants in the first trimester, but he did not find any association between periodontal infection and preterm birth [34].

Michalowicz et al. randomized 800 pregnant women to study the impact of treatment of periodontal disease on preterm birth, fetal growth restriction, or low birth weight. They found no difference in the treated or untreated groups [35].

Periodontal Infection and Prematurity Study (PIPS) was a large RCT conducted in African–American origin women in three centers in Philadelphia and Pennsylvania, to compare the efficacy of scaling and root planing treatment of periodontal disease to polishing (placebo) in preterm birth prevention (delivery at<35 weeks). This study also could not document any positive association of periodontal disease and preterm birth [36]. In further continuation of the PIPS study, no association was demonstrated with still birth or low birth weight rates and periodontal disease. In the study conducted by Newnham et al. in Australia, nearly 1000 pregnant women

with periodontal disease were randomized to treatment for periodontal infection versus placebo, and its impact on preterm birth was evaluated. They also found no difference between the two groups in rate of preterm birth in spite of demonstrating successful treatment. Thereafter, 3 more meta-analyses have been published, but neither suggested that treatment of periodontal disease could lead to a reduction in preterm birth [37–39].

Therefore, the current evidence does not support screening and treatment of periodontal disease to improve pregnancy outcomes.

30.6 Management of Dental Conditions during Pregnancy

It is extremely important on the part of the dental care provider to ask all the female patients in childbearing age group about their pregnancy status. Generally, the patient is not knowledgeable of her being pregnant during the initial 2 weeks of conception, so it is wise for the practitioners to enquire about the last menstrual period (LMP).

The dental management guidelines can be divided into:

- General guidelines
- Guidelines during different trimesters of pregnancy
- Management of dental pain
- Pharmacotherapy

30.6.1 General Guidelines

Detailed history should be obtained from the patient which includes her previous pregnancies, history of abortion (spontaneous and elective), dental history during previous pregnancies and history of any chronic medical condition including hypertension and diabetes and any allergies.

- Patients having an increased vomiting tendency (due to morning sickness) should not be given appointment in the morning.
- Short appointments should be scheduled.
- It is recommended that the pregnant patient should be examined in the left lateral position with the head of the dental chair elevated to avoid the risk of supine hypertension syndrome.
- Elective dental procedures should be deferred to be undertaken after delivery. If unavoidable, then should be performed during the second trimester.
- Dental radiographs should be avoided until absolutely indicated.
- Utmost care should be taken by the dentist when prescribing any medication.

30.6.2 Guidelines for Management during Different Trimesters of Pregnancy

30.6.2.1 First Trimester (Conception to 12th Week of Pregnancy)

In the course of first trimester, it is highly recommended that all pregnant women should be examined and evaluated for their oral health status.

The dentist must inform the patient regarding the several changes that the patient should expect throughout her pregnancy. Also, they should converse about how these changes can lead to certain dental problems, which can be avoided if proper oral hygiene is maintained by the patient.

If a dental condition requires a procedure to be performed, then the concerns about performing such procedures in the first trimester should be discussed with the patient. She should be counseled regarding the risk of spontaneous abortion as well as teratogenic effects of the drugs.

30.6.2.2 Second Trimester (13th–28th Week of Pregnancy)

There is completion of organogenesis by the second trimester, thereby lowering the risk to the developing child. Second trimester is considered as the safest period during pregnancy for routine

dental care and performing elective and emergent dental procedures. The mother by this time gets adjusted to her pregnancy and can easily sit for comparatively longer period.

It is advisable that the dentist may ask for obstetrician consent prior to any dental treatment.

30.6.2.3 Third Trimester (29th Week Till Parturition)

Elective dental care can be provided in the early part of the third trimester but should be avoided during the latter part of the trimester. Although the risk to the fetus at this time is minimal the pregnant woman may experience some level of discomfort as the fetus has grown to a size that makes positioning of the patient difficult on the chair. Also, stress related to dental procedures can induce labor pains and may risk the birth process (Table 30.1).

30.6.3 Management of Dental Pain

Pain originating from the teeth can be very distressing. This can arise due to multiple reasons such as periodontitis, gingivitis, dental caries, following tooth extraction, root canal procedure, or any other surgical cause. Treatment has to be ensued according to the cause but initial pain relief is essential as the pain is usually unbearable. They can also be a cause of the initiation of preterm labor pains. Analgesics recommended for pain relief should be in consultation with the obstetrician and according to the FDA recommendations (Table 30.2). Narcotic analgesics can depress the central nervous system and non-steroidal anti-inflammatory drugs can cause PDA (patent ductus

Table 30.1 Dental recommendations during pregnancy

First Trimester	Second Trimester	Third Trimester
To inform & educate the expecting mother about oral changes during pregnancy To stress over strict maintenance of oral hygiene To restrict any dental treatment to oral prophylaxis and emergency procedures To avoid dental radiographs and prevent unnecessary exposure	Oral health care along with plaque control measures Control of acute oral infections Elective dental procedures are safe to perform Short appointments (late morning preferred) Radiation exposure to be avoided unless highly indicated, with all safety measures	Oral hygiene maintenance with plaque control Elective procedure to be avoided during second half of trimester Avoid radiographs Left lateral position in case of any emergency procedure

Table-30.2 Analgesic recommendation for pain management as per FDA

Analgesic	FDA category	Recommendation
Acetaminophen	B	Can be used
Diflunisal	C/D	Category C in second trimester Cannot be used in third trimester
Flurbiprofen	B/D	Category B in second trimester Cannot be used in third trimester
Ibuprofen	B/D	Category B in second trimester Cannot be used in third trimester
Ketorolac	B/D	Category B in second trimester Cannot be used in third trimester
Ketoprofen	B/D	Category B in second trimester Cannot be used in third trimester
Naproxen	B/D	Category B in second trimester Cannot be used in third trimester
Codeine	C	Can be used short term, low dose
Oxycodone	B	Can be used short term, low dose
Hydromorphone	B	Can be used short term, low dose
Meperidine	B	Can be used short term, low dose
Pentazocine	B	Can be used short term, low dose

arteriosus) in the fetus, therefore should be avoided in pregnancy; acetaminophen is preferred throughout pregnancy.

30.6.4 Pharmacotherapy

Pregnancy is associated with increase in distribution of drug volume and clearance while the maximum plasma concentration and half-life of the drug are decreased. Certain drugs are known teratogens while others may cause miscarriage or low birth infants. The knowledge of teratogenesis is very important and crucial in regard to the safety of drugs administered during pregnancy to ensure that the drug is not a teratogen and does not lead to congenital defects.

Hence, a dental caregiver should exercise utmost caution and prescribe safe medication to a pregnant patient. Also, a lot of drugs are secreted in breast milk of a lactating mother which can cause neonatal toxicity when consumed by the child. Therefore, the drug's composition, frequency, dose, and duration of exposure plays a vital role in preventing fetal and neonatal toxicity.

30.6.4.1 Antibiotics

Amoxicillin, Erythromycin, Penicillin, Clindamycin, Cephalosporins, and Metronidazole are all FDA category B. Drugs and can be used safely in pregnant or nursing women if required.

30.6.4.2 Antifungal Drugs

Nystatin and clotrimazole are category B drugs and can be used safely in pregnancy; Fluconazole and Ketoconazole are both category C drugs and should be used with caution in pregnant women.

30.6.4.3 Local Anesthetics

Lidocaine and Prilocaine (FDA Category B) can be used safely for dental pain relief in pregnant and nursing mothers; Mepivacaine and Bupivacaine are to be used with caution.

30.6.4.4 Steroids

Prednisolone is an FDA category B drug and can be used safely throughout pregnancy.

30.7 Dental Radiography in Pregnancy

X-rays are electromagnetic radiations that possess the property to ionize matter while passing through it.

The ionization causes damage and destruction to the living cells by mainly affecting the DNA component of the cell. Amount of radiation exposure and the trimester of pregnancy during which the patient is exposed decides the degree of damage to the cellular structure of the fetus which can then subsequently lead to spontaneous abortion, congenital defects, and mental disability. The fetus in comparison to the mother is more radiosensitive and is vulnerable to effects of radiation. Majority of the cellular response to x-rays happen during the initial 14 days of pregnancy and during this time, the mother is generally not aware of her being pregnant. Any radiation exposure during this period may lead to spontaneous abortion. Miscarriages following radiation at doses less than 25 rads (250 mgy) during this course of time is uncertain. Congenital abnormalities are not of much concern in the first 2 weeks. The National Radiation Protection Committee suggests that the cumulative amount of radiation should not exceed 0.20 Gy; higher doses may cause microcephaly and mental retardation [40–42].

It is approximated that an exposure of 10 rads (100 mgy) of fetal dose increases the chances of congenital abnormalities by 1%. In dentistry, the fetal exposure during maternal dental X-ray is 01 millirads, hence these abnormalities cannot be accredited to dental radiographic exposure. Kusame et al. stipulated that fetus absorbs less than 100 mgy of radiation during a head and chest X-ray exposure to the mother. It was suggested that a woman who had received any exposure in account of her being unaware of her pregnancy does not require any termination

when the fetus is exposed to a dose less than 100 mgy. The United States Nuclear Regulation Commission (USNR Commission) recommends a total fetal exposure during pregnancy to be less than 5.0 mSv(500 mrem) as safe. Center for Disease Control (CDC) recommends that radiation dose between 50–100 mGy are inconclusive and only doses more than 150 mGy are considered to have potential negative fetal effects.

Nonetheless, it is advisable not to expose the pregnant woman to radiation unless absolutely indicated. In conditions where radiographs are mandatory, all precautions should be undertaken so as to minimize the radiation absorption. Use of well-collimated beams, high-speed films, high kVp technique, and covering the patient's abdomen with a lead shield is indicated in such cases.

CT scan—CT is quite helpful in diagnosing deep-seated infection and more commonly used for viewing lateral pharyngeal infection. The resolution and definition of internal structure is way better than the normal film radiographs and at the same time, CT doses are much more than the plain radiographs. The fetal doses can be achieved to a minimum by proper usage of shielding devices.

MRI—When considering fetal radiation, MRI is better than CT as it does not involve any ionizing radiation. Magnetic field-assisted nuclear alignment helps in creating imaging in an MRI without any ionizing radiation but the risk of magnetic fields to fetus is not properly known.

Pregnant females can undergo dental procedures keeping in mind the above-specified principles and following all possible protective measures.

30.8 Obstetrical Emergencies in Dental Office

The following emergencies can be commonly seen in dental office (Table 30.3)

(a) Syncope
(b) Morning sickness
(c) Seizure
(d) Bleeding and Cramping

Table 30.3 Obstetrical emergencies in dental office

Condition	Cause	Trimester	Signs & Symptoms	Management
Syncope	Hypotension Dehydration Anemia Hypoglycemia Neurogenic disorder	Any	• Pallor • Cold extremities • Tachycardia • Low BP • Low blood sugar (on glucometer)	• Check PR, BP • Inhalational oxygen • Change position to left lateral, raise lower limbs • Establish wide bore IV line • Start volume expander • Check blood sugar levels
	Psychological	Any, but more in the first trimester	No specific finding	Respond to ammonia
Morning sickness	Increased gonadotropins	First Trimester • More common in multiple pregnancy and molar pregnancy	• Vomiting more in morning hours	• Immediate turn to lateral position • Anti-emetic to be given
Seizure	Eclampsia	Third Trimester • More in primigravida and women aged < 18/35 years	• Blood Pressure > 140/90 • Pedal edema • Prodromal symptoms of blurring of vision, epigastric pain, headache	• Consult obstetrician • Initiate Magnesium sulphate after confirming on history and examination
	Seizure disorder	Any	• Past history of seizure disorder	• Confirm past history of seizure disorder • Physician consultation • Initiate anti-epileptics

(continued)

Table 30.3 (continued)

Condition	Cause	Trimester	Signs & Symptoms	Management
Pain	Abortion	First	• Cramp like pain • Associated vaginal bleeding	• Consult obstetrician
	Preterm labor	Third	• Tightening of uterus with period of relaxation • Associated bleeding or leaking vaginally	• Consult obstetrician
	Uncomfortable position	Any	• Generalized discomfort	• Change position by placing a rolled towel or take rest in between the procedure

30.9 Prevention of Oral Diseases in Pregnancy

30.9.1 Preconception Counseling

Dental health plays an important role in the overall health of the individual and more so during pregnancy. Many of the pregnancy-induced dental conditions have their links to pre-pregnancy oral health conditions, like gingivitis, periodontitis, and dental caries. The following recommendations help reduce the need for dental procedures during pregnancy which themselves can be detrimental to the mother and the fetus.

- Initiate good oral hygiene habits of brushing twice daily and using floss
- Perform saltwater rinses and/or nonalcoholic mouth wash rinse for treatment of gingivitis
- Visit the dentist to clean all plaque and calculi
- Attend to and treat dental caries
- If diabetic, achieve adequate control before planning pregnancy

30.9.2 Diet for Good Oral Health

- Fruits, vegetables, cereal, milk, dairy products, meat, fish, and eggs that are rich in vitamins A, C, D, calcium and phosphorus must be taken in a balanced diet
- Sugar should be avoided as much as possible, especially between meals
- Dried fruit and toffees should be avoided
- There is no clear evidence that prenatal fluoride use can prevent tooth decay
- Avoid nicotine and alcohol intake

30.10 Conclusion

Pregnancy is a period that results in creation of a new life. It is the responsibility of the medical and dental professional to educate the patient about her general and oral health care during pregnancy. The gynecologist must advice the patient to get a pre-natal dental counseling and to seek required dental care. It would be ideal if the obstetrician and the dentist join hands in making the patient understand the importance of oral hygiene during pregnancy and encourage them to maintain proper dental care as it will contribute to the well-being of both the mother and the child, momentarily and for the future.

Key Points

- During pregnancy, there is alteration in the oral microbiome under the influence of hormones estrogen and progesterone, which may predispose to oral infections.
- Physiological changes in pregnancy predispose to gingivitis, periodontitis, pyogenic granuloma, dental caries, and perimolysis.
- Association of periodontitis with adverse perinatal outcomes has not been documented.

- Any female patient requiring dental treatment should be evaluated with detailed history regarding her LMP, pregnancy gestation, and associated chronic illness.
- Patients with hyperemesis should not be given early morning dental appointments to avoid exacerbation of the condition.
- The ideal position of pregnant woman in dental chair is the left lateral with right buttocks and hip elevated by 15%.
- Radiation exposure should be avoided unless strongly indicated and should be done adhering to all safety measures.
- Second trimester and early third trimester is safe for performing elective dental procedures but they should be avoided during the rest of the pregnancy.
- The dentist should exercise utmost caution in prescribing medications to a pregnant patient.

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Management of Animal Bite

31

Kanika Gupta

31.1 Introduction

Animal bites are responsible for significant human morbidity and mortality and contribute to the substantial expenditure in healthcare. The risk of injury following animal bites in pregnant women is similar to that of general population. Any injury to pregnant woman calls for an urgent medical attention. Animal bites, especially dog bites account for substantial number of pregnant women presenting to emergency department.

31.2 Rabies in Pregnancy

31.2.1 Introduction

Rabies is a zoonotic viral disease caused by Rabies lyssavirus. It has been classified by WHO under the category of Neglected Tropical Diseases (NTD) [1]. In-spite of availability of vaccines and immunoglobulins, about 80% cases occur in the underprivileged and poor people living in remote areas. Children between 5–14 years are most vulnerable. Excepting Antarctica, rabies has been found to exist on all parts of the World; Asia and Africa account for more than 95% of rabies deaths. The most common sources of human rabies infection are cats, dogs, bats, cattle, raccoons, and foxes. Dog bites are responsible for approximately 1% of all injury-related visits to the emergency department of the hospitals. The financial burden of managing dog-bite mediated rabies is estimated to be about US$ 8.6 billion per year. WHO has united with multiple organizations for generating awareness and educating the masses through "One Health Collaboration " for the movement "United Against Rabies" to achieve a goal of "Zero human deaths from dog-mediated rabies by 2030" [1]. Pregnant women are at same risk of animal bite as routine population, however, they often fear receiving a rabies vaccine and immune globulin though rabies post-exposure prophylaxis (PEP) is not contraindicated [2].

31.2.2 Etiology and Transmission

Rabies is a zoonotic, viral disease which is preventable by vaccination. Rabies lyssavirus, formerly known as Rabies virus, is an RNA virus belonging to the order of Mononegavirales. It is a neurotropic virus, which is uniformly fatal if left untreated and is characterized by acute progressive encephalitis [1]. The transmission is through direct contact of the broken skin and mucous membrane with the saliva of the infected animal. Though rabid dogs bite still account for human transmission in 99% of cases worldwide, but emergence of bat rabies is of concern in America, Australia and Western Europe. In these countries 100% vaccination of dogs has bro-

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ken the dog to human chain. Transmission via other host species like raccoons, foxes, jackals, skunks and mongooses is very rare. Rodent bites are not known to cause rabies. Rarely inhalation of the aerosolized rabies virus can cause the infection, especially in the laboratory workers. Its incubation period is of 60–90 days usually but can vary from 7 days to 1 year depending upon the site of injury, viral load and the viral strain involved. The advent of rabies vaccine has brought down the mortality associated with the infection drastically. Globally, more than 29 million people receive post-bite vaccination every year, which helps to prevent thousands of rabies deaths annually.

There are two classic forms of rabies:

1. *Encephalitic*: It is characterized by hyperactivity, hydrophobia, or aerophobia, altered consciousness, sometimes fever and hypersalivation. Death occurs within a few days as a result of cardio-respiratory arrest.
2. *Paralytic*: It is a less common form found in 20% of cases, with a longer course. A coma slowly develops, eventually causing death.

31.2.3 Diagnosis [3]

Animals—Direct fluorescent antibody test, mouse inoculation technique and polymerase chain reaction are the various tests used for diagnosis of rabies in animals. These tests are performed and interpreted as per WHO recommendations. A positive result is not directed by any specific location of the tissue in the brain. But a negative result must rule out the presence of the viral antigen from at least two tissue samples in the brain, preferably brain stem and cerebellum. The suspected animal has to be euthanized for the testing.

Humans—Various diagnostic techniques that detect whole viruses, viral antigens, or nucleic acids in the infected tissues (brain, skin, or saliva) are available for antemortem and postmortem diagnosis of rabies in humans. Saliva can be tested by virus isolation or reverse transcription followed by polymerase chain reaction (RT-PCR). Serum and spinal fluid are tested for antibodies to rabies virus. Skin biopsy specimens are examined for rabies antigen in the cutaneous nerves at the base of hair follicles.

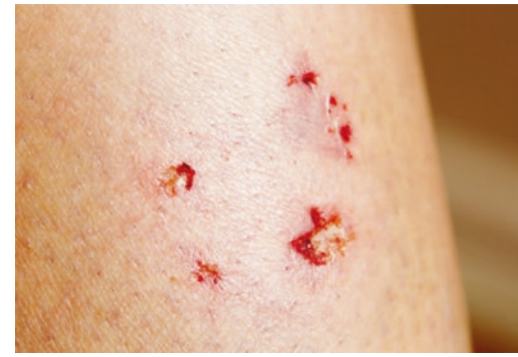

Fig. 31.1 Dog bite with broken skin and bleeding at wound site

31.2.4 Effect of Rabies on Pregnancy

Limited data is available regarding rabies in pregnancy as the number of cases documented is few. Like in any other individual, it results in fatal outcome if untreated. Rabies virus has not been shown to effect pregnancy or the growing fetus.

31.2.5 Treatment

31.2.5.1 General Considerations

1. Animal bite wounds are grossly contaminated; so, it is essential to treat the wound appropriately to prevent secondary wound infection. The injured area should be washed immediately and thoroughly with soap and plenty of water, with the help of a 20-mL or larger syringe or a 20-gauge catheter [4].
2. The devitalized tissue should be debrided to reduce the incidence of infection.
3. Detailed examination of the wounded area should be done to look for tendon or bone involvement and foreign bodies, such as teeth fragments. Torn tendons affecting movements of the limbs at the joints may warrant referral for repair.
4. Risk of tetanus, rabies, and blood-borne viral infections should be assessed.

5. Routine use of antibiotics is not recommended in bites without any broken skin or bleeding.
6. Antibiotic prophylaxis is advised for [5, 6]:
   - Animal bites causing broken skin, bleeding at wound site (Fig. 31.1)
   - Bites involving extremities
   - Wounds at the skin overlying joints or cartilaginous structures
   - Bites near prosthetic joint implants
   - Cat bites as they are mostly deep puncture wounds
   - Women with diabetes mellitus or immune-compromised
   - Delayed presentation
     - Greater than 6 to 12 hours for bites in the extremities: for example, the arm or the leg
     - Greater than 12 to 24 hours for bites at the face

Antibiotic Prophylaxis for Uninfected Animal Bites

Culture of the bite wounds is not routinely advocated unless they are already infected or an abscess has developed. Common microorganisms causing infection are Staphylococcus, Streptococcus, Pasteurella, Corynebacterium Neisseria, Moraxella, and anaerobic bacteria [7]. Cat bites are responsible for *Pasteurella multocida* infection as it is a commensal found in the mouth of cats.

Infected individuals are given oral antibiotics if feasible. If due to the severity of the disease or due to inability to take orally, injectable antibiotics are started and the condition is reviewed within 48 hours and switched to oral antibiotics if possible. (Table 31.1 and 31.2).

Woman should be reassessed if there is no clinical improvement in 24–48 hours despite starting antibiotics or if there is deterioration in the general wellbeing of the woman or if she complaints of severe pain that is out of proportion to the infection.

Review the skin swab which was sent for microbiological testing. If the change of antibiotic is required, narrow-spectrum antibiotic reflected in the swab report should be prescribed.

Table 31.1 Oral Antibiotic prophylaxis for uninfected dog bite in pregnancy [8]

Antibiotic	Dosage and course length for prophylaxis and treatment
Co-amoxiclav (First-choice oral antibiotic) OR	250/125 or 500/125 mg three times a day Give for 3 days for prophylaxis Give for 5 to 7 days for treatment
Azithromycin (in pregnancy) with Metronidazole	500 mg once a day Give for 3 days for prophylaxis Give for 3 days for treatment 400 mg three times a day Give for 3 days for prophylaxis Give for 5 to 7 days for treatment

Source: https://www.nice.org.uk/guidance/ng184/documents/draft-guideline

Table 31.2 Intravenous Antibiotics for Prophylaxis and Treatment [8]

Antibiotic	Dosage prophylaxis and Treatment
Co-amoxiclav (First-choice oral antibiotic) OR	1.2 g three times a day
Cefuroxime (caution in penicillin allergy) with Metronidazole OR Ceftriaxone (caution in penicillin allergy) with Metronidazole	750 mg to 1.5 g three or four times a day 500 mg three times a day 2 g once a day 500 mg three times a day

Source: https://www.nice.org.uk/guidance/ng184/documents/draft-guideline

Tetanus Immunization

Tetanus immunization should be advised to all pregnant women with last vaccination more than 5 years ago [9]. (Table 31.3).

31.2.5.2 Specific Treatment of Rabies in Pregnancy

As pregnancy is not a contraindication for the treatment of animal bite, there is no reason to delay using inactivated vaccine and immunoglobulin to prevent lethal infection. If used properly, post-exposure prophylaxis has been found to be 100 percent effective.

Table 31.3 Assessment of Tetanus Immunization

History of Tetanus Immunization	Clean, Minor Wounds		All Other Wounds	
	Vaccine	Immune Globulin	Vaccine	Immune Globulin
Uncertain or < 3 doses	Yes	No	Yes	No
≥ 3 doses	No, unless >10 years since last dose	No	No, unless >5 years since last dose	No

Adapted from: CDC.gov/tetanus/clinicians.html

Safety of Post Exposure Prophylaxis of Rabies in Pregnant Woman

The dilemma regarding administering rabies vaccination and immunoglobulin in a pregnant patient following animal bite is due to paucity of large cohort studies documenting their safety profile. The rabies vaccine is a killed virus vaccine. The risk of developing congenital anomalies as postulated with live vaccines is not there with killed vaccines. Also, immunoglobulin is a fractionated blood product, which can be safely used in pregnancy. Research on 251 women who received post-exposure prophylaxis carried out by Toovey et al found no adverse fetal effects or increased risk of abortion [10]. Sudershan et al also reported similar safety profile in the 14 cases they followed post administration of post exposure prophylaxis, upto 1 year post delivery [11]. Therefore, as per recommendations of ACIP, post-exposure prophylaxis must be administered as per requirement even during pregnancy [12]. To guide treatment rabies exposure has been divided into four categories. (Table 31.4).

Table 31.4 Rabies exposure categories [12]

Category of exposure	Description	Post-exposure Prophylaxis
Category I	Touching or feeding animals, licks on intact skin, contact of intact skin with secretions or excretions of rabid animal or person	Not regarded as exposures, therefore no PEP required
Category II	Nibbling of uncovered skin, minor scratches or abrasions without bleeding	Vaccine should be injected as soon as possible.
Category III	Single or multiple transdermal bites or scratches, licks on broken skin, contamination of mucous membrane with saliva from licks and exposure to bats	Vaccine and rabies immunoglobulin should be administered at distant sites as soon as possible. Immunoglobulin can be administered upto 7 days after injection of the first dose of the vaccine

Adapted from: Centers for Disease Control and Prevention. Recommendations of the Advisory Committee on Immunization Practices (ACIP). Human rabies prevention–United States. MMWR Recomm Rep. 1999; 48(RR-1):1–21

Post-Exposure Prophylaxis (PEP)

PEP comprises immune globulin at presentation and a potent and effective rabies vaccine subsequently. Exposure to rabies or definite diagnosis of rabies in a pregnant woman is not an indication for termination of pregnancy. However, the animal should be monitored for at least 10 days. If the animal does not show any signs of rabies-like abnormal behavior, dysphagia, ataxia, paralysis, altered vocalization, or seizures; PEP can be avoided. If the animal shows features of rabies or dies, immediate PEP is recommended. If the immune globulin is not available immediately, it can be given within 7 days of the first dose of vaccine. Patients presenting even months after having been bitten should be treated with PEP, as if the contact had recently occurred.

Rabies Immune Globulin (RIG)

Rabies immune globulin is considered of major importance in category 3 wounds [12]. It should be infiltrated as much deep anatomically in and around the wound as possible. Remaining RIG should be injected at an intramuscular site that is distant from that of vaccine inoculation.

Dosage of Rabies Immune Globulin [13].

1. Human Rabies Immune Globulin (HRIG)—20 IU/ Kg of body weight, with a maximum dose of 1500 IU.
2. Equine Rabies Immune Globulin (ERIG)—40 IU/Kg of body weight, up to a maximum of 3000 IU.

If RIG is unavailable at the first visit, it can be given within 7 days of administration of the first dose of vaccine.

At times, the calculated dose of RIG is insufficient to infiltrate all wounds; diluting it with 2–3 times volume of sterile saline will allow thorough infiltration.

ERIG—Though a routine skin sensitivity test prior to administration of ERIG is not recommended, but still the treating physician should be prepared to manage anaphylaxis if it happens during administration of ERIG.

Antirabies Vaccine

1. Intramuscular Regimens for Rabies Post-Exposure Prophylaxis

Vaccines should be injected into the deltoid muscle

- The 5 dose **Essen regimen** (1–1–1-1-1)—To be given as single dose on days 0, 3, 7, 14, and 28
- The 2-1-1 **Zagreb regimen** (2-0-1-0-1)—Two doses are given on day 0 in the deltoid muscle, right and left arm. An additional single dose is administered in the deltoid muscle on day 7 and day 21.

The efficacy and safety profile of both the regimens is same. Compared to Essen, another IM schedule recommended by WHO, Zagreb, has a better compliance, reduced medical costs and better immunogenic response in the early stage. This difference in immunogenicity is only for the initial stages and does not last beyond 14 days. There is some concern, however, that HRIG administration may reduce early seroconversion when using the Zagreb regimen, whereas when the Essen regimen is employed, HRIG does not lower virus neutralizing antibodies levels. It is uncetain, however, whether this delay in seroconversion is clinically significant. Further research is necessary to explore the influence of HRIG on the immunogenicity of the Zagreb regimen [14].

2. Intradermal Regimens for Rabies Post-Exposure Prophylaxis

Intradermal administration of rabies vaccine is an equally safe and efficacious alternative to intramuscular vaccination. The cost of the vaccination is reduced by 60–70% and is appropriate where vaccine or/and finances are in short supply, particularly in rural areas or in clinics with high-patient load.

PVRV (Verorab™) and PCECV (Rabipur™) have been proven to be safe and efficacious. 0.1 ml of the vaccine is required per site. A visible and palpable bleb is created in the skin if correctly administered. A repeat intradermal dose should be given if, inadvertently, it is given subcutaneous or intramuscular.

- The 2-site intradermal method: (2-2-2-2): One dose of vaccine of 0.1 ml is given intradermal at two different lymphatic drainage sites.
  - Usually administered in the deltoid muscle on the left and right upper arm and suprascapular area.
  - Given on days 0, 3, 7, and 28.

Check serology between day 14–21 days after the last dose. If the titres are less than 0.5 IU/ml, another dose is recommended.

Short Rabies Prophylaxis for Previously Vaccinated Women [15]

Women who have been vaccinated in the past or are on pre-exposure prophylaxis should be given only vaccine. RIG is not recommended for them. Routine wound care as recommended before should be given.

- Schedule 1:
  - Single dose to be given intramuscularly or intradermally on days 0 and 3.

  - The intramuscular (IM) dose is1 ml or 0.5 ml, depending on vaccine type or intradermal (ID) dose of 0.1 ml per site.
- Schedule 2:
  - A "4-site" intradermal (ID) PEP can be used.
  - It consists of 4 injections of 0.1 mL equally distributed over left and right deltoid, thigh or suprascapular areas during a single visit.

31.3 Snake Bite in Pregnancy

31.3.1 Introduction

Snake bite is a not a common event in pregnancy and it is important to note that most of the snake species are not venomous. Of the 3500 species found in the world, around 600 species are venomous. Of the 5000 venomous snakebites reported per year in the USA, less than 1% of them are in pregnancy [16]. In India, the reported incidence is 1% in pregnancy [17, 18]. The degree of envenomation during snakebite correlates with the severity of feto-maternal complications. On review of literature of snakebite in pregnancy by Langley et al., maternal case-fatality of 4.2% and fetal death rate of 43–58% was noted. Envenoming and mortalities due to snake bites are significant public health problems in the rural areas of South Asia, South-East Asia, Sub-Saharan Africa, and Latin America. Snakebite is generally less common in the later half of pregnancy as the woman is generally confined to her home, especially in rural areas. Delay in seeking medical help, use of traditional practices, and harmful unscientific treatment increase the morbidity and mortality.

31.3.2 Snakes and Their Species

Snakes are poikilothermic carnivorous reptiles. The clinical manifestations seen following snake bite are dependent on the species of snake involved. The three main families of venomous snakes are- Elapidae, Viperidae, and Hydrophidae. Their appearance, geographic distribution, and venom profiles differentiate them from each other. The common snakes grouped under this classification are

- Elapidae family—Cobra, King cobra, krait, and coral snake.
- Viperidae family—Rattlesnake, cotton-mouths, and copperheads Russell viper and the sawscaled viper.
- Hydrophidae family—Sea snakes are found in the vicinity of the seacoast. Though venomous, they seldom bite.

31.3.2.1 Snake Venom

Snake venom is the poisonous secretion of the venomous snakes which is injected into the prey to immobilize it and assist in its digestion. The toxic substances present in the venom are further classified as enzymes, polypeptides, glycoproteins, and compounds of low molecular weight [19]. The composition of these varies in the different types of snakes. The enzyme hyaluronidase helps to disseminate the venom to the various tissues [20]. All poisonous snakes venom contains the enzyme phospholipase A2, which is responsible for the destruction of the red blood cells, leukocytes, platelets, vascular endothelium, peripheral nerve endings, the myoneural junction and the skeletal muscle [19]. Polypeptides, alpha and beta neurotoxins damage nerve endings, block the release of neurotransmitters and result in flaccid paralysis of the prey [20].

31.3.2.2 Characteristics of Bites

Elapid bites—Characteristic picture of a wet gangrene is seen at the site of the bite. The bite wound has a typical putrid smell as a result of the cytolytic action of the venom on the tissues. The Elapid bites present characteristic "Skip lesions." The venom is neurotoxic and results in ptosis, ophthalmoplegia, followed by paralysis of facial muscles, neck muscles, tongue, and palate. Paralysis of intercostal muscles and diaphragm lead to respiratory failure and death [19, 20].

Viper bites—are primarily vasculotoxic and a swelling develops rapidly at the site of the bite.

Thrombosis of the local blood vessels develops, followed by ischemia, resulting in dry gan-

grene. Absorption of the venom takes place slowly via the lymphatics leading to lymphangitis. Alteration in clotting factors leads to oozing from bite site. Hemorrhage, and increased capillary permeability, lead to pulmonary edema, renal failure and death [19, 20].

Sea snake bite—The venom is both myotoxic and neurotoxic. The bite results in pathological changes in the skeletal muscles. Patients can have chronic muscle pains lasting for several months unless treated. The damaged skeletal muscles release potassium and myoglobin, resulting in renal failure and cardiac arrest due to rise in levels of potassium [20].

31.3.3 Complications of Snake Bite in Pregnancy

31.3.3.1 Maternal

Maternal complications documented include the development of anemia, thrombocytopenia, abruptio placentae, and preterm labor [21–23]. Placental abruption following snake bite is due to the toxic venom reaching the decidua-placental cleavage zone and causing disruption in the coagulative activity leading to hemorrhage and placental separation [24]. Few cases reported in literature also document that pregnant women had systemic envenomation and developed abruption without signs of local envenomation. The effect of the venom resulting in premature uterine contractions has been studied in animal models and on uterine tissue ex-vivo. It was observed that venom directly acts on the uterine muscles by potentiating the effects of bradykinins [25–28]. This effect is more commonly observed with rattlesnakes, cobra, and green mamba. Vasotoxic venoms of Elapidae cause the release of catecholamine, which may theoretically cause hypertension. This postulated theory requires further prospective reviews. Disturbances in coagulation profile may lead to the development of DIC.

31.3.3.2 Fetal

Review of literature suggests a 20–30% incidence of abortions or fetal death after snake bite in the mother [29, 30]. The various mechanisms suggested for the abortions and fetal demise are maternal shock after envenomation leading to fetal anoxia. The direct toxic effect of the venom can result in placental and uterine hemorrhage resulting in abruptio placentae. Other causes of fetal damage can be the result of cytokine release after tissue damage, maternal pyrexia, maternal hemorrhage leading to acute fetal anemia, supine hypotension syndrome, and anaphylaxis to antisnake venom [31, 32]. Rattlesnakes and Russell viper bites are mostly associated with fetal deaths and adverse outcomes. Congenital malformations such as hydrocephalus have been documented in the literature, in pregnant women with snake bites in the first half of pregnancy. It is believed that snake venom crosses the placenta. The causal relationship between envenomation and embryotoxic and teratogenic effects has been documented in mice study models. Cleft palate and facial deformities have been described in pregnant mice after injection of venom of *Vipera aspis* [33]. Hepatic and myocardial damage was documented with the venom of *Naja nigricollis* [34]. Studies using Arin, the active defibrinating fraction of the Malayan pit viper in pregnant rabbits at 11–15 days of gestation was found to cause abortions and hemorrhage [35].

The antivenom, used as treatment of the envenomed pregnant woman, is known to cause anaphylactic reactions. Fetal death rate of 55% to 58% has been reported in mothers who were given antivenom [36].

31.3.4 Diagnosis

Diagnosis of snakebite in pregnancy is made by a good history taking, complete examination and laboratory tests.

31.3.4.1 Detailed History

After initiating emergency care, a detailed history is elicited to ensure the patient was bitten by a snake. It is important to note that many times patients may present with nonspecific symptoms related to anxiety like sweating, palpitations, cold extremities, tachycardia, tachypnea, ele-

vated blood pressure, and paresthesia. These patients may also have dilated pupils suggestive of sympathetic over activity. In such patients, signs for envenomation are checked, such as fang marks, redness, and swelling. If the patient can recollect, establish if the snake was venomous by showing pictures of common venomous snakes of that area. If the dead snake has been brought along, careful handling is advised as species Crotalids can envenomate even after death. Take note of the time elapsed since bite and any other relevant medical history.

Physical Examination

- Check for signs suggestive of local envenomation (edema, petechiae, bullae, oozing from the wound).
- Mark the bite site and circumference of the limb. In case of swelling, demarcate its extent and monitor every 15 minutes till there is no further progression of swelling.
- Palpate draining lymph nodes for enlargement and to note evidence of lymphangitis.
- Palpate for digital pulses in the presence of gross swelling. Compartment syndrome is ruled out by direct measurement of pressure via a 22 gauge intravenous catheter connected to a manometer. A pressure above 55 cm water/saline warrants fasciotomy.
- Monitor uterine contractions.
- Fetal heart rate monitoring is done to assess for fetal bradycardia, tachycardia, or late deceleration after each uterine contraction.
- Watch for vaginal bleeding.

Signs and Symptoms of Severe Envenomation

- There is early and rapid spread of local swelling from the site of the bite. In case of Cobra bite on the finger, necrosis has been seen to set in within a few minutes.
- Spread of venom in the lymphatic system leads to rapid tender enlargement of local lymph nodes.
- Early development of neuromuscular paralysis presenting as ptosis, muscular weakness, respiratory distress or respiratory arrest.
- Early onset of systemic bleeding such as bleeding from the gums, bite site, hematuria, hemoptysis, epistaxis, or ecchymoses.
- Unconsciousness which may be associated with respiratory arrest.
- Passage of dark brown urine(seen in myotoxicity).

31.3.4.2 Laboratory Investigations (Table 31.5)

31.3.4.3 Other Nonspecific Tests

EEG changes are seen in 96% of patients bitten by snakes of which majority have grade I mild changes(62%), while 31% cases have grade II changes (moderate to severe abnormality) and the rest have severe abnormality.

Imaging- Routine imaging is not required after snake envenomation. Pleural and pericardial effusion can be picked up on ultrasound and echocardiography, respectively. Neuroimaging may be required in women with intracranial hemorrhage with altered mental status. Duplex ultrasound can help in diagnosing deep vein thrombosis in case of clinical suspicion.

31.3.5 Treatment of Snakebite [37]

Managing a pregnant woman with a snake bite involves a multidisciplinary team involving medical toxicologist, obstetrician, and neonatologist. The most important factor affecting the outcome of snake bite is the time taken to diagnose and treat the woman. Any pregnant woman who comes with history of snakebite should be managed urgently and aggressively.

31.3.6 Initial Management (at Site of Snakebite)

The recommended first aid management is based on a pneumonic: “CARRY NO R.I.G.H.T.” (As per WHO guidelines 2016).

Table 31.5 Laboratory investigations

S.no	Specific investigations	Interpretation
1.	**20 WBCT** [36] **(20-minute whole blood clotting test)**	Simple bedside test of coagulopathy to diagnose viper envenomation Few millilitre of fresh venous blood sample is drawn and left undisturbed in the test tube for 20 min. If after 20 minutes the blood has not clotted, it confirms coagulopathy and possibility of bite by viper.
2.	**Enzyme-linked immunosorbent assay (ELISA)**	**Used to identify the species involved.** **Expensive test; used in research or epidemiological studies**
S.no	*Nonspecific investigations*	*Interpretation*
1.	Haemogram • Rise in hemoglobin • Neutrophilic leukocytosis • Thrombocytopenia	• Hemoconcentration d/t extravasation of fluid • Fragmented red cells ("helmet cell," schistocytes) signifying microangiopathic hemolysis • Systemic absorption of the venom • Viper envenomation
2.	Kidney function test • Raised Serum creatinine	• Sign of renal failure post-Russell's viper, Humpnosed pit-viper and sea-snake envenoming
3.	Rise of Serum amylase Rise of Creatinine phosphokinase (CPK)	• Seen in sea snakes, some kraits, some Australian Elapidae, and Russell's viper bites • Muscle damage post myotoxic venom envenomation
4.	Coagulation profile • Rise in Prothrombin time (PT) • Rise in activated partial thromboplastin time (aPTT) • Fall in fibrinogen and fibrin degradation products (FDPs)	• Venom interfering with clotting mechanisms in Viper bite
6.	Urine examination • Hematuria • Proteinuria • Hemoglobinuria • Myoglobinuria	• Progression to systemic toxicity

CARRY—The victim should not be allowed to walk even for a short distance. She should be carried in any form, especially when bite is at leg.

NO—No sucking of venom should be done at the site of the bite. Do not use tourniquet, electrotherapy, or any application of pressure.

R—Reassure the patient. It is important to note that about 70% of all snakebites are by nonvenomous species, and in only 50% of bites by venomous species, the snake actually envenomates the patient.

I—Immobilize in the same way as a fractured limb. Bandages or cloth should not be tied tightly so as to block the blood supply or apply pressure; they should be used to hold the splints. Pressure immobilization method (PIM) [38] has been developed by the Australian Venom Research Unit, University of Melbourne, Australia, for the rapidly acting neurotoxic elapid snake venom. It constitutes applying an elastic or firm bandage in overlapping turns such that it is not very tight to occlude but allows the health worker's finger to slide underneath. The patient is asked to keep the limb immobilized strictly, and the site of the bite is marked over the bandage. (Fig. 31.2).

GH—Get to the hospital immediately.

T—Tell the doctor of any systemic symptoms that manifest on the way to the hospital. Traditional methods should be discarded as they have NO PROVEN benefit in treating snakebite.

31.3.6.1 Care at the Hospital

Emergency Care

- Assessment of consciousness.
- Check for ABC—airway, breathing, circulatory status.
- Monitor vitals.
- Immediate resuscitation in case the patient is in shock and has respiratory failure or cardiac arrest.
- Every envenomed patient should be put on oxygen support.
- Establish a large-bore intravenous catheter.
- In every suspected case of envenomation, a bolus of normal saline 0.9% or Ringer's lactate is given to maintain euvolemia.
- Analgesia with intravenous opioids is preferred. NSAIDs are to be avoided as they can precipitate the coagulation defects of the venom.
- To prevent secondary bacterial infection, a broad-spectrum antibiotic with anaerobic cover and penicillin are used.

31.3.6.2 Specific Treatment

Anti-Snake Serum

The only effective antidote for snake venom is the anti-snake serum and it is the only WHO-approved specific treatment for snakebite. Anti-snake venom(ASV) is purified pepsin-refined fragment of whole IgG, obtained from the plasma of a horse, mule or donkey (equine) or sheep (ovine) that have been immunized with the venom of more than one species of snakes. The extracted serum is purified and dispensed in either liquid or lyophilized form. The liquid form is labile and requires a cold chain. The lyophilized form is diluted before use. The anti-snake serum can be monovalent, i.e., it can be species specific or polyvalent, i.e.,containing

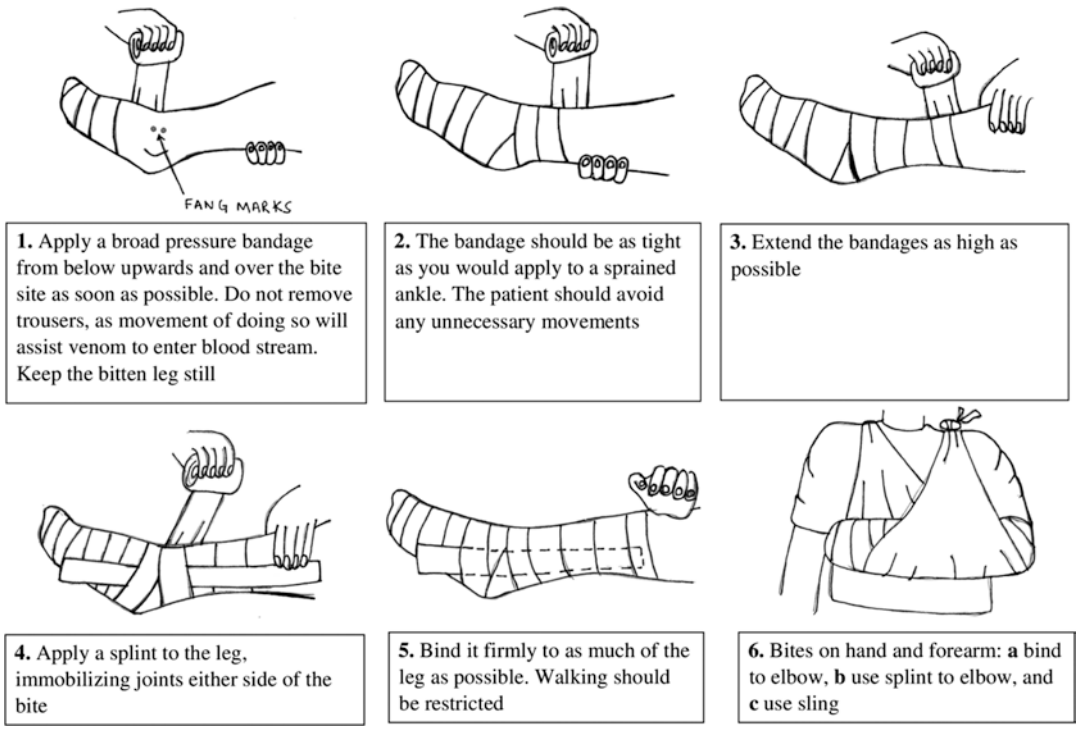

Fig. 31.2 Pressure immobilization method

immunoglobulins against multiple species according to the prevalent snake species of that area. WHO recommends species-specific antidote but its high cost and lack of availability restrict its use. Also, the patient is not always able to identify the correct species of the snake thus, it is safer to use the polyvalent anti-snake venom. Pregnancy is not a contraindication to ASV.

Indications for Anti-Snake Venom

Anti-snake venom should be used with caution as it is associated with anaphylaxis. Its use is advocated only if its benefits outweigh the risks. Indications for its use include:

- Hematological Abnormalities:
  - Spontaneous onset of bleeding from any site distant from the bite site.
  - Documentation of coagulopathy by positive 20WBCT or laboratory tests: INR >1.2, prothrombin time (PT) >4 to 5 seconds longer than the laboratory control value.
  - Thrombocytopenia with platelets count <100,000/mm^3
- Development of neuromuscular paralysis evident as ptosis, external ophthalmoplegia or paralysis.
- Cardiovascular abnormalities: Hypotension, shock, cardiac arrhythmia, and abnormal ECG.
- Features suggestive of acute renal failure: oliguria/anuria and rising serum creatinine or urea.
- Haemoglobinuria or myoglobinuria which signify intravascular hemolysis resulting in dark brown urine.
- Signs of local envenoming seen as rapid development of local swelling in more than half of the bitten limb. Swelling is evident on the toes and fingers, especially after bite on the digits and beyond the wrist or ankle, following bites on the hands or feet within 48 hours.

Timing-Ideally ASV should be given within 4 hours of the bite but can be given up to 24 hours.

Table 31.6 Assessment of severity of envenomation

No envenomation	Fang marks (+/−) Absence of local or systemic reactions
Mild envenomation	Fang marks (+), Local reactions- moderate pain, minimal local edema (0–15 cc), erythema (+), ecchymosis (+/−), No systemic reactions
Moderate envenomation	Fang marks (+) Severe pain, moderate local edema (15–30 cm), erythema and ecchymosis (+) Systemic weakness, sweating, syncope, nausea, vomiting, anemia, or thrombocytopenia
Severe envenomation	Fang marks (+) Severe pain, severe local edema (>30 cm), erythema and ecchymosis (+) Hypotension, paresthesia, coma, pulmonary edema, respiratory failure

Source: Guidelines for the management of snakebites, 2nd edition August 2016. WHO/Regional Office for South-East Asia

Dose—Anti venoms available are based on the species of snakes prevalent in that area. The manufacturers generally recommend a suggested dosage protocol based on the calculated lethal dose (LD) and effective dose (ED) in mouse models. The fatal dose for cobra bite is120 mg, for Russell's viper bite is 150 mg and that of krait bite is 60 mg. One ml of polyvalent ASV can neutralize 0.6 mg of cobra venom, 0.6 mg of Russell's viper venom and 0.45 mg of Krait venom. Thus, the total effective dose of ASV required is 200, 250, and 134 ml in Cobra, Russel viper and Krait bite, respectively, to counter the fatal dose of venom. According to the composition of the ASV and the severity of envenomation, the treating physician can make the dose assessment. In case of mild envenomation, a low dose protocol can be initiated and repeat dose can be given in cases of severe envenomation. (Table 31.6).No ASV for Sea snakebite (Green Pit) is available.

31.3.6.3 ASV Reaction

Anaphylactic reactions are seen in 20% of the individuals who receive ASV. These can be classified as early and late reaction. Close monitoring

of all patients during and after ASV administration is recommended. ASV sensitivity tests are not recommended as these reactions are not IgE mediated but compliment mediated and they may pre-sensitize the patients and put them at a greater risk of anaphylaxis.

Early Anaphylaxis—occurs within 10 min to 3 h from the initiation of the therapy. The patient develops itching, urticaria, dry cough, nausea, and vomiting, abdominal colic, diarrhea, tachycardia, and fever. Life threatening, severe reaction may be seen in some manifested as hypotension, bronchospasm, and angioedema. The reaction is treated by stopping the antivenom administration, administering intramuscular adrenaline, antihistaminic, and corticosteroids.

Late anaphylaxis—develops within 7 days after the treatment. Patient develops fever, nausea, vomiting, diarrhea, itching, recurrent urticaria, arthralgia, myalgia, lymphadenopathy, immune complex nephritis and, rarely, encephalopathy. The reaction is treated with antihistaminic and corticosteroids.

Pyrogenic reactions—the patient develops chills, fever, and rigors within 1–2 hours of intravenous transfusion of ASV. Contamination of ASV with pyrogens during manufacturing process can be responsible for this.

The safety profile of antivenom during pregnancy is not clearly defined. But the benefits of administration in clinically correct situations outweighs its omission. In the event of a anaphylactic reaction to the antivenom, ephedrine, or phenylephrine are used in place of epinephrine, as the latter may cause reduction in placental blood flow.

31.4 Lymphocytic Choriomeningitis Virus (LCMV)

31.4.1 Introduction

Lymphocytic Choriomeningitis Virus (LCMV) is a viral infection of the cerebrospinal fluid and the meninges. LCMV belongs to the Arenaviredae family, whose natural hosts are rodents, hamsters, and guinea pigs. LCMV infection can cause an influenza-like illness or aseptic meningitis that resolves spontaneously in immunocompetent hosts in most cases. Infection during pregnancy occurs following bite by house mouse or when humans come in contact with secretions of the house mouse. The infection can be transmitted transplacentally to the fetus resulting in abortion, in-utero fetal demise, ocular malformations and anomalies of central nervous system with the persistence of severe neurological sequelae in the neonate.

31.4.2 Epidemiology

LCMV is prevalent worldwide, except Antarctica as due to its extreme weather conditions, the continent is not a habitat for the rodent. The disease is more prevalent in lower socio-economic strata, where contact with mice is more frequent. LCMV infections are particularly more common during autumn and winter when mice look for shelter indoors. The seroprevalence in the USA is about1–5% [39].

31.4.3 Virus Morphology and Transmission

LCMV is a member of the family Arenaviridae. The RNA virus is spherical and enveloped with a diameter of 60 and 300 nm [40]. The RNA genome consists of two negative single-stranded RNA segments arranged in a helical pattern [41]. The virus has a predilection for nervous tissues and was first identified in the cerebrospinal fluid of a meningitis patient in 1933. The original strain of LCMV is LCMV Armstrong which has been named after Charles Armstrong, the US physician who isolated the completely unknown virus and named it lymphocytic choriomeningitis in 1934.

The common house mouse, *Mus musculus*, is the natural vector for the virus [42]. The infected mice retain the virus chronically and keep shedding the virus in their urine. They also exhibit vertical transmission to their offspring. Humans

are affected by this virus when they come in direct contact with the fresh urine droppings, saliva, or nesting materials of the infected rodents. Direct inoculation of these materials into the nose, eyes, mouth, or broken skin can also be a route of transmission. Infection can happen through inhalation of aerosolized particles and by direct bite by the infected rodent [43].

31.4.4 Clinical Manifestations

The incubation period of the disease is 1–7 days. It generally presents as fever which has a biphasic pattern. During the incubation period, the patient may present with headache, muscle aches, malaise, nausea, and vomiting. Few patients may also have accompanying pain in the joints, parotid glands and chest. The second phase of the disease sets in after several days with features of meningitis or encephalitis, which include fever, headache, stiff neck, myalgia, nausea, and malaise. In some patients, the disease gets complicated by transient or permanent cranial nerve palsies, sensorineural hearing loss, parotitis, arthritis, and hydrocephalus. It is usually not a fatal disease, with mortality being less than 1% [39].

31.4.5 LMCV in Pregnant Women

31.4.5.1 Maternal Effects

The disease does not have any specific features during pregnancy. Immunocompetent mothers have similar features as in non-pregnant women.

31.4.5.2 Fetal Effects

The disease is of particular concern as there is transplacental transmission of infection to the embryo or fetus.

Effects on the fetus/neonate include

- In the first trimester, there is an increased risk of spontaneous abortion [44].
- Neurological manifestations like hydrocephalus (triventricular dilatation), intracranial calcifications, microcephaly, or macrocephaly can occur with approximately 30% risk of mortality in infants [44–46]. In the fetuses which survive, almost all have neurological sequelae and in about two-thirds the abnormalities are severe [44].
- Low birth weight infants are seen in approximately 30% of cases [39].
- Chorioretinitis, progressing to chorioretinal scarring and finally optic nerve atrophy is seen in 89–100% [47–49].
- Ocular defects including optic atrophy, microphthalmia, vitritis, leukocoria, and cataracts.
- Isolated cerebellar hypoplasia and symptoms of ataxia and jitteriness.
- Delayed development, intellectual disabilities, and seizures [50, 51].
- Spastic diplegia or quadriparesis/quadriplegia.

31.4.6 Differential Diagnoses

Infectious pathogens which can cross the placenta and cause damage to the developing fetus, such as Parvovirus B19 and TORCH-S infections(toxoplasmosis, rubella, CMV, herpes simplex virus, enteroviruses, and syphilis) form the primary differential diagnoses of congenital LCMV infection.

Non-infectious differential diagnosis of congenital LCMV infection includes chromosomal abnormalities causing microencephaly and intracranial calcifications. Several genetic disorders can mimic congenital LCMV infection like Aicardi-Goutieres syndrome.

Clinical findings or imaging studies can help in differentiating LCMV from other diseases and serological tests thereafter can help in confirming the diagnosis. LCMV infected infant or child typically presents with chorioretinitis, hydrocephalus, and micro or macrocephaly. CMV and enterovirus infection have associated hepatosplenomegaly, which is usually absent in LCMV. In rubella and syphilis-infected infants, characteristic salt and pepper retinopathy is present, which is not seen with LCMV. Syphilitic infants present with typical hepatic and osseous involvement which is not seen in this disease.

Congenital toxoplasmosis is most confusing as both are associated with chorioretinitis with macular scarring. Diagnostic differentiation is made by intracranial calcifications, which are periventricular in LMCV and diffuse intracerebral in toxoplasmosis.

31.4.7 Diagnosis

During the initial stage of disease, the most common laboratory findings are leukopenia, thrombocytopenia, and deranged liver enzymes.

In the advanced disease, clinical diagnosis is made with history of prodromal symptoms presenting about 15–21 days prior to the onset of meningitis. CSF examination reveals a rise in the protein levels, a low glucose level and leucocytosis.

Serological tests—Immunofluorescence antibody test or ELISA to detect both IgM and IgG antibodies in blood or CSF is used for diagnosis in humans. Virus-specific IgM or a rising antibody titer can be seen in acute cases. Congenitally infected infants and their mothers generally have specific IgG from an infection earlier in the pregnancy, and IgM is absent.

RT-PCR is sometimes used to aid in viral nucleic acid diagnosis. Virus detection by PCR or virus isolation in CSF can be done in active stage of disease; in congenital infections, the virus is absent.

31.4.8 Treatment of LCM in Pregnancy

LCM is usually not a fatal disease. Treatment is mainly supportive. Hospitalization is based depending upon the severity of disease, like in patients with meningitis, encephalitis, or meningoencephalitis. Anti-inflammatory drugs, like corticosteroids, may be used under specific circumstances. Ribavarin, an antiviral drug, has been found effective against LCMV, but its use in pregnancy is not recommended. Supportive management is recommended in case of the development of aseptic meningitis or meningoencephalitis during pregnancy.

31.5 Pre-Exposure Prophylaxis of Animal Bites in Pregnancy

It is a preventive strategy that consists of series of intradermal or intramuscular injections of rabies vaccine to build up the immunity and can be considered for at risk population like laboratory workers, veterinarians, animal handlers, wildlife officers and certain international travelers. **If the risk of exposure to rabies is considerable, then pre-exposure prophylaxis may be advisable during pregnancy also**.

Pre-Exposure Rabies Prophylaxis Regimens:

1. Intramuscular
   - Intramuscular single dose on the deltoid area of the arm on day 0, 7, and 21 or 28.
2. Intradermal
   - Intradermal injection of 0.1 ml is given on day 0, 7, and 21 or 28.
   - If antimalarial chemoprophylaxis is applied concurrently, intramuscular injections must be used.

There is a definite risk of exposure to rabies in women working in diagnostic laboratories, research laboratories, vaccine production laboratories, where they are in direct contact with the live rabies virus. These women are monitored by regular antibody titer and booster dose of vaccine is give if the titer falls below 0.5 IU/ml.

31.6 Conclusion

Pregnant women are at similar risk to animal bites like general population. The most common complication noted after animal bite is skin infection, but the most dreaded complication is rabies. Termination of pregnancy is not recommended in diagnosed cases of rabies and post-exposure prophylaxis (PEP) for rabies is considered safe in pregnancy. Snake bite though not common in

pregnancy, can result in complications like anemia, thrombocytopenia, abruptio placentae and preterm labor. ASV for management of snake bite is not contradicted in pregnancy. LCMV infection in pregnancy subjects the fetus to risk of abortion, in-utero fetal demise and congenital infections such as occular malformations. But Ribavarin is not recommended for use in pregnancy.

Key Points

1. Animal bites are a common problem, and pregnant women are at same risk of animal bite as the general population; 85–90 percent of the animal bites are caused by dogs.
2. Rabies is a zoonotic, viral disease with neurotropic predilection, which is uniformly fatal if left untreated and is characterized by acute progressive encephalitis. It has an effective vaccine against it which when appropriately used, prevents the disease.
3. Termination of pregnancy is not recommended in the event of exposure to rabies or definite diagnosis of rabies in the mother. Neither is pregnancy a contraindication for post-exposure prophylaxis with immunoglobulin and vaccine.
4. Snakebite is a not a common event in pregnancy, with an incidence of 1%.
5. Maternal complications after snake bite include development of anemia, thrombocytopenia, abruptio placentae and preterm labor. Congenital malformations following snakebite have also been reported in literature.
6. Pregnant women with snakebite should be treated in the same way as non-pregnant women with no contraindication to ASV.
7. Lymphocytic Choriomeningitis Virus (LCMV) is a viral infection with predilection for the nervous tissues caused by bite of rodents(house mouse).
8. LCMV infection in pregnancy results in nearly 100% fetal affection and 30% fetal mortality.

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Part VIII

Puerperal Infections

Puerperal Sepsis and Septic Shock

32

Garima Yadav

32.1 Introduction

Puerperal sepsis is one of the major contributors to maternal mortality globally. Around one-tenth of maternal deaths worldwide are secondary to peripartum maternal infections and sepsis, most of which occur in low-income countries [1]. Puerperal sepsis and septic shock are not only associated with severe acute morbidity but also lead to long-term complications like chronic pelvic pain and tubal infertility. Neonatal morbidity and mortality are also directly associated with peripartum infections which are responsible for around one million neonatal deaths worldwide. In India, maternal sepsis is the third leading cause of maternal mortality, accounting for 16.7% of all mortalities [2]. In low-income countries, most of these maternal deaths occurring secondary to peripartum infections can be prevented by ensuring proper infection control practices at primary health care level, timely referral to higher centers, and provision of intensive care services. In a recently published World Health Organization (WHO) Global Maternal Sepsis Study (GLOSS) [3], it was found that the contribution of direct and indirect infections to maternal mortality is higher than what was previously estimated and early recognition of these infections with prompt management using protocolized care bundles can substantially prevent maternal sepsis-related mortality. Maternal sepsis is found to be increasing even in high-income countries with the recent US data reporting an incidence of 4–5 cases per 10,000 live births [4]. This increase is being attributed to rising maternal age, increasing antibiotic resistance, and increasing incidence of infections with Escherichia coli and group A streptococcus(GAS) [5]. The incidence of maternal sepsis further increases when infection following abortions and fetal demises is also included.

Various factors that are associated with puerperal sepsis are either preexisting maternal comorbidities, delivery-related conditions or community-based problems. The Society of Maternal Fetal medicine (SMFM) recommends that puerperal sepsis and septic shock must be considered medical emergencies and resuscitation with initial treatment must begin with no delay [6]. Various strategies have been suggested to prevent and manage puerperal sepsis with the core principles of early recognition, resuscitation, and appropriate use of antibiotics. In the present chapter, we will discuss the updated definition and terminologies, pathophysiology, risk factors, preventive strategies, diagnostic criteria, and management guidelines for puerperal sepsis and septic shock.

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32.2 Definitions

WHO defines puerperal sepsis as "infection of the genital tract occurring at any time between the onset of rupture of membranes or labor and the 42nd day postpartum in which two or more of the following are present: pelvic pain, fever, abnormal vaginal discharge, abnormal smell/foul odor discharge, or delay in uterine involution [7]. WHO working group argues that the use of the word "puerperal" indicates only childbirth-related genital infections and hence, they proposed the term "maternal peripartum infections" which include both genital and extragenital infections like those of breast, urinary tract, and other incidental infections diagnosed around the time of birth but are not childbirth related.

The third International Consensus definition for Sepsis and Septic shock Task Force defined sepsis as "life threatening organ dysfunction caused by a dysregulated host response to infection" and septic shock is defined as "presence of persistent hypotension requiring vasopressors to maintain mean arterial pressure (MAP) ≥ 65 mm HG and a serum lactate level of >2 mmol/L despite adequate volume resuscitation in the clinical background of sepsis," [8]. This is the Sepsis-3 definition which emphasizes on the presence of organ dysfunction which needs to be diagnosed early in the course of disease process. This new Sepsis-3 definition is different from Sepsis-2 definition which required patients to have documentation of infection along with at least two systemic inflammatory response criteria (SIRS) like tachycardia, tachypnoea, fever or hypothermia, and leukocytosis. But now, sepsis can be labelled if organ dysfunction is documented in the setting of suspected infection.

32.3 Risk Factors for Puerperal Sepsis and Septic Shock

The factors that might increase a women's risk of developing sepsis and further progression to septic shock can be categorized into delivery related or obstetric factors, patient related and community-related risk factors [9, 10] as described in Table 32.1. These risk factors can lead to infection-related morbidities including chorioamnionitis, puerperal endometritis, wound infections, mastitis, and urinary tract infections in the peripartum period.

32.3.1 Delivery-Related Risk Factors

The risk factors increasing the odds of maternal sepsis may vary according to the period of gestation but are mostly related to invasive interventions. In the first trimester, sepsis may occur following surgical abortion at an unauthorized place, by an unauthorized person and retained infected products of conception. In the early second trimester, maternal sepsis can follow invasive procedures like amniocentesis or cervical encer-

Table 32.1 Risk factors for puerperal sepsis and septic shock

Delivery related	Patient related	Community related
Operative vaginal delivery or cesarean section	Obesity	Delivery by untrained attendant
Cervical cerclage	Impaired glucose tolerance	Delivery in underequipped or unhygienic facilities
Prolonged rupture of membranes	Impaired immunity or on immunosuppressant drugs	Long distance from health care facilities
Third- and fourth-degree perineal tears	Malnourishment	Delay in seeking treatment
Wound hematoma	Primipara	Lack of transportation
Retained products of conception	Anemia	Lack of diagnostic facilities
History of pelvic infections	Preexisting medical conditions	Lack of intensive care facilities
Postpartum hemorrhage	GAS infection in close contacts	Poor socioeconomic condition

clage. In the late second and third trimester, preterm premature rupture of membranes (PPROM) is an established risk factor for chorioamnionitis which might progress to sepsis in the peripartum period [10]. For postpartum maternal sepsis, the most common risk factor is an operative delivery either by cesarean section (CS) or by instrumental vaginal delivery. CS is found to be associated with a 5–20% increased risk of maternal infections as compared to vaginal delivery [11].

32.3.2 Patient-Related Risk Factors

The presence of comorbidities like obesity, diabetes mellitus, congestive heart failure secondary to severe anemia or heart diseases, chronic kidney disease or liver disease, immunodeficiency status due to Human Immunodeficiency Virus (HIV) or autoimmune diseases like systemic lupus erythematosus increase the risk of "maternal peri-partum infections." Group A streptococcus (GAS) infection is a common cause of puerperal pyrexia especially in women already harboring the infection or are close contacts of individuals infected with GAS like small children or other family members. The UK Obstetric Surveillance System report also identifies primiparity and black race or ethnic minority to be other risk factors for maternal sepsis [12].

32.3.3 Community-Related Risk Factors

These risk factors are important contributors of increased incidence of puerperal sepsis and septic shock in the low-income countries. Lack of basic infrastructure at primary health care centers lead to deliveries being carried out by untrained professionals under poor hygienic conditions. Moreover, due to lack of transport and presence of fewer referral centers, there is always a delay in provision of care for women with childbirth-associated infections. The delay in diagnosis of sepsis may lead to progression to septic shock and maternal mortality. Lower socioeconomic status has been found to be associated with increased chances of operative vaginal delivery and cesarean section which in turn are independent risk factors for puerperal infections [13].

32.4 Strategies for Prevention of Puerperal Sepsis

Following measures can be included in antepartum, intrapartum, and postpartum care of patients in order to prevent infections-related morbidity:

(a) *General infection prevention practices*
1. Proper hand hygiene before and after delivery.
2. Treatment of sexually transmitted infections.
3. Malaria prevention.
4. Maintaining clean delivery kits.
5. Keeping all delivery surfaces clean.
6. Proper sterilization of delivery instruments and ensuring their sterile storage.
7. Appropriate waste collection.
8. Educating the mothers as well as health care providers about the importance of these practices.

(b) *WHO recommends following guidelines for prevention of peripartum infections* [14]:
1. Avoiding routine perineal and pubic hair shaving prior to vaginal birth.
2. Digital vaginal examination for assessment of labor progress, must not be done at intervals shorter than 4 hours in low-risk women.
3. Routine use of chlorhexidine for vaginal cleansing during labor is not recommended.
4. Antibiotic administration is recommended for women with PPROM; it is not recommended for women in preterm labor with intact membranes.
5. Routine antibiotic prophylaxis is recommended for women undergoing manual removal of placenta and third- or fourth-degree perineal tear while it is not recommended for operative vaginal birth or following episiotomy repairs.

6. Prior to CS, vaginal cleaning with povidone-iodine is recommended.
7. Antiseptic skin preparation and routine use of antibiotics prior to skin incision is recommended in women undergoing CS.

Cochrane systematic review also supports the routine prophylactic use of antibiotics prior to cesarean section for reducing the incidence of febrile morbidity, wound infections, puerperal endometritis, and puerperal sepsis. Although routine use of antibiotics is not recommended following operative vaginal deliveries, but, the 2018 ANODE study did demonstrate a 56% reduction in maternal infection with single dose of intravenous antibiotic given within 3 hours of vaginal delivery [15].

32.5 Pathogenesis of Sepsis and Septic Shock

Sepsis is the result of exposure to infective agents which then evokes a dysregulated host immune response. Pregnancy and puerperium are physiological states of immunosuppression [1] and hence, pregnant women may have an impaired immune response to infection. Moreover, many physiological adaptations of pregnancy like hyperventilation and respiratory alkalosis, hypercoagulation, cardiovascular changes, etc. mimic signs of sepsis; hence, the treating clinician may fail to make an early diagnosis of sepsis in pregnancy [16]. Multiple organs can get affected secondary to the systemic inflammatory response (SIRS) to infection [17] as described in Table 32.2. The new Sepsis-3 definition does not include SIRS criteria for diagnosing sepsis as it focuses more on inflammation rather than resultant organ dysfunction.

The various pathological processes involved in development of sepsis and its progression to septic shock are as follows:

1. Extravasation of intravascular fluid and albumin secondary to inflammation-induced increased capillary leak causing third space loss.

Table 32.2 Organ-based effects of immune response and their manifestation

Organ system affected	Manifestation
Central nervous system	Altered mental status
Cardiovascular system	Reduced myocardial function, decreased systemic vascular resistance, tachycardia, hypotension, hemodynamic collapse
Pulmonary system	Acute Respiratory Distress Syndrome (ARDS), pulmonary edema, hypoxia, reduced ability to compensate for metabolic acidosis
Hematological system	Thrombocytopenia, coagulation disorder or DIC due to increase in procoagulant factors, increased thrombin production and decreased fibrinolysis
Hepatic system	Abnormal transaminases or hepatic failure
Renal system	Acute kidney injury secondary to ischemia or direct cytokine mediated cell injury
Endocrine system	Increased insulin resistance, adrenal dysfunction
Gastrointestinal system	Paralytic ileus

2. Various cytokines are released in this inflammatory response that can directly cause tissue injury like cardiomyocyte death and reduced myocardial function.
3. In sepsis, endothelium-derived nitric oxide (NO) is upregulated secondary to the release of various intracellular cytokines and chemokines which results in smooth muscle relaxation and vasodilatation. This release of NO is increased in pregnancy secondary to estradiol with increased prostaglandins leading to even more vasodilatation. Hence, the pregnant females are at increased risk of sudden hypotension during sepsis.
4. Hypotension resulting from above two processes leads to tissue hypoperfusion and organ dysfunction leading to what is defined as septic shock.
5. Pathogens are also likely to stimulate the coagulation cascade leading to fibrin deposition, microthrombi formation, and disseminated intravascular coagulation (DIC).

32.6 Infective Etiological Agents in Puerperal Sepsis

Various infective organisms have been identified which are responsible for puerperal sepsis. For intra- and postpartum infections the source is usually pelvic in origin. These infections are introduced in the female genital tract either secondary to unhygienic delivery practices or may be endogenous to the female's genital tract. Laboratory cultures can identify infections in only two-third of cases while the source of infection can be identified in around three-fourth of cases [18]. P.sepsis is usually a polymicrobial infection and the most common infective agents present in genital and extragenital sources are as follows:

1. *Streptococcus Pyogenes (Group A streptococcus)*: This is one of the common pathogens isolated from genital tract in maternal infections [19]. GAS is a common pathogen colonizing the upper respiratory tract of children hence, close contact with young children is an established chronology in most of these cases. This bacterium has the capacity to invade intact epithelium secondary to its various surface proteins and hence, can cause genital tract infections, necrotizing fasciitis, or pneumonia [20]. It can also lead to toxic shock syndrome by directly activating the T cells with its exotoxins leading to massive cytokine release and septic shock.
2. *Escherichia coli (E.coli)*: This is known to be the most common infectious agent in maternal sepsis responsible for 37% of the total cases [17]. *E.coli* is also commonly responsible for extragenital infections like urinary tract infections along with being a common pathogen causing chorioamnionitis following PPROM.
3. *Group B streptococcus (GBS)*: This Gram-positive coccus frequently colonizes the genital tract and gastrointestinal system. The incidence of this infection is low in India but in Western countries like the UK and the USA, the population is routinely screened for GBS and routine antibiotic prophylaxis is recommended for women harboring the same in their genital tract in order to prevent maternal and neonatal sepsis.
4. *Staphylococcus aureus*: *Staphylococcus aureus* is a likely infective agent in skin, soft tissue and wound infections during puerperium. Staphylococcal toxic shock syndrome (TSS) is also a known complication in puerperal sepsis and may be associated with necrotizing fasciitis.
5. Other less common infective agents: Methicillin-resistant staphylococcus aureus (MRSA), clostridium, klebsiella, influenza virus, Extended Spectrum β-Lactamase (ESBL) producing bacteria, and anaerobic bacteria.

32.7 Diagnosis of Puerperal Sepsis and Septic Shock

32.7.1 Clinical Features Suggestive of Puerperal Sepsis and Septic Shock

It is prudent to identify sepsis related symptoms and clinical signs for early recognition, resuscitation and referral of these patients. The major roadblock in early diagnosis is the fact that pregnancy-related physiological adaptations may mask signs of sepsis response. The major clinical features appearing in genital and extragenital sites responsible for maternal peripartum infections [21, 22] are described in Table 32.3.These clinical features are secondary to genital infections like postpartum endometritis, pelvic abscess, and episiotomy/cesarean wound infection or due to extragenital infections like mastitis, pharyngitis, urinary tract infections, septic phlebitis, skin or soft tissue infections, gastroenteritis, spinal abscess, and pneumonia. The details of each one of these causes, their individualized treatments and complications are discussed in various dedicated chapters of this book.

Puerperal sepsis is suspected once the postpartum patient presents with typical clinical features as described above. The working diagnosis can be made in the presence of symptoms described in the WHO definition, i.e. pelvic pain,

Table 32.3 Clinical signs and symptoms of Puerperal Sepsis and Septic shock

Clinical feature	Description
Puerperal pyrexia	Temperature more than 38 °C on two occasions or single episode of temperature > 38.5 °C, 24 hours after delivery. Fever within 12 hours of birth can still be an early sign of sepsis secondary to streptococcal infection. Fever may be associated with chills, rigors, sweating, diarrhea, or vomiting which are signs of toxic shock
Hypothermia	Core temperature < 36 °C
Tachycardia	Heart rate > 90 beats/minute
Tachypnoea	Respiratory rate > 20 breaths/minute
Abnormal vaginal/ wound discharge	Foul smelling lochia, purulent discharge from the episiotomy or cesarean wound site Malodorous discharge is suggestive of anaerobic infection while serosanguinous and watery discharge indicates streptococcal infection
Abdominal pain	Generalized constant severe pain out of proportion to clinical signs indicate necrotizing fasciitis or deep pelvic abscess Renal angle tenderness indicates pyelonephritis Uterine tenderness indicates puerperal endometritis
Redness, pain, and induration at the wound site	Signs of inflammation secondary to wound infections
Hypoxia	Oxygen saturation < 90% at room air, PaO_2/FIO_2 < 300
Hypotension	Systolic blood pressure (SBP) of <90 mmHg or Mean Arterial Pressure (MAP) < 70 or an SBP decrease of >40 mmHg
Oliguria	Urine output of <0.5 ml/kg/hr for at least two hours despite adequate fluid resuscitation Can be associated with symptoms of UTI like dysuria and increased frequency of micturition
Subinvolution of the uterus	This can occur secondary to retained products of conception getting infected causing endometritis and myometritis
Lethargy and reduced appetite	Generalized symptomatology of sepsis
Persistent or excessive vaginal bleeding	Women can present with secondary postpartum hemorrhage along with other signs of sepsis
Generalized maculopapular rashes	Feature suggestive of toxic shock syndrome following staphylococcal or streptococcal infection, may be associated with conjunctival suffusion and other symptoms like nausea, vomiting, and diarrhea
Breast engorgement or tenderness	Feature suggestive of mastitis or breast abscess
Impaired consciousness	Seen in severe sepsis or septic shock leading to multiple organ failure
Failure to respond to treatment	Atypical symptoms in the postpartum period like persistent vaginal bleeding and unexplained abdominal pain not responding to routine empirical treatment can be secondary to underlying sepsis

fever, abnormal vaginal discharge, abnormal smell/foul odor discharge, or delay in uterine involution in a woman who has delivered in the last 42 days. A detailed history of the chief complaints along with personal and medical history of sore throat, exposure to children suffering from sore throat, recent foreign travel, exposure to person with influenza like illness, prior history of infections with multi-resistant organisms like ESBL—producing Gram-negative bacteria, vancomycin-resistant enterococci or MRSA along with history of chronic medical diseases or immunosuppression must be sought. Following the history, a detailed examination must be done including the following parameters in the postpartum patient:

1. General well-being and appearance.
2. Vital signs including pulse rate, blood pressure, temperature, and respiratory rate.
3. Higher mental function.
4. Respiratory and cardiovascular examination.
5. Breast examination to look for breast redness, engorgement, tenderness, or abnormal discharge from the nipples.

6. Abdominal examination to look for any rashes, localized tenderness (renal angle/uterine/epigastric), free fluid, and uterine involution.
7. Wound site examination of the cesarean scar or episiotomy scar and look for signs of inflammation or abnormal discharge.
8. Examination of lochia for its color and odor.
9. Bilateral lower limb examination to rule out venous thrombophlebitis.

Based on the severity of the clinical signs, the women can be categorized under sepsis or septic shock and risk assessment for adverse outcomes can be done using bedside assessment scores. In the new "Sepsis-3" definition, the stress has been laid on proving organ dysfunction in the setting of infection and not on diagnosing inflammatory response secondary to it. Hence, the sepsis-3 committee proposed a bedside score known as the quick Sequential Organ Failure Assessment (qSOFA) score for prediction of organ dysfunction-related adverse outcomes. The Society of Obstetric Medicine of Australia and New Zealand modified this qSOFA score to fit the physiological adaptations in pregnancy. The obstetric qSOFA score is described in Table 32.4. An early transfer to a tertiary care center must be considered in the presence of the following "red flag" signs:

(a) Pulmonary edema, need for airway protection or mechanical ventilation
(b) Refractory hypotension (BP < 90/60 mmHg) not responding to initial fluid resuscitation
(c) Significantly decreased level of consciousness
(d) Hypothermia
(e) Uncorrected acidosis
(f) Evidence of multi-organ failure

Table 32.4 Modified qSOFA score

Bedside clinical parameter	qSOFA score	
	0	1
Systolic blood pressure (mmHg)	≥ 90	< 90
Respiratory Rate	<25 breaths/minute	≥ 25 breaths/minute
Altered mentation	Alert	Not alert

Table 32.5 Bedside clinical parameters included in MEOWS chart

Clinical parameter	Red trigger	Yellow trigger
Temperature (°C)	<35 or > 38	35–36
Systolic blood pressure (mmHg)	<90 or > 160	150–160 or 90–100
Diastolic blood pressure	>100	90–100
Heart rate (beats per minute)	<40 or > 120	100–120 or 40–50
Respiratory rate (breaths per minute)	<10 or > 30	21–30
Oxygen saturation (%)	<95	N/A
Pain score	N/A	2–3/10
Neurological response	Unresponsive or responsive only to pain trigger	Responsive to voice but not fully alert

A score of more than equal to 2 indicates increased risk of sepsis-related adverse outcomes, immediate need for evaluating organ dysfunction, close monitoring, initiation of aggressive therapy, and need for transfer to an intensive care unit [23]. Septic patients having a qSOFA score of at least 2 were found to have a mortality rate of 28% [24]. Another bedside tool recommended for identifying ill obstetric patients for signs of sepsis is Modifying Early Obstetric Warning Signs (MEOWS) chart but it has been found to be highly non-specific [25]. MEOWS chart monitors several clinically measurable parameters and defines them as red trigger or yellow trigger based on their severity (Table 32.5). The presence of two yellow triggers or one red trigger calls for involvement of one senior anesthetist and one senior obstetrician in the care of the postpartum woman.

32.7.2 Investigations

After the bedside suspicion of puerperal sepsis, a battery of investigations are done to establish organ dysfunction along with source of infection and infective agent responsible for p.sepsis. The

following tests are routinely recommended in the work up:

1. *Blood culture*: The sample is collected before administering the antibiotics and preferably at the peak of fever. Despite being the gold standard test to prove systemic bacterial infection, it has a poor specificity with only 30–40% [26] cultures coming out positive in patients with severe sepsis. Another limitation is the time taken for the results to get available which is always more than 24 hours.
2. *Serum biochemistry*: Complete blood count, blood sugar, blood urea, electrolytes, serum creatinine, and liver function test.
3. *Inflammatory markers*: C-reactive protein, leukocyte count and procalcitonin are now routinely used serum markers to identify early stages of sepsis and inflammation secondary to infective pathologies. Raised levels are directly proportional to clinical severity and adverse outcomes. Procalcitonin has been proved to be highly specific marker for bacterial infection [27, 28]. It is important to note that these markers should not be used to guide early initiation of treatment in women suspected to have puerperal sepsis on clinical grounds. This is so because these markers may have a normal value in early disease course but that should not stop the clinician to begin empirical antibiotics in case there is high clinical suspicion of sepsis.
4. *Serum Lactate levels*: Lactate levels of >2 mmol/l urges involvement of a critical care expert and values of 4 mmol/l indicates tissue hypoperfusion. Serum lactate levels are not affected by the physiological changes of pregnancy but pregnant women are less equipped to compensate for lactic acidosis and hence, raised lactate levels in pregnancy are associated with adverse maternal outcomes. Hyperlactataemia is a direct marker of tissue hypoperfusion and a surrogate marker for mitochondrial dysfunction, increased glycolysis due to catecholamine surge in sepsis and hepato-renal dysfunction. Every 1 mmol/L rise in lactate levels is associated with a 2.34-fold rise in the risk of ICU admission [29].
5. *Culture studies*: On the basis of clinical suspicion of source of infection, various samples like urine, wound swab, high vaginal swab or endocervical swabs, cerebrospinal fluid, placental tissue or retained products of conception (RPOC), and breast milk can be sent for culture in maternal sepsis.
6. *Imaging studies*: Chest X-ray, pelvic ultrasound to look for RPOC and pelvic abscess, CT scan for deep seated abscesses and necrotizing fasciitis.
7. *Other blood investigations*: Tests for malarial antigen, chikungunya virus, dengue virus, and salmonella typhi titers are routinely done in endemic areas or in the presence of typical presentations.
8. *Polymerase chain reaction and Mass spectrometry*: These are newer modalities that can detect DNA sequences of multiple pathogens from blood samples or tissue culture, however, their routine clinical use is still limited. Mass spectrometer utilizes the matrix-assisted laser desorption/ionization (MALDI) using a time-of-flight (TOF) technique to detect a variety of bacteria and fungi from positive cultures with good accuracy and speed. Since, these techniques are expensive, they are presently used only in limited scenarios and set-ups.

32.7.3 Identification of Critically Ill Patients with P.sepsis

Besides the above-mentioned qSOFA score which utilizes basic bedside parameters to identify critically ill patients, another obstetrically modified SOFA score [30] has been formulated by the Society of Obstetric Medicine Australia and New Zealand which also incorporates few other pregnancy-specific physiological variables in order to increase the specificity of predicting adverse outcomes in critically ill pregnant or postpartum women and their prognostication (Table 32.6). A similar prognostic tool known as "Sepsis in Obstetrics score" (SOS) was developed by Albright et al. [31] incorporating the previously defined parameters in MEOWS chart

Table 32.6 Obstetrically modified SOFA score

Organ system Parameter	Score 0	1	2
Respiration (PaO_2/FiO_2)	≥ 400	300–400	<300
Coagulation (Platelets x10^6/L)	≥ 150	100–150	<100
Liver (Bilirubin in umol/l)	≤ 20	20–32	>32
Mean arterial pressure (mmHg)	≥ 70	<70	Vasopressors required
Central nervous system	Alert	Aroused by voice	Aroused by pain
Renal (creatinine in umol/l)	≤90	91–120	>120

Table 32.7 The Sepsis in Obstetric Score (SOS)

Clinical Variable	Score +4	+3	+2	+1	0	+1	+2	+3	+4
Temp(°C)	>40.9	39–40.9		38.5–38.9	36–38.4	34–35.9	32–33.9	30–31.9	<30
SBP(mmHg)					>90		70–90		<70
HR(bpm)	>179	150–179	130–149	120–129	≤119				
RR(breaths/min)	>49	35–49		25–34	12–24	10–11	6–9		≤ 5
SpO_2 (%)					≥ 92	90–91		85–89	<85
TLC(No/uL)	>39.9		25–39.9	17–24.9	5.7–16.9	3–5.6	1–2.9		<1
Immature Neutrophils			≥10%		<10%				
Lactic acid (mmol/L)			≥ 4		<4				

with a few blood investigations. The SOS scores come in handy to predict the need for ICU care in women with P.sepsis (Table 32.7).

A maximum SOFA score of ≥1 and ≤ 2 represents organ dysfunction while a score of ≥3 is considered as organ failure. The maximum total SOFA score is directly proportional to increased mortality risk.

Women with a SOS score of ≥6 were more likely to get admitted in intensive care unit and had increased incidence of adverse outcomes in terms of maternal morbidity and mortality secondary to p.sepsis.

32.8 Management of Puerperal Sepsis and Septic Shock

Most guidelines used for management of maternal sepsis are derived from the protocolized "care bundles" of the widely acclaimed Surviving Sepsis Campaign (SSC) [22] to decrease sepsis-related morbidity and mortality. Pregnancy-specific care bundles have also been developed such as the one by the UK Sepsis Trust [32] which is largely an adaptation of the "Hour-1" bundle proposed by SSC for adult patients with septic shock [33]. The key elements in the management are described as "the sepsis six" which includes sending cultures, measuring blood lactate levels, hourly monitoring of urine output, early commencement of oxygen support, administration of intravenous fluids, and initiation of antibiotics [34]. Diagnosis of organ dysfunction in an otherwise healthy postpartum female must raise suspicion of P.sepsis following which urgent investigations like lactate levels along with relevant cultures from blood, urine, sputum, or vagina must be sent. The key to successful management of P. sepsis is early identification and initiation of antibiotics within 1 hour of clinical diagnosis [30]. Empirical antibiotics are started to cover likely microorganisms without waiting for culture reports. In order to reduce maternal mortality secondary to sepsis, it is prudent to place individual institutional protocols for maternal sepsis which take into account the local health care and referral system, intensive care facilities,

local microbial prevalence, and antibiotic resistance patterns. Broadly, the management of P. sepsis and septic shock must be a multidisciplinary approach following below mentioned principles of treatment:

1. *Early recognition of P.sepsis* using both clinical and diagnostic parameters along with close monitoring of vital signs like temperature, pulse rate, blood pressure, and respiratory rate in order to diagnose organ dysfunction at the earliest. Relevant blood and tissue cultures must be sent along with serum lactate levels. Risk stratification must be done using the qSOFA, SOFA, or SOS score as described above and vital monitoring charts like MEOWS can be used for record keeping.
2. *Resuscitation*: If the diagnosis of organ dysfunction is made on initial assessment, immediate methods for resuscitation must begin to restore adequate organ perfusion at the earliest. Fluid resuscitation must be given within 6 hours of diagnosis of severe sepsis or septic shock. An initial bolus of 30 ml/Kg of crystalloid was recommended by the surviving sepsis campaign care bundles for adult population in the management of septic shock with a blood lactate of >4 mmol/L [30] although, this approach may lead to increased risk of pulmonary edema in pregnant patients secondary to decreased colloid oncotic pressure. Around 1–2 L or 20 ml/Kg [10] of fluid can be initially administered using a 14 or 16G cannula in most pregnant females following which one should check for fluid responsiveness by looking at pulse pressure variation. Less than 50% of women with severe sepsis and septic shock are fluid responders and remaining require vasopressors for the same. Otherwise, aggressive and blind fluid replacement in non-responders may lead to third spacing resulting in pulmonary edema, diastolic dysfunction, cerebral edema, and ascites leading to increased mortality [35]. A reasonable guide to document response to fluid therapy is lactate clearance within 6 hours of initiation of treatment [36]. Patients with septic shock who do not respond to the initial fluid resuscitation, vasopressors are recommended for increasing the blood pressure. The recommended first-line agent is norepinephrine and the target Mean Arterial Pressure (MAP) is ≥65 mm Hg [30]. In case of non-response to vasopressors, sepsis-induced adrenal failure must be suspected and low dose hydrocortisone (200 mg/day) as a continuous infusion can be started [6].
3. *Antibiotic therapy*: Broad-spectrum antibiotics covering Gram-negative, Gram-positive, and anaerobic bacteria must be administered within 1 hour of diagnosis of P.sepsis after collecting culture specimens. Each hour of delay in the initiation of antibiotics following the diagnosis of sepsis, may increase mortality by 6–8% [37]. Absolute indications for intravenous antibiotics include abdominal pain, fever >38.0 °C, and tachycardia >90 bpm. The most commonly recommended empiric antibiotics in the treatment of P.sepsis are ampicillin, gentamicin with metronidazole or clindamycin. Another option as proposed by the confidential enquiries into maternal deaths in the UK (2003–2005), is the combination of cefuroxime and metronidazole, although cefuroxime was found to be associated with clostridium difficile infection and hence, this combination is no longer recommended for treatment of genital tract sepsis [38]. If resources allow, another commonly preferred regimen is piperacillin-tazobactam or carbapenem plus clindamycin which provides broad bacterial coverage in treatment of severe sepsis including MRSA and ESBL producing bacteria. MRSA may be resistant to clindamycin, hence if there is a high suspicion of MRSA infection, drugs like vancomycin or teicoplanin may be added until sensitivity is known. Clindamycin is also a preferred choice in GAS infections because it reduces the exotoxin production and hence, improves outcomes [39]. The empiric antibiotics may be de-escalated or changed to targeted antibiotics following reports of culture and sensitivity tests.

4. *Source control*: It refers to identification of origin of infection and controlling it using available treatment options. For instance, retained products of conception must be evacuated from the uterine cavity and sent for culture, pyo-peritoneum secondary to septic abortion or unhygienically carried out cesarean sections, may require a laparotomy and drainage of pus along with evaluation of uterine or bowel injury. Wound site abscesses (episiotomy or LSCS incision) may require incision and drainage, removal of necrotic tissue followed by sterile dressings under antibiotic cover. Since P.sepsis commonly results due to a polymicrobial infection, combination of two classes of antibiotics is usually required. Treatment of resistant and uncommon organisms like MRSA and ESBL may require inputs from a microbiologist and infective disease specialist. In case of a nonresponsive patient, maximum efforts must be taken to identify a less common site of infection, early in the course of disease process as observational studies suggest that delay in source control results in increased 28-day mortality from 26% to 42% [40].
5. 5. *Adjunctive treatment*: Supportive treatment in the form of fluid replacement, dialysis in case of kidney injury, respiratory support to achieve a saturation of ≥94%, inotropic support, etc. is to be continued till the organ recovery occurs. Adequate nutrition must be maintained but at the same time hyperglycemia above 180 mg/dl must be avoided with the use of oral hypoglycemic agents or insulin therapy to control bacterial growth. Other measures like use of thromboprophylaxis is indicated in severe sepsis to prevent deep vein thrombosis (DVT) as pregnancy is a hypercoagulable state and the risk of DVT worsens with sepsis, prolonged hospitalization, and recumbency [6].
6. *Intravenous immunoglobulins (IVIGs)*: Dysregulated immune response in the underlying pathology of sepsis and septic shock and immune regulation in this setting has shown to improve outcomes [41]. Harmful pro-inflammatory cytokine production can be targeted using neutralizing antigens in the form of IVIGs [42]. The use of IVIGs in the obstetric population though is limited but inferences can be drawn from the Cochrane review which demonstrated the benefit of IVIGs in reducing sepsis related mortality in adult population along with a small RCT done in obstetrics and gynecologic patients with septic shock which also showed reduction in morbidity and mortality with use of antiendotoxin immunoglobulin [43]. RCOG also supports the use of IVIG in the management of toxic shock syndrome [44].

32.9 Conclusion

Puerperal sepsis is one of the major contributors of maternal mortality globally. Around one-tenth of maternal deaths worldwide are secondary to peripartum maternal infections and sepsis, most of which occur in low-income countries. Sepsis is the result of exposure to infective agents which then evokes a dysregulated host immune response leading to organ dysfunction. The newer sepsis management guidelines focus on organ dysfunction in diagnosing sepsis rather than inflammatory markers. Various sepsis scores are formulated for bedside diagnosis, need for intensive care and prognostication. The key elements in the management of severe sepsis and septic shock are early recognition by sending cultures, prompt initiation of fluid resuscitation and administering broad-spectrum antibiotics at the earliest. Broad-spectrum antibiotics which cover Gram-positive, Gram-negative, and anaerobic bacteria must be empirically started as early as possible and it is the single most intervention that can reduce maternal mortality in women with puerperal sepsis. Multi-organ dysfunction needs a multidisciplinary approach in a critical care set up using various organ support elements till the recovery is documented.

Key Points

1. Puerperal sepsis refers to infection of the genital tract occurring at any time between the onset of rupture of membranes or labor and the 42nd-day postpartum in which two or more of the following are present: Pelvic pain, fever, abnormal vaginal discharge, abnormal smell/foul odor discharge, or delay in uterine involution.
2. It is a major cause of mortality and morbidity worldwide and is the third leading cause of maternal mortality in India, accounting for 16% of cases.
3. The common risk factor is an operative delivery followed by history of PPROM, prolonged labor, delivery in unsterile conditions, and presence of comorbidities in the mother like obesity, diabetes mellitus, history of antepartum infections, and immunosuppression.
4. Preventive strategies include use of utmost sterile delivery practices, use of antibiotics in the management of women with PPROM, avoiding unnecessary operative deliveries, provision of safe abortion practices, improving health care and referral facilities and ensuring easy access to health care.
5. P.sepsis is a polymicrobial infection and the two most commonly isolated organisms are Group A Streptococcus (GAS) and Escherichia coli.
6. Early recognition using bedside and clinical scores like qSOFA, SOFA, and SOS is the key to successful management and reduction in associated maternal mortality.
7. Standardized sepsis protocols must be followed which include fluid resuscitation, initiation of broad-spectrum antibiotics within 1 hour of sepsis diagnosis and organ support.
8. The management of severe sepsis and septic shock should be done by a multidisciplinary team including an obstetrician, an intensivist and an infectious disease specialist.
9. Local incidences of P.sepsis, infection control practices, bacterial profile, and antibiotic resistance patterns must be sought after through continuous research-based activities.

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Postpartum Endometritis

33

Swati Dubey and Sumita Mehta

33.1 Introduction

Infection is a preventable cause of maternal morbidity and pregnancy-related sepsis accounting for 11% of maternal deaths [1]. Infection leads to subsequent complications like PID, ectopic pregnancy, and infertility [2]. Nevertheless, the frequency of infection in pregnancy is not well understood [3]. Recent data (2017) of Global burden of disease reports 12.1 million incident cases of maternal sepsis and other maternal infections, including mastitis [4].

Puerperal sepsis, seen up to 42 days after delivery has a varied presentation ranging from localized signs and symptoms of genital tract infection to more disseminated disease including peritonitis and sepsis [5–7].

Physiologically, the endometrium is infiltrated by various cells like neutrophils, lymphocytes, natural killer cells, throughout the normal menstrual cycle in different proportions and concentrations [8]. This process is required to remodel the endometrial tissue so as to obtain endometrial receptivity.

Endometritis is an infectious and inflammatory disorder of the endometrium and can be defined as an infection of the upper genital tract including endometrium, myometrium, and surrounding tissue. Mostly it occurs after childbirth when vaginal bacteria might have access to the upper genital tract [9, 10]. According to Cochrane review (2012), the incidence of endometritis following vaginal delivery is around 1–3% and following C-section is around 5–10 times higher [11]. Endometritis is classified as either acute or chronic according to the histopathology [12]. Microabscess formation and neutrophil infiltration of the endometrium is referred to as acute endometritis which has no effect on the fertility of a woman and also does not alter the pregnancy rate. On the other hand, chronic endometritis (CE) which is characterized by endometrial superficial edema, high stromal cell density, dissociated maturation between epithelium and stroma and infiltration of endometrial stromal plasmacytes (ESPCs) negatively affects fertility [13, 14]. Presently there is no universally accepted standardized definitions or diagnostic guidelines for chronic endometritis but *the presence of multiple endometrial stromal plasmacytes is the most specific and sensitive finding in this pathology* [15, 16]. Acute endometritis presents with fever, pelvic pain, and vaginal discharge whereas chronic endometritis leads to nonspecific symptoms like pelvic discomfort and leukorrhea, which are usually neglected by the patients. As endometritis is a benign disease and does not have a malignant potential so invasive

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procedures like endometrial biopsy are not advocated regularly. However, the relationship between chronic endometritis and fertility outcome needs attention.

33.2 Incidence of Postpartum Endometritis

The incidence of puerperal sepsis (both postpartum endometritis (PPE) and chorioamnionitis) ranges from 1 to 10% across the world [17]. Deaths and morbidity due to sepsis after childbirth are seen more commonly in low- and middle-income countries as compared to the developed nations. Among deaths due to puerperal sepsis, postpartum endometritis is the leading cause of death in the first postpartum week [18].

Postpartum endometritis is one of the leading causes of postpartum infections and is seen in 1–3% of women following vaginal delivery and in around 27% following C-section [19]. Other causes of postpartum infections include mastitis, urinary tract infections (UTI), and surgical site infections, the frequency of each depending on the clinical setting. An observational study in Sweden found out that the leading causes of infection following childbirth were mastitis (3–4.5%), UTI (2.4–3%), and endometritis (1.7–2%) [20].

33.2.1 Incidence of Infection Following Incomplete or Complete Abortion

Abortion is the expulsion or extraction from the mother of an embryo or fetus weighing 500 gm or less when it is not capable of independent survival and is a common outcome of pregnancy. In one of the systematic reviews, the accumulative possibility of infection after an abortion varied between 11 and 22% [21]. Abortions can be spontaneous (75%) or induced (25%) and the annual rate of abortion in women of reproductive age group is about 35 per 1000 [22]. Incidence of infection following a spontaneous abortion is low but increases to 0.1–4.7% after a surgical abortion [23]. Uterine manipulation/instrumentation, any retained products of conception in the uterine cavity and abortions performed in unsafe conditions increase the risk for infection and any delay in treatment can even lead to death [24].

33.3 Risk Factors for PPE [25]

Many factors like the labor duration, number of vaginal examinations done, and premature rupture of membranes (PROM) contribute to postpartum endometritis. Rupture of the membranes for more than 6 hours is linked to a higher incidence of infection. Postpartum endometritis is more common in immunocompromised women than immunocompetent ones. The common risk factors for postpartum endometritis are shown in Table 33.1.

Any infection of the genital tract is an important cause of postpartum endometritis. Bacteria like Ureaplasma urealyticum can migrate through the amnion and multiply if the response of the amniotic fluid against it is poor. This will extend to the chorio-amnion followed by successive involvement of the endometrium. Hence, infection plays an important role in etiopathogenesis of preterm delivery, thereby establishing a positive relationship between prematurity and postpartum endometritis. Intrapartum bacteriuria has also been correlated with endometritis in women who undergo vaginal delivery. The manipulation

Table 33.1 Risk factors for PPE

	Risk factors
Antepartum factors	• Maternal age • Low socioeconomic status • Obesity • Anemia • Antepartum infection with Gp B streptococcus • Immune status
Intrapartum factors	• Preterm labor • Premature rupture of membranes • Number of internal examinations • Amnionitis • Protracted labor • Cesarean section • Increased blood loss • Intrapartum bacteriuria

during vaginal delivery may lead to dissemination of infection from the bladder and hence early recognition of UTIs may prevent endometritis. Unsterile techniques or an extension of the uterine incision and positive endometrial cultures at the time of the operation are the factors associated with high chances of PPE after C-section delivery. Conversely, elective or a planned repeat C-section has less chance of febrile morbidity due to absence of bacterial contamination of the lower segment of the uterus by labor forces and cervical effacement.

33.4 Microbiology of PPE

Postpartum endometritis is typically a mixed infection which involves both aerobic and anaerobic bacteria including genital mycoplasmas and sexually transmitted organisms like C. trachomatis [26]. As postpartum endometritis is an upper genital tract infection involving bacteria from the cervicovaginal flora, the microorganisms frequently encountered are common to the latter. The microbiology of PPE in low resource countries is different from that in the developed countries with microorganisms like E. coli, Proteus, N. gonorrhoeae, and S. pneumonia frequently isolated in low and middle-income nations [27]. Group B Streptococcus, commonly present in the genital tract of pregnant women is accountable for high cases of postpartum infections worldwide viz-a-viz group A Streptococcus which is quite rare and is associated with a particularly acute and severe course of postpartum endometritis [28, 29]. Additionally, in postoperative patients receiving beta-lactam prophylaxis, there is an increased association of Gram-positive isolates and nonfragilis strains of Bacteroides.

The common organisms causing PPE include the aerobic Gram-positive cocci (group B streptococci, enterococci, and staphylococcal species), anaerobic Gram-positive cocci (peptococci and peptostreptococci spp.), aerobic Gram-negative bacilli (Escherichia coli, Klebsiella pneumonia, and Proteus species), and anaerobic Gram-negative bacilli like Bacteroides and Prevotella [30]. Though endometritis affects the inner lining of the uterus, it can also spread outside the uterus and lead to abscess formation, pelvic thrombophlebitis, and even peritonitis.

Infection following abortions results from either uterine manipulation or any retained products of conception in the uterine cavity that acts as a nidus for infection to flourish. Organisms causing infections after abortion include commensals of genital flora and anaerobic bacteria. N. gonorrhoeae, C. trachomatis, and Trichomonas have also been implicated in causing infections after abortions. Clostridium perfringens and Group A streptococcus infections which are uncommon following abortion can lead to severe morbidity due to the toxins released by them [31, 32].

33.4.1 Chronic Endometritis [33]

Chronic endometritis is a polymicrobial infection of the uterine cavity. The microorganisms found frequently in endometrium with chronic endometritis are Streptococcus species, Escherichia coli, Enterococcus faecalis, staphylococcus, mycoplasma/ureaplasma species, proteus, Gardnerella vaginalis, Klebsiella pneumoniae, and Pseudomonas aeruginosa. Fungal infections such as Candida and Saccharomyces cerevisiae have also been isolated. The most important feature for chronic endometritis diagnosis is the *presence of multiple endometrial stromal plasmacytes on pathology* (Fig. 33.1).

Chronic endometritis caused by Mycobacterium tuberculosis is seen in some developing countries. It is characterized by caseous granulomas surrounded by lymphocytic infiltration and presence of stromal plasma cells in the endometrium. In contrast, numerous studies have shown that the occurrence of Chlamydia trachomatis and Neisseria gonorrhoeae, the main pathogens responsible for acute endometritis are very low in patients with chronic endometritis. Furthermore, antibiotics like azithromycin which is administered to target C. trachomatis and N. gonorrhoeae fail in preserving fertility of women with chronic endometritis. Hence, these two organisms are not likely to be the main organism responsible for

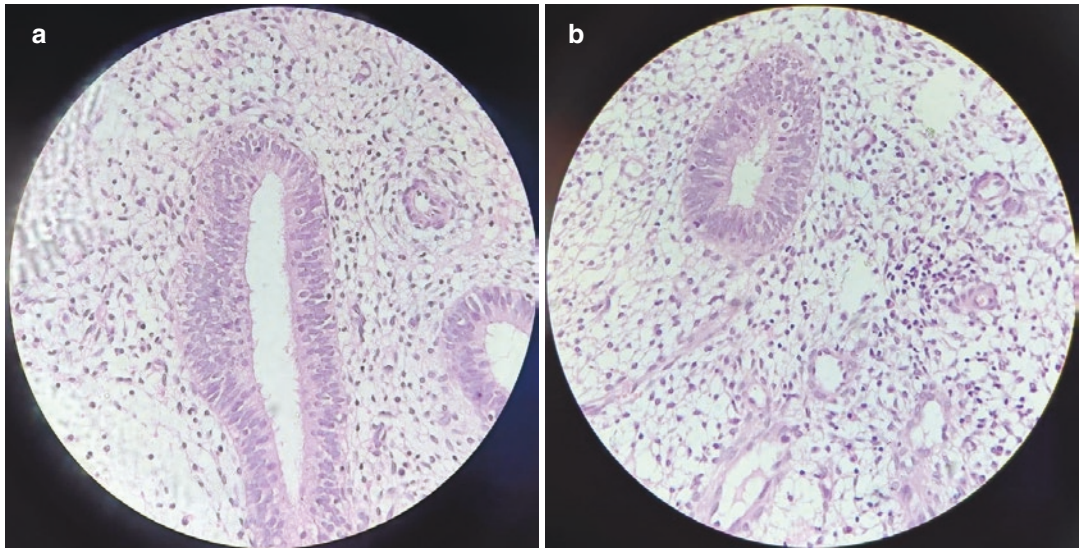

Fig. 33.1 (**a**) and (**b**) - Lymphoplasmacytic infiltrate in the stroma suggestive of Chronic Endometritis

chronic endometritis. Some reports suggest both HIV and CMV as causative agents for chronic endometritis; though the relationship between these viral infections and chronic endometritis remains unknown. Most of the time, the pathogens revealed in the endometrium are different from those found in the endocervical tissue or vaginal discharge, suggesting that the microbe examinations using samples from the lower genital tract cannot detect the organisms of chronic endometritis.

33.5 Pathophysiology [12]

The factors responsible for colonization of any susceptible tissue include:

1. Defense mechanisms of the host must be weak either as a result of trauma or any breach in the normal mechanical barriers to microbe invasion.
2. A weakened host immunity, which could be due to anemia, drug intake, or immunocompromising illness.
3. The virulence or invasiveness of the bacteria in question.

Endometritis is an ascending infection, which advances from the lower segment of the uterus to the uterine cavity and ultimately to the peritoneal cavity by the infected cervicovaginal flora. The infection originates in the denuded implantation site of an untraumatized uterus. Hence, postpartum endometritis is much more common after a C-section than vaginal delivery, where the site of infection is the suture line in the contaminated lower uterine segment. Puerperal endometritis presents as two different clinical situations with a lot of overlap between the two. Late-onset endometritis, is more common after vaginal delivery than after C-section and is referred to be an infection that has an onset within 2 days to 6 weeks after childbirth and usually presents with only mild signs and symptoms. Microbes like C. trachomatis, mycoplasmas, and anaerobic bacteria are considered to be causative agents for late-onset endometritis. Early-onset endometritis which is generally seen within 48 h of cesarean section happens due to the damaged tissue around the suture line with accompanying collection of blood and serum which predisposes to microbial growth.

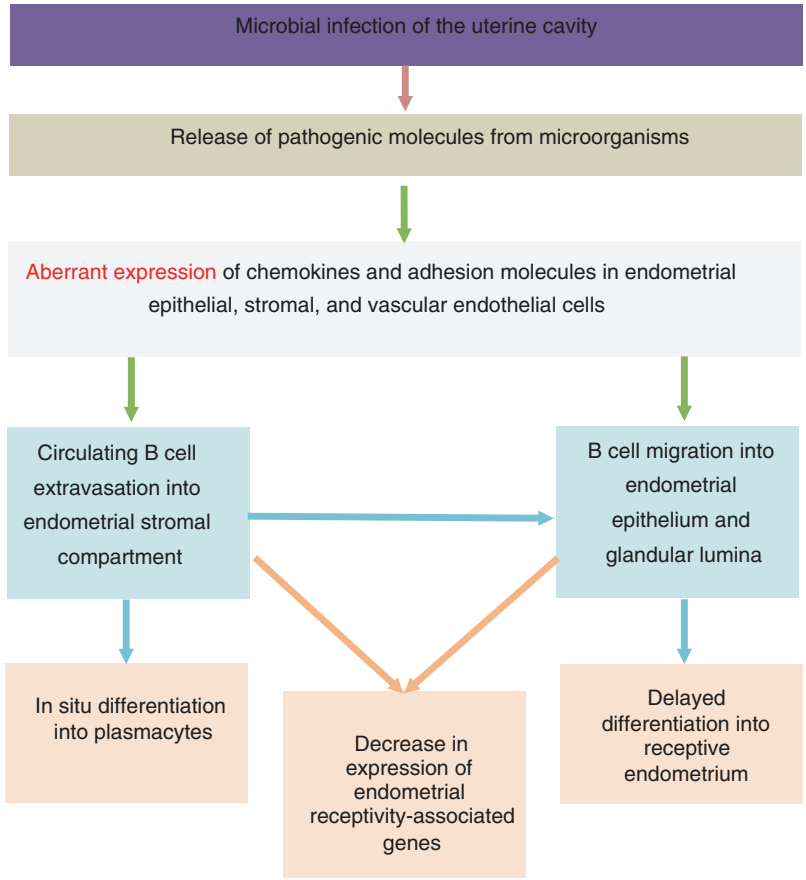

Fig. 33.2 Pathophysiology of endometritis

Introduction of ascending infection into the uterine cavity, can be a result of the breakdown of protective host mechanisms by instrumentation or as a result of immunocompromised state. The protective mechanisms are the cervical mucus plug, the cellular immune system of the endometrial epithelium (macrophages, neutrophils, and the natural killer cells) and innate immunity. The introduction of the pathogens results in aberrant expression of paracrine mediators, chemokines, and adhesion molecules in the endometrium and vascular endothelial cells. The pro-inflammatory cytokines interleukin IL-6, IL-1β, and tumor necrosis factor α are increased out of proportion. There is also overexpression of B cells in the endometrial basal and functional layer. These overpopulated B cells invade the glandular lumina and result in decreased expression of endometrial receptivity-associated genes (Fig. 33.2).

33.5.1 Inflammation in Chronic Endometritis

Endometrial B cells which make up <1% of total leukocyte count in normal endometrium are usually present in the basal layer of the endometrium (the deepest layer of the endometrium). They are seen as central cells in lymphocyte aggregates which are further surrounded by many CD8 T cells and macrophages. The purpose of B cells and lymphocyte aggregates in the human endometrium has

not been elicited yet. In contrast, in chronic endometritis, a large number of B cells invade not only the basal layer but also the functional layer infiltrating the stroma and gland lumina [33].

33.6 Clinical Presentation

Historically, PPE is known as puerperal fever and can be classified as early and late postpartum [30]. Early postpartum refers to PPE which occurs within 24–48 h after delivery and fever occurring after 48 h of delivery is classified as late. Generally, the first sign of endometritis is fever, which can be accompanied with bleeding per vaginum, foul-smelling lochia, or uterine tenderness. Group A Streptococcus infection should be suspected in patients who present with abdominal pain, diarrhea, and severe systemic illness which is disproportionate to the physical findings [30]. If PPE is not managed timely, the infection can further progress to systemic inflammatory response syndrome (SIRS) and full-blown sepsis. The diagnosis is mainly clinical and ultrasonography does not help improve diagnostic accuracy. Testing for Chlamydia trachomatis infection may be helpful in cases of chronic endometritis.

33.7 Diagnosis

Diagnosis of postpartum endometritis is mainly clinical and is suspected in postpartum women with maternal pyrexia and physical signs of endometrial infection. Radiological methods like ultrasound do not help in diagnosis and laboratory evidence is mainly supplementary (raised WBC count; raised lactic acid levels which signify hypoperfusion related to sepsis). Blood cultures detect bacterial infection and are useful in initiating antibiotic treatment in severe form of infections, but the polymicrobial nature of infections limits its use. Hence, even in patients with mild to moderate form of infection or uncomplicated infection, broad-spectrum antibiotic treatment is recommended; the only exception being Group A Streptococcus (GAS) infection, which is sensitive to penicillin. Patients presenting with features of severe systemic illness, diarrhea, and/or abdominal pain which is disproportionate to the physical findings should raise doubt about GAS infection requiring immediate management in view of toxic-shock syndrome (TSS), necrotizing fasciitis, and death. Late postpartum endometritis (beyond 47 days) raises suspicion for chlamydia, besides the usual microbes.

Like postpartum endometritis, infections that occur after abortions are also diagnosed clinically in presence of fever, foul-smelling discharge, uterine tenderness, and retained products of conception seen on ultrasonography at times.

Investigations are helpful in diagnosis and management of endometritis include:

1. *Blood test*—Complete blood count used to look for possible infection or inflammatory conditions.
2. *Cervical cultures*—A swab is taken from the cervix to look for chlamydia, gonorrhea, or other bacteria.
3. *Wet mount*—Cervical discharge may be collected and examined under a microscope.
4. *Endometrial biopsy*— An endometrial biopsy can help in the diagnosis of chronic endometritis. It is an OPD procedure where the cervix is dilated and a small sample of the endometrial lining is collected, which is sent for histopathological analysis to the laboratory.

33.8 Differential Diagnosis of PPE

Other important conditions that cause puerperal fever also need to be considered. The common conditions that can present with similar complaints as PPE include mastitis, UTI, respiratory infections such as pneumonia or atelectasis, intravenous site infection, thrombophlebitis, and wound infection.

33.9 Treatment

A combination of antibiotics like clindamycin (900 mg 8 hourly IV or 600 mg 6 hourly IV) and an aminoglycoside (mostly gentamicin; 5 mg/kg

Table 33.2 Treatment for endometritis

	Parenteral antibiotic regimes	Oral antibiotic regimes
	Clindamycin 900 mg 8 hourly + Gentamicin 5 mg/kg 24 hourly (or Aztreonam) OR Ampicillin 2 g stat followed by I g 4 hourly + Gentamicin 5 mg/kg 24 hourly + Metronidazole 500 mg 8 hourly Alternative treatment with Piperacillin/Tazobactam and Imipenem/Cilastatin is reserved for severe disease	Doxycycline 100 mg BD + Metronidazole 500 mg BD OR Levofloxacin 500 mg daily + Metronidazole 500 g TDS OR Amoxicillin-clavulanic acid 850 mg BD

q24 h or 1.5 mg/kg 8 hourly) has proven to be the most efficacious treatment protocol for postpartum endometritis [34]. Cochrane study published in 2012 including 39 studies, concluded that a combination of clindamycin and gentamycin has better effectiveness than other combination regimens including fluoroquinolones or regimens without coverage for Bacteroides fragilis. No significant increase was seen in treatment failures among those regions which had a high level of Bacteroides fragilis resistance to clindamycin [34]. Gentamicin in a dose of 5 mg/kg once a day is found to be more effective treatment in contrast to its traditional eight hourly treatment protocol [11]. A recent comparison study done between combination treatment with clindamycin and gentamicin (with or without ampicillin) in comparison to ertapenum revealed same treatment outcomes and duration of illness but the cost involved with ertapenum group was high [35]. Parenteral therapy is advised for patients till they are symptom free that is fever subsides for 24 h, there is improvement in pain and the WBC becomes normal. The majority of patients respond well to intravenous antibiotic therapy within 48 h. The patients who fail to respond to therapy are the ones with abdominal wound infection and septic thrombophlebitis. Superinfection with enterococcus is another cause for treatment failure as neither cephalosporins used commonly in C-section nor combination therapy with clindamycin plus gentamicin is effective against enterococcal infection. The combination of clindamycin and aminoglycoside like gentamicin remains the "gold standard" treatment for endometritis. If enterococcal infection is doubted or isolated from the endometrial sample then the addition of a third agent like ampicillin or vancomycin is recommended as this is found to be highly effective (90–97%) [11]. Changing parenteral therapy to oral therapy after fever has resolved and WBC counts have normalized does not reduce the recurrence rates of the disease [30]. In patients with mild disease, aggressive treatment is not required and they can be treated with oral antibiotics. Late endometritis is mostly less severe and manageable as outpatient treatment with oral medications like doxycycline or erythromycin and metronidazole (Table 33.2).

33.10 Reproductive Failure and Chronic Endometritis

A growing body of evidence suggests a correlation between chronic endometritis and infertility. Chronic endometritis has been detected in 28% of infertile patients with unidentified causes, 14–41% of patients with recurrent implantation failure, and 8–28% of patients with recurrent pregnancy loss (RPL) [33]. Patients with chronic endometritis and recurrent implantation failure have significantly reduced rate of implantation after embryo transfer in an IVF cycle after an endometrial biopsy compared with patients suffering from recurrent implantation failure without chronic endometritis. Similarly, untreated chronic endometritis in women with RPL leads to poor live birth rate per pregnancy. In addition, women of reproductive age who have had chronic endometritis are at increased risk (60%) for infertility in comparison with those not suffering from chronic endometritis [36].

Chronic deciduitis characterized by plasma cell infiltration in the basal plate of the placenta has been shown to be associated with obstetric complications like preterm labor (41%) and neonatal periventricular leukomalacia/cerebral palsy (20%) [37–39]. Incidence of chronic deciduitis is often higher in IVF pregnancies using donor eggs (2.8–42%) than the ones with autologous eggs (1.6–1.8%), indicating that chronic deciduitis may represent chronic semi-allograft rejection of the conceptus by the maternal immune system.

33.10.1 Pregnancy Outcome After Antibiotic Treatment for Chronic Endometritis [33]

Few studies recommend the use of oral antibiotics in infertile women with chronic endometritis to improve the outcome of pregnancy. Cicinelli et al. retrospectively analyzed outcomes of pregnancy after antibiotic treatment in women with history of recurrent implantation failure and chronic endometritis [40]. He found that in the subsequent fresh day 3 embryo transfer, the live birth rate was high among the chronic endometritis group that had been cured than the one with persistent infection group (60.9 vs 13.3%). No difference was found in the live birth rate among patients receiving single or multiple courses of antibiotics. In another study done by McQueen et al., the per-pregnancy live birth rate was increased with antibiotic treatment in women with a history of RPL and chronic endometritis (7% before vs. 56% after treatment) [41]; antibiotic treatment also had a significant effect in the frozen embryo transfer cycles. Reproductive outcomes also improved in infertile patients with chronic endometritis due to tuberculosis after receiving antitubercular therapy. Six month treatment with antitubercular drugs, improved the clinical pregnancy rate within 12 months to around 90%. Hence, antibiotic treatment in infertile women with chronic endometritis improves pregnancy outcomes though more prospective trials are required for further verification of these results.

33.11 Prevention of Postpartum Endometritis

33.11.1 WHO Guidelines for Prevention of Postpartum Endometritis

1. There was a remarkable reduction in postpartum endometritis in high-risk pregnant women (women with a history of preterm birth, low birth weight, stillbirth, or early perinatal death) and postpartum detected gonococcal infection in the group receiving antibiotics compared to the placebo group.
2. Rates of maternal infection, including chorioamnionitis and endometritis were significantly lower in women with preterm labor(with intact membranes) who received antibiotics (oral or IV) compared with women who had no routine antibiotic prophylaxis.
3. The risk of post-cesarean endometritis is significantly reduced in women who receive vaginal cleansing with povidone-iodine before C-section though the risk of postpartum fever remains unchanged.
4. Among women with postpartum endometritis, use of a particular antibiotic regimen in comparison to other regimens was analyzed for improving maternal outcomes. Clindamycin plus an aminoglycoside (mostly gentamicin) was reported to show a significant reduction in the rate of treatment failure in comparison with regimens using penicillin and cephalosporins. Other regimens including lincosamides in comparison to monobactams showed no benefit. No difference in treatment failure rate was observed between lincosamides and penicillin after antibiotic prophylaxis for cesarean section.

The following did not alter the rate of PPE:

1. Usage of antibiotic prophylaxis among pregnant women with prelabor rupture of membranes at or near term:Using antibiotic prophylaxis in this group of women did not decrease maternal infectious morbidities like chorioamnionitis, endometritis, or wound infection.

2. Usage of antibiotic prophylaxis in pregnant women with meconium-stained amniotic fluid during labor: The incidence of chorioamnionitis was significantly reduced in the treated group compared with placebo but no difference was observed in the incidence of postpartum endometritis among the groups.
3. Routine vaginal cleansing with antiseptic in labor: Cleaning of vagina with antiseptics in labor does not decrease the incidence of postpartum endometritis and chorioamnionitis.
4. The two regimens of antibiotics using different doses of gentamycin (2 g IV ampicillin six-hourly plus 5 mg/kg (every 24 h) of gentamicin or 2 g IV ampicillin six-hourly plus 80 mg of gentamycin eight-hourly) do not affect the incidence of postpartum endometritis.

33.12 Conclusion

Endometritis is commonly seen after delivery when cervicovaginal organisms gain access to the upper genital tract. Septicemia has been reported in approximately 8–20% of cases of endometritis after cesarean section and around 5% after vaginal delivery. Complications and antibiotic failure are also seen to be higher with abdominal delivery. Mostly the infections are polymicrobial involving both aerobic and anaerobic bacteria, fungal infections and sexually transmitted organisms like Neisseria and chlamydia. So, prevention and timely recognition of infection followed by optimal management are crucial in postpartum women.

Key Points

1. Endometritis is defined as an infection of the upper genital tract including endometrium, myometrium, and surrounding tissue. It occurs commonly after childbirth, when vaginal bacteria gain access to the upper genital tract.
2. Postpartum endometritis is typically a mixed infection which involves both aerobic and anaerobic bacteria, genital mycoplasma, and sexually transmitted organisms like C. trachomatis.
3. Presently there is no universally accepted standard definition or guidelines for diagnosis of chronic endometritis but the presence of multiple endometrial stromal plasma cells is the most specific finding in chronic endometritis.
4. The symptoms of chronic endometritis are non-specific and tend to be ignored by patients in comparison to the symptoms of acute endometritis which presents with fever, pelvic pain, and vaginal discharge.
5. Chronic endometritis is diagnosed in 28% of infertile patients with unknown etiology, 14–41% of patients with recurrent implantation failure, and 8–28% of patients with recurrent pregnancy loss.
6. A combination of antibiotics like clindamycin and an aminoglycoside (mostly gentamicin) has proven to be the most efficacious treatment protocol for postpartum endometritis. If enterococcal infection is doubted or isolated from the endometrial sample, then addition of a third agent like ampicillin or vancomycin is found to be highly effective (90–97%).
7. Reproductive outcomes improve in infertile patients with tuberculosis-induced chronic endometritis after receiving antitubercular therapy.

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Episiotomy Site Infection

34

Anjum Darukshan and Anshul Grover

34.1 Introduction

An episiotomy is an operative procedure involving a guarded incision in the perineum aimed at enlarging the vaginal orifice during the second stage of labor. The primary indication for this easily repairable incision is to facilitate difficult vaginal deliveries and to reduce undue perineal pressure. It was once described as the commonest obstetric surgical procedure performed [1] but now with evidence-based practice, routine episiotomy is not recommended. Episiotomy site infection is an uncommon occurrence in modern-day obstetrics with great emphasis on asepsis. An episiotomy site infection can be defined clinically as the presence of raised temperature, pain at the episiotomy site, erythema, or discharge from the site of incision [2]. The anatomical proximity of the episiotomy site to vaginal, urethral, and intestinal orifices, makes it susceptible to their microbial flora infections. Episiotomy complications like hematoma and wound dehiscence can be important predisposing factors for development of infection. It is an important cause of prolonged hospitalization, re-hospitalization, mental and physical suffering to the puerperal woman [3, 4].

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34.2 Episiotomy—Historical Perspective

The first mention of episiotomy can be traced back to 1742. Sir Feilding Oudh, a midwife, in his book "Treatise of Midwifery in Three parts" recommended this procedure as a measure for enlargement of a tight external vaginal orifice in women in whom it may cause undue prolongation of labor [5]. 110 years later, Taliaferro reported the use of a mediolateral incision in the perineum to facilitate difficult vaginal delivery of a woman with eclampsia [6]. In 1921, DeLee in his publication "The Prophylactic Forceps Operation," proposed the use of mediolateral episiotomy along with forceps application to protect the fetus from neurological injury during labor [7]. In the first half of the nineteenth century, the practice of performing an episiotomy became a routine for all vaginal births in spite of limited data regarding its benefits to the mother and the fetus. It was proposed to reduce the incidence of perineal injury, subsequent sphincter damage, pelvic floor dysfunction, and sexual dysfunction. In addition to these benefits, it was promoted that repair of an episiotomy would result in virginal status of the vagina. Cochrane review of 1980, documented that episiotomies were performed in 60% of vaginal deliveries in the United States [8]. With the advent of evidence-based practice, questioning the above-mentioned benefits and highlighting the associated side effects like sore-

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ness, itching, bleeding, hematoma formation, infection, wound dehiscence, and scarring of perineal body, the practice of universal episiotomy has shifted to restricted and selective use [7]. A Cochrane review of 8 randomized control trials reported that restrictive use of episiotomies resulted in fewer severe perineal trauma, less requirement for suturing, and lesser wound complications [9].

This practice was also endorsed by the American College of Obstetrics and Gynecologists (2016) who have proposed that restricted use of episiotomy is preferable over routine use [10].

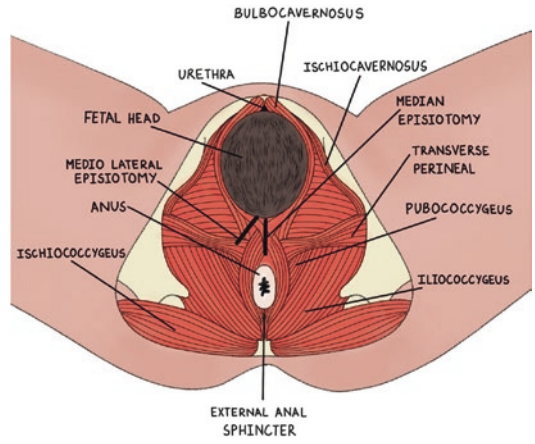

Fig. 34.1 Anatomy of the perineum showing sites of episiotomy

34.3 Relevant Anatomy

The perineum is anatomically described as the area between the external genitalia and the anus. It is a diamond-shaped structure bounded anteriorly by the pubic symphysis, posteriorly by the tip of the coccyx; inferior pubic rami, inferior ischial rami, and sacrotuberous ligament from its lateral boundaries. The perineum is divided into two triangles by an imaginary line drawn between the ischial tuberosities—urogenital and anal triangle. The perineal body is a fibromuscular mass located at the junction of urogenital and anal triangle. It lies deep to the skin. It is the point of attachment of muscle fibers of the pelvic floor and the perineum. The levator ani, bulbospongiosus, superficial and deep perineal muscles, external anal sphincter, and external urethral sphincter muscle fibers are attached to it. The perineal body is an important support of the pelvic floor (Fig. 34.1).

The episiotomy is an incision in the perineum to enlarge the vaginal orifice to facilitate childbirth. The most common types of episiotomies as defined by their location on the perineum are median and mediolateral (Fig. 34.1). The median episiotomy incision is made in the midline from the hymenal ring, through the fibroconnective tissue joining the perineal muscles—bulbocavernosus, superficial transverse perinei, and urogenital diaphragm. The incision does not include the anal sphincter. This incision does not cut the muscles, so causes less hemorrhage. It also protects against vaginal lacerations, repair is easy and patients have less discomfort and dyspareunia. It has the disadvantage of restricted enlargement of the vaginal introitus. Extension of the incision can cause injury to the anal sphincter and anal mucosa. The mediolateral episiotomy begins in the midline and extends at an angle of 60° laterally for 3–4 cm. The structures cut during mediolateral episiotomy are the posterior vaginal wall, superficial and deep perineal muscles, bulbospongiosus, and part of levator ani muscle. The fascia covering the muscles, the transverse perineal branches of the pudendal vessels and nerves and the skin with subcutaneous tissue are also incised. The incision cuts through the muscles, so cause more hemorrhage and subsequent hematoma formation. Repair of the mediolateral episiotomy involves suturing of all the three layers-mucosa of the posterior vaginal wall, perineal muscles and skin with subcutaneous tissue. The mediolateral episiotomy can have vaginal extensions but are protective against rectal involvements.

34.4 Prevention of Episiotomy Infection

Maintaining adequate asepsis, assessment of episiotomy prior to repair, proper repair, and care of wound after repair go a long way in reducing the

chances of infection. The following steps are enlisted for guidance:

- Maintain asepsis—Clean the wound with povidone-iodine antiseptic solution/chlorhexidine gluconate 4% and drape it before starting the repair.
- Evaluate the episiotomy under good light to assess the apex, the depth and to rule out any obstetric-anal sphincter injury.
- Repair is to be performed in minimum of three layers—mucosa, muscle, and skin with rapid absorbing suture such as 2.0 polyglactin910 rapid. In the presence of a deep episiotomy, the muscle may be sutured in multiple layers using the same suture.
- The anchor stitch should be taken 0.5 cm beyond the apex in the posterior vaginal wall to secure the mucosa. This is an important step in reducing bleeding and development of hematoma.
- Ensure that dead space in the muscle is obliterated and complete hemostasis is achieved to prevent hematoma formation.
- Proper alignment of skin edges is required with minimal suture, without stretch at the stitch line to allow proper healing and reduce the pain. Reactionary edema develops in the tissue 24–48 h after repair. Presence of tight sutures can constrict the tissue, decrease the blood supply, delay healing, and cause perineal discomfort.
- The procedure completes with a per-rectal examination to rule out the presence of any inadvertent suture in the rectum which may lead to the development of recto-vaginal fistula.

34.4.1 Care of Episiotomy after Repair

- For pain relief, the patient can be advised ice pack in the first 24 h and a warm bath or sitz bath after 24 h. Appropriate analgesics (Non-steroidal anti-inflammatory drugs) can be prescribed.
- The sanitary pad should be changed every 2–4 h.
- The area in and around the stitches should be kept clean and dry. The puerpera should be explained that she should wash the perineum after micturition and defecation with warm water and then dry the area with a cloth. In this way, she will reduce contamination from surrounding microflora.
- Eating a proper diet with high protein facilitates healing. Drinking plenty of water and intake of high fiber content prevents constipation and undue stress on the stitches. Stool softeners may be used if required.
- Kegels exercises help to regain perineal muscle strength and also increase the blood circulation in the area. This improves healing process of the episiotomy.

34.5 Episiotomy Site Infections

Episiotomy or perineotomy is a clean-cut wound, which is anatomically similar to a second-degree perineal tear. The chances of it getting infected are like any other surgical wound. The infection can arise either from the puerpera's perineal microbial flora or iatrogenic sources like infected medical staff, infected instruments, aseptic surgical techniques, or poor hygienic conditions. Infection at episiotomy site is defined in the same terms as any other perineal wound. It is the presence of purulent discharge (with or without laboratory confirmation), increased pain at the episiotomy site, localized swelling, fever, redness, ecchymoses, episiotomy dehiscence, or abscess [11–15].

34.6 Prevalence

Episiotomy infections are a rare occurrence now, primarily because of less number of episiotomies being performed and also due to maintenance of adequate sepsis during conduct of vaginal birth. There is little information on the exact prevalence of post episiotomy infection.

Pritchard et al. (1985) reported an incidence of 1% in uncomplicated episiotomies [1]. In a Nigerian study, Sule and Shittu (2003) reported a greater prevalence rate of 23%, which may be attributed to the fact that in a large number of vaginal deliveries (88.5%) episiotomies had been performed [16]. Uygur et al. (2004) reported a 1 percent dehiscence rate in episiotomies of which 75% were as a result of infection [17]. Other researchers have reported prevalence between 0.3 and 5% [18–20]. Zhang H (2017) found the incidence of episiotomy dehiscence to be 2. 5%, while Tandon and Dalal (2018), reported a prevalence of 0.8–2% in their study [21, 22]. This variance can be attributed to the difference in the number of episiotomies, the characteristics of women, demographic profile, and preferences and expertise of the caregiver. Episiotomy itself is a significant contributory factor for development of infection. The prevalence also varies according to the presence of various risk factors associated with development of infection.

34.7 Risk Factors

- Episiotomy

  Larsson et al. demonstrated that risk of wound infections was 10% in women with episiotomies as compared to 2% in women with tears($p < 0.001$) [23]. Macleod et al. in a prospective cohort study comparing use of episiotomy with no episiotomy in instrumental delivery, inferred that the presence of an episiotomy is associated with increased risk of infections (5.1 vs. 1.4) [24].
- Proximity to perineum

  The location of the episiotomy incision in the perineum makes it prone to infections [25, 26]. Various studies have reported the prevalence of perineal wound infections between 0.49 and 10.42% [21, 27].
- Body mass index

  A strong correlation has been demonstrated between episiotomy site infection and Body Mass Index (BMI) of more than 28. A higher BMI, would translate into greater body mass or adipose tissue in the ischiorectal space. Excess of adipose tissue is also related to immune system dysregulation, and lowers the cell-mediated immune responses, which predisposes to infection. Zhang et al. reported a 2.2 times increased rate of infection in puerpera with BMI > 28 [21]. Wang et al. also found an association between postoperative infections and increased BMI [28].
- Repeated vaginal examination

  Zhang et al. found that more than 3 vaginal examinations in the intrapartum period and birthing process (active labor) of more than 8 h are associated with increased risk of episiotomy infection by three times and two times, respectively [21]. Johnson et al. also reported a 13% risk in episiotomy infection with multiple vaginal examinations (>4) in active labor. These studies emphasize the need to restrict vaginal examinations and standardization of the birthing process [29].
- Premature rupture of membranes

  Various authors have identified prolonged rupture of membranes as another risk factor for development of infections [21, 29–32].
- Prolonged birth process

  Zhang et al. reported an increase in wound infection rate by 4% (p value 0.025) if the duration of active phase of labor is more than 8 h [21].
- Postoperative hospitalization time >5 days.

  Prolonged hospital stay which is accepted as a risk factor for any surgical infection, is implicated as a risk factor for episiotomies also [21, 33].
- Instrumental delivery

  Lydon-Rochelle et al. (2000) and Kabiru et al. found assisted vaginal delivery as a risk factor for development of surgical wound sepsis [30, 32].
- Dimitrov et al. has reported the use of catgut suture for repair of episiotomy and experience of the surgeons as risk factors for development of infection [31].
- Medical conditions like diabetes and infections like urinary tract infections, reproductive tract infections, and HIV are also documented to be risk factors [14, 34].

34.8 Etiology

Episiotomy site infections are generally polymicrobial. Pathogens implicated in episiotomy-site infections are either skin pathogens (streptococci and staphylococci) or those which form the microflora of the perineal organs—vagina, urethra, and intestine (Gardnerella vaginalis, group B streptococci, Escherichia coli, Pseudomonas aeruginosa) [35, 36]. Bacterial concentrations in the groin, anus, urethra, and vagina can be as high as 104–109 per cm^2 of tissue [37]. Some authors have reported the most common organisms to be streptococci and staphylococci. Zhang et al. during evaluation of episiotomy site infection reported Gram-positive bacteria in 63.04% cases, Gram-negative bacteria in 32.61%, and fungi in 4.35%. The common Gram-negative bacteria found were Pseudomonas aeruginosa, Escherichia coli, Aerobacter cloacae, and Acinetobacter baumannii. The Gram-positive bacteria reported were Staphylococcus aureus, Staphylococcus epidermidis, and Streptococci [21]. In the presence of myonecrosis, a rare entity now, Clostridium perfringens, and C. sordellii can be isolated. Methicillin-resistant Staphylococcus aureus has also been isolated from episiotomy wounds [38].

34.9 Clinical Presentation

Care of episiotomy after delivery is a standardized protocol. Till the puerpera is in the hospital, this is generally taken care of by the midwife or the nursing attendant. Once discharged, the puerpera is guided regarding perineal care but as newborn care and breastfeeding take priority over this, it seems like a neglected issue. Most mothers report back for medical help when the wound has dehisced under the pressure of the pus collection inside. The common presentations include:

- Perineal pain
- Purulent discharge
- Wound dehiscence (Figs. 34.2 and 34.3)
- Feeling feverish/unwell
- Seeking medical help for wound infection

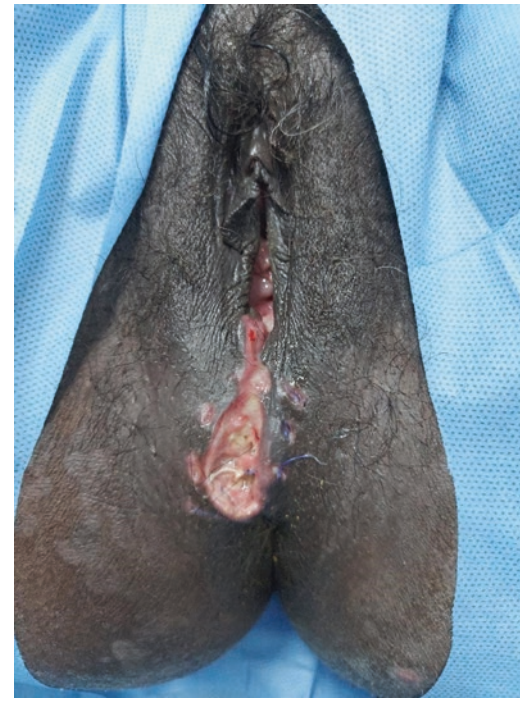

Fig. 34.2 Infected episiotomy with fungal infection of perineum

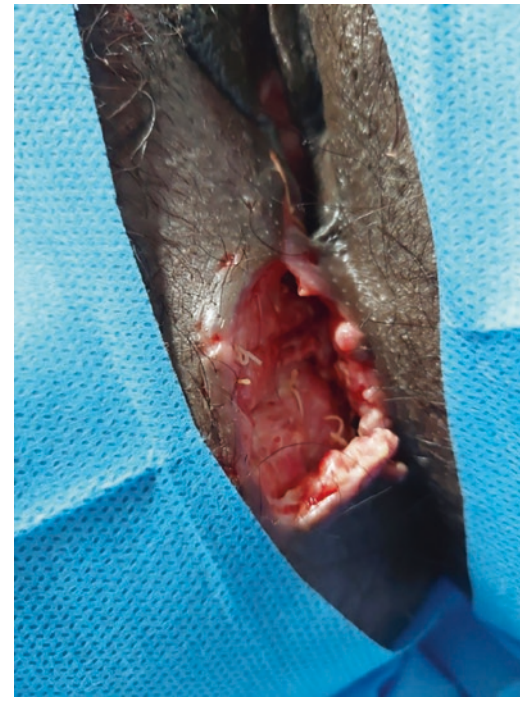

Fig. 34.3 Infected episiotomy wound with breakdown of sutures

Table 34.1 Reeda score

	0	1	2	3
Redness	None	Within 0.25 cm of the incision bilaterally	Within 0.5 cm of the incision bilaterally	Beyond 0.5 cm of the incision bilaterally
Edema	None	Perineal, less than 1 cm from incision	Perineal and/or between 1 and 2 cm from incision	Perineal and/or vulvar and more than 2 cm from incision
Ecchymosis	None	Within 0.25 cm bilaterally or 0.5 cm unilaterally	0.25–1 cm bilaterally or 0.5–2 cm unilaterally	More than 1 cm bilaterally or 2 cm unilaterally
Discharge	None	Serous	Serosanguinous	Purulent
Approximation	Close	Skin separation 3mmor less	Skin and subcutaneous separation	Skin, subcutaneous fat and facial layer separation

Reference: Hill PD. Psychometric properties of the REEDA. J Nurse Midwifery. 1990; 35(3):162–165

The most common reported symptoms are perineal pain, purulent discharge, and wound dehiscence. Hemsel et al. (1994) and Duggal et al. (2008) defined the presence of any two of these symptoms as a criteria for identifying wound infection [13, 39]. Wound dehiscence can either be a cause or a result of wound infection. An open wound due to improper suturing or breaking of sutures under pressure exposes a large surface area to surrounding microflora for genesis of infection. Also, episiotomy wounds may dehisce under pressure of accumulating pus in the presence of infection. Johnson et al. found the prevalence of wound infection similar to that of wound dehiscence (11 and 10%, respectively) [29].

Assessment scores for evaluation of postpartum perineal healing have been developed for ease of the patient as well as the assessor; though they are still not a part of standard protocol.

PAT score: Perineal assessment tool was developed based on 4 factors related to wound breakdown duration of irritant, intensity/type of irritant, perineal skin condition, and contributory factors that may cause perineal skin breakdown like diarrhea. This scoring system is mainly used to assess the development of bedsores. The PAT scoring system is less objective, therefore, the REEDA score is considered more reliable [11].

REEDA Score: This scoring system was developed by Davidson and further reviewed by Carrey [40, 41]. It is a tool that assesses the signs of inflammation and healing of tissue through five signs. These include erythema (redness), edema (edema), ecchymosis, discharge, and co-optation of the wound edges (approximation). Each of which these five signs is given a score of 0–3, with a maximum score of 15, which suggests the worst perineal condition (Table 34.1). This scoring system has been used by researchers to evaluate postpartum perineal care, suture-related pain, various suture techniques, and even the effect of laser irradiation on healing of the episiotomy wound [42–44]. As this scale lacks statistical validation and inter-observer agreement in assessment, it is therefore not included as a standard procedure for perineal assessment [45]. Alvarenga et al. in their study to assess episiotomy wounds using the REEDA score concluded that redness, secretion/discharge, and approximation of wound were the more consistent parameters in assessment correlation with severity of infection. Edema and ecchymosis were found to be unreliable. The scoring system was found to provide a better evaluation of perineal healing when utilized 7–10 days after the delivery [46].

34.10 Differential Diagnosis

- Cellulitis—It is a rapidly spreading bacterial infection involving the dermis and the underlying subcutaneous tissue. The infection usually follows a break in the epithelium—injury or a surgery. Group A streptococcus (GAS) is

the most common organism responsible for cellulitis. The infection rapidly spreads and results in systemic symptoms like fever, limb edema, suppurative arthritis, thrombophlebitis, and even shock. Episiotomy wounds can also develop cellulitis. Patients with serious systemic manifestations, septic shock, or signs of wound infection beyond the immediate episiotomy area must be evaluated for this possibility.

- Necrotizing fasciitis—It is a rapidly spreading bacterial infection of the soft tissue—fascia, muscles, and subcutaneous fat followed by necrosis of the overlying skin. It follows a breach in the epithelium. Signs of necrotizing fasciitis include swelling of the affected area with tense shiny overlying skin, unresponsive high-grade fever, and features of systemic illness. Immunocompromised state is a major risk factor. The condition if untreated can be fatal. Aggressive antibiotic therapy along with radical surgical debridement of infected tissue is required.
- Endometritis—Postpartum endometritis should be differentiated from wound site infection. Both can present as foul-smelling discharge and fever. Endometritis, in addition also presents as lower abdominal pain, irregular bleeding per vaginum, and foul-smelling lochia (confused for discharge). It should be kept in mind that episiotomy site infection can result in ascending infection to the endometrium.

34.11 Management

34.11.1 Evaluation at Admission

- Look for evidence of sepsis—presence of fever, tachycardia, foul-smelling discharge from episiotomy site.
- Evaluate the wound for infected sutures, purulent discharge, hematoma formation, depth of wound, erythema, and tenderness.
- Perform a per-vaginal examination to rule out ascending pelvic infection and to rule out any retained gauze or surgical pad.
- Basic investigations like complete blood count, fasting blood sugar, routine urine examination are performed to identify any infection or comorbid factor like diabetes or underlying urinary infection.
- A culture swab from the wound site is taken, prior to start of antibiotics.

34.11.2 Antibiotic Therapy

A short course of broad-spectrum antibiotics, penicillin-like congeners or cephalosporins which are categorized as category B drugs by the US FDA is used initially to treat the wound infection. The use of these antibiotics is considered safe in pregnancy and breastfeeding. Most patients respond to broad-spectrum antibiotics. If the patient does not respond to the antibiotics by 48 hours, a change of antibiotics according to culture and sensitivity pattern is made.

34.11.3 Pain Relief

Use of non-steroidal anti-inflammatory drugs like Ibuprofen is advised for pain relief and to reduce the inflammatory response. This also facilitates perineal care and debridement which in the presence of infection are painful procedures.

34.11.4 Wound Debridement and Perineal Care

To facilitate healing, wound care should be performed at least twice daily. Depending on the severity of infection the frequency of care can be increased.

- Drainage of pus from the wound by removing loose stitches.
- Debridement of all dead and necrosed tissues.
- Application of local antiseptic (povidone-iodine) at all exposed wound tissue to avoid surrounding microflora contaminating the wound site.

34.11.5 Good Diet and Psychological Support

A good high protein diet is essential for healing infected tissues.

Episiotomy site infection not only causes perineal discomfort but is also associated with emotional trauma faced by the mother due to rehospitalization. The patient should be counseled as this event can precipitate postpartum depression.

34.11.6 Resuturing

Episiotomy wound dehiscence usually heals naturally by secondary intension if left untreated. This approach results in a longer period of morbidity for women. There is emerging evidence that early resuturing of the dehisced wound may result in a better outcome. Resuturing should be performed only when the wound is free of infection to avoid dehiscence. The wound surface will show evidence of granulation tissue once infection has subsided (Fig. 34.4). If there are any signs of infection the wound should not be resutured. This is because it can trap the infection inside, and infected tissues may not stitch back together well.

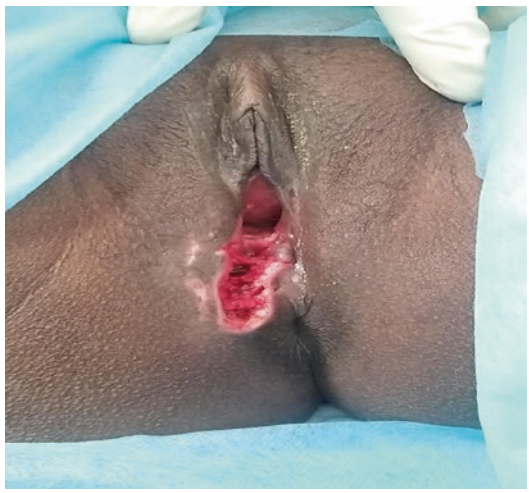

Fig. 34.4 Healing episiotomy with fresh granulation tissue and no signs of infection

34.11.7 Principles of Resuturing

- Preferably to be performed in an operation theater under complete asepsis.
- The wound should be debrided and fibrosed edges should be freshened before resuturing.
- The wound should be stitched in layers in case of a deep wound using polyglactin 2. 0; superficial wounds may be stitched in a single layer only.
- Sutures should approximate well without undue pressure on the skin.

34.11.8 Follow up

Patient should be discharged with advice for strict perineal care. Additional pain relief with non-steroidal anti-inflammatory drugs can be provided as per requirement. Patient is advised a high protein diet. Follow up after 1 week of resuturing to check for integrity of the wound and any reinfection should be done.

34.12 Role of Prophylactic Antibiotics

According to WHO, the worldwide incidence of puerperal infection is 5.7 million cases per year, that is 4.4% of all live births [47]. They can result in considerable perinatal morbidity and mortality. As per data available, puerperal infections account for 15% of maternal deaths in low- and middle-income countries even during the present times [48, 49]. Recent evidence supports selective use of episiotomy, but the practice of performing an episiotomy routinely with vaginal births is still very common in some parts of the world. Like other obstetrical infections, episiotomy site infections are also polymicrobial. General infection control measures like hand washing, disinfecting the surgical site and sterilization of instruments definitely go a long way in reducing surgical site infection [2, 19]. The aim of administering prophylactic antibiotics is that the drug will achieve therapeutic levels well before the probability of development of microbial infection [50]. ACOG 2011 recommends

the use of broad-spectrum antibiotics like ampicillin, cephalosporin with a proven role against the common pathogens implicated. These antibiotics are recommended for use before, during, or immediately after the procedure as a single dose or for less than 24 h, even in the absence of signs of infection [50]. As per recommendations of WHO in 2015, antibiotic prophylaxis is needed for infection-prone obstetrical procedures like cesarean section, manual removal of placenta, and third- or fourth-degree perineal tears [51]. The use of prophylactic antibiotics, in episiotomy which is similar anatomically to a second-degree perineal laceration is not warranted [50–53]. In developed countries, use of prophylactic antibiotics for obstetrical procedures like episiotomy has not been reported [18]. In contrast to this, use of prophylactic antibiotics in majority of the episiotomies performed has been reported in low-income countries [54]. Tharpe et al. had suggested that prophylactic antibiotics might have a role in conditions at higher risk of perineal infections like extension of the incision, midline episiotomy, or operative deliveries but evidence supporting this is lacking [2]. Liabsuetrakul et al.(2014) in a trial including 393 women found insufficient evidence supporting the use of prophylactic antibiotics in operative deliveries [55]. Another study by Buppasiri et al. (2014) did not find evidence to justify the use of routine antibiotic prophylaxis in third- or fourth-degree perineal tears [56]. Indiscriminate use of antibiotics, poses a greater concern regarding development of antibiotic resistance. WHO Global Strategy for Containment of Antimicrobial Resistance (WHO 2001), recommends medically indicated use of antibiotics, after weighing the benefits against the potential harms [57]. Widespread use of antibiotics can cause disruption of the normal microflora, increase the development of antibiotic resistance, can result in allergic reactions and definitely increase the cost of health services (ACOG 2011, Newton 2008, WHO 2014).

Individualization of every case is required for need of episiotomy and for need of antibiotic prophylaxis.

34.13 Recommendations to Reduce Episiotomy Infections.

34.13.1 For Health Professionals—During Intrapartum and Postpartum Period:

- Restrictive use of episiotomy.
- Prompt resuturing of all tears (except first-degree tear without bleeding).
- Use of synthetic suture material.
- Standardized suturing techniques.
- Aseptic suturing procedure.
- Use of prophylactic antibiotics for obstetric anal sphincter damage associated with episiotomy.

34.13.2 For Puerperal Woman:

- Routine review of perineal trauma by the midwife to identify any signs of infection.
- Maternal education.
- Good high protein diet.
- Pelvic floor exercises.

34.14 Conclusion

Episiotomy site infection is now a rare entity due to a lot of emphasis on aseptic techniques and also due to selective use of episiotomy. The infections are generally polymicrobial, arising from common skin pathogens. Presence of risk factors should alert the surgeon to look for signs and symptoms of infection during the postpartum period. Routine use of prophylactic antibiotics is not recommended. Management of this wound infection follows the same principles as any other wound infection, that is, to eliminate the infection before resuturing.

Key Points

- Incidence of episiotomy wound infection ranges from 0.1 to 23.6% and wound dehiscence from 0.21 to 24.6%.
- Episiotomy infections are polymicrobial mainly due to Gram-negative bacteria like E. coli, Enterococci, and Gram-positive bacteria such as Staphylococcus and Streptococcus species.
- Risk factors can be due to maternal conditions like diabetes and anemia and intrapartum factors like repeated vaginal examinations, prolonged second stage of labor, instrumental deliveries, episiotomy extensions, and vaginal hematomas.
- An episiotomy site infection can be defined clinically as the presence of purulent discharge, increased pain, localized swelling, redness, or ecchymoses at the episiotomy site or episiotomy dehiscence.
- REEDA score which is a tool used to assess the signs of inflammation and healing of tissue through five signs has been used by researchers to evaluate postpartum perineal care, suture-related pain, various suture techniques, and even the effect of laser irradiation on healing of the episiotomy wound.
- Management mainly composed of broad-spectrum antibiotics, surgical debridement, and resuturing of the wound.

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Skin and Soft Tissue Infections in Pregnancy

35

Deepti Choudhary and Pankaj Kumar Garg

35.1 Introduction

Infection is a potentially preventable cause of maternal morbidity and mortality as well as fetal and neonatal well-being. Skin and soft tissue infections (SSTIs) represent an important cause of infectious morbidity and mortality in pregnancy. SSTIs comprise diverse pathological conditions involving skin and the underlying subcutaneous tissue, fascia, or muscle varying from simple superficial infection to severe necrotizing infections. SSTIs are common problems worldwide and result from the microbial invasion of the subcutaneous tissue. They are usually of mild to moderate severity and respond to standard treatment; however, they may progress to fulminating sepsis in the presence of the virulent organism, patient-related risk factors, or delay/inappropriate treatment resulting in severe morbidity and mortality.

SSTIs may be categorized as—uncomplicated or complicated—depending upon the severity and associated morbidity and mortality. Uncomplicated SSTIs include superficial infections such as simple abscesses, cellulitis, and mastitis which carry minimal risk for life-threatening complications. They are usually monomicrobial and present with localized infection. The majority of simple infections are caused by Staphylococcus aureus and beta-hemolyticus streptococci. Complicated SSTIs comprise rapidly progressive streptococcal cellulitis, clostridial myonecrosis, and necrotizing fasciitis and are characterized by the involvement of deep soft tissue. They may be either monomicrobial or polymicrobial and may result in systemic inflammatory response syndrome (SIRS) and sepsis. If they are not managed properly, they may lead to limb or life-threatening complications.

The diagnosis of SSTIs is usually clinical which should aim to identify the cause and to assess the severity of infection; however, laboratory and radiological investigations are warranted to confirm the uncertain diagnosis, evaluate the degree of deep infection or sepsis, and evaluate and treat co-morbid conditions. Mild to moderate infections respond to empirical antibiotics, supportive therapy (analgesia, anti-inflammatory, limb elevation, etc.), and correction of co-morbid conditions. In addition to that, complicated SSTIs may require broad-spectrum polymicrobial antibiotics, in-patient treatment, and surgical intervention.

SSTIs are also common during pregnancy and the postpartum period and are usually of mild to

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moderate severity. They may initiate at infected wound sites following surgical procedures or traumatic vaginal deliveries. The true incidence of SSTIs during pregnancy is largely unknown as the majority of the infections are mild to moderate in severity, treated on an outpatient basis, and not recorded. Severe SSTIs, if not promptly diagnosed and treated, may lead to adverse maternal and fetal outcomes.

This chapter is aimed to review the epidemiology, etiopathogenesis, causative micro-organisms, clinical features, and management of SSTIs during pregnancy and the postpartum period.

35.2 Mastitis and Breast Abscess

Mastitis is a common breast condition seen during pregnancy, lactation, and weaning. It is defined as inflammation of the breast which may or may not be related to the infection [1]. It is relatively uncommon during pregnancy but is common in the post-partum period during lactation [2]. Mastitis has thus been classified as Puerperal (lactational) and Non-Puerperal (non-lactational). Lactational mastitis is an important cause of maternal morbidity that not only affects the well-being of the mother but their babies as it may lead to discontinuation of breastfeeding. The majority of the cases of lactational mastitis are infectious and caused by Gram-positive bacteria; non-infectious mastitis is very rare and is related to trauma, allergic, or connective tissue disorders.

Breast abscess usually develops as a complication of bacterial mastitis and is defined as a confined collection of purulent material within the breast parenchyma [3]. The majority of the cases of infectious mastitis respond to antibiotics and do not cause significant maternal morbidity and mortality. Early recognition and timely management of breast infections are essential for optimum treatment outcomes. If the breast infections are not treated promptly or treated partially, they may lead to a breast abscess, necrotizing fasciitis, and sepsis resulting in adverse pregnancy outcomes. Treatment of acute bacterial mastitis includes supportive care, appropriate antibiotics, and percutaneous or surgical drainage in case of breast abscess.

35.2.1 Epidemiology

Breast infections—mastitis and abscess are the commonest breast-related problems in pregnancy and puerperium [4]. An estimate from prospective studies indicates 3% to 20% of lactating women develop mastitis. The incidence of breast infections is maximum within the first few weeks of childbirth and decreases after that. The incidence of lactational, or puerperal, breast abscesses varies from 0.4 to 11% among lactating women. A recent Cochrane review estimated the incidence of lactational mastitis to be as high as 33% [5].

35.2.2 Etiopathogenesis

Lactation-associated mastitis and abscess are related to the milk stasis that provides an optimum environment of lactose-rich culture media for the growth of the bacteria that enter through the terminal ducts of the nipple. While the child suckles the nipple, the bacteria present in the mouth of the child enter the breast through the cracks or fissures present on the nipple surface. Rarely, the infection is hematogenous in origin. The loose parenchymal tissue of lactating breast with milk stasis provides an ideal environment for rapid bacterial dispersion and inflammation of the stromal segment of the breast through milk ducts. Any factor that reduces milk drainage/emptying like infrequent feeding, missed feeding, poor attachment or suckling by infant either due to illness in a baby or improper positioning during feeding, rapid and non-gradual weaning and maternal stress and fatigue may predispose to milk stasis and thus the development of mastitis [6]. Untreated mastitis may result in tissue destruction leading to a breast abscess. Other risk factors for the development of lactational breast abscess are first pregnancy, maternal age over 30 years, and post-dated gestation [7].

There are two types of lactational mastitis-epidemic and endemic mastitis [8].

Epidemic mastitis: Epidemic mastitis occurs early in the postpartum period, usually within 2–3 days. It is usually caused by Staphylococcus aureus. The infection passes from one infant to another in the nursery, and then to a mother. Epidemic mastitis is usually severe and progresses to an abscess.

Endemic mastitis: Endemic mastitis is usually observed after a week of lactation and is caused by Staphylococcus aureus, Staphylococcus epidermis, and Streptococci species. Endemic mastitis is usually benign in clinical course and responds to antibiotics. The risk factors for endemic mastitis are cracked nipples, incomplete breast emptying, and stress.

35.2.3 Microbiology

The primary causative organisms responsible for mastitis and breast abscess are Staphylococcus aureus followed by Streptococci species. Methicillin-resistant staphylococcus is also increasingly being isolated from breast abscesses nowadays. In a study of 46 specimens from breast abscesses, Moazzez A et al. [9] reported that 61% of the samples yielded bacterial growth; 39% were polymicrobial. The common bacteria isolated were S aureus, MRSA, Coagulase-negative Staphylococcus, Pseudomonas aeruginosa, diphtheroids, Proteus mirabilis, and others (22%). Table 35.1 displays the common bacteria causing lactational mastitis.

Table 35.1 Common bacteria causing lactational mastitis

- Aerobic bacteria
  - Staphylococcus aureus
    - Methicillin-resistant
    - Methicillin sensitive
  - Coagulase-negative Staphylococcus aureus
  - Enterobacteriaceae
  - Pseudomonas aeruginosa
  - Proteus mirabilis
  - Others—Streptococcus species, Enterococcus species, Escherichia coli, Citrobacter
- Anaerobic bacteria
  - Propionibacterium
  - Peptostreptococcus
  - Fusobacterium
  - Clostridium

35.2.4 Clinical Features

Lactating women are vulnerable to mastitis and breast abscess within the first few weeks of lactation following the first pregnancy when inexperience and inadequate hygiene leads to cracked nipples and infrequent feeding resulting in milk stasis.

The patient usually presents with a short duration of breast pain, swelling, and redness. There may be constitutional symptoms of fever and malaise. Physical examination reveals a tender breast with overlying redness. A well-defined fluctuant swelling may also be palpable in case of the development of breast abscess; however, a deep-seated breast abscess may not always be palpable. Lactational breast abscesses are usually peripheral in location compared to a non-lactational abscess which is typically found in the periareolar or subareolar region. A breast abscess may also complicate into necrotizing fasciitis depending upon the virulence and host factors (Fig. 35.1).

35.2.5 Investigations

Mastitis or breast abscess is a clinical diagnosis when the patient presents with classical clinical features. Usually, laboratory and other diagnostic investigations are not routinely warranted for mastitis. However, if breast abscess is suspected, ultrasonography is helpful in the identification of the pus collection especially if it is deep-seated. On ultrasonography, an abscess is visualized as a hypoechoic lesion that can be well-circumscribed,

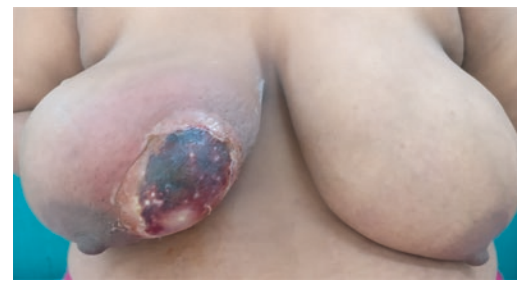

Fig. 35.1 Necrotizing fasciitis of breast in a lactating woman

macro-lobulated, irregular, or ill-defined with possible septa. The presence of a hypoechoic rim may suggest a thick rim of breast abscess. Percutaneous needle aspiration (with/without ultrasound-guided) can be used to drain breast abscess for diagnostic and therapeutic purposes. Aspiration of pus on needle aspiration drainage confirms the diagnosis of breast abscess. Pus must be tested for bacterial culture and sensitivity. A complete blood count and blood cultures should be sent in the presence of suspected systemic infection. Blood sugar should be checked to rule out diabetes mellitus. Breast milk and nipple discharge culture and sensitivity should also be undertaken in all cases of hospital-acquired mastitis, recurrent mastitis, mastitis not responding to antibiotics within 2 days and severe or unusual cases [6].

35.2.6 Management

All patients with mastitis who do not have signs of sepsis should be managed with oral antibiotics, supportive care (analgesia, breast support, warm compresses), and effective milk removal from the affected breast.

The choice of antibiotic in lactational mastitis depends upon the following factors –

- The antibiotic should be excreted and concentrated in breast milk
- The drug should remain active in breast milk (acidic pH)
- The drug should not adversely affect the suckling child.

As the majority of the cases with mastitis and breast abscess are caused by Staphylococcus aureus, beta-lactamase-resistant penicillins should be prescribed as initial empirical antibiotics (dicloxacillin, cloxacillin, or flucloxacillin). The antibiotics are usually given for 7 to 10 days. In a patient with penicillin allergy, erythromycin or clarithromycin may be used. If MRSA is present on culture or prevalent in the local area, the patient should be treated with amoxicillin+clavulanate or clindamycin [1]. Intravenous antibiotics including vancomycin should be considered for MRSA if the patient does not respond to oral antibiotics.

Analgesics are prescribed to reduce pain and inflammation. Ibuprofen is regarded as the most effective and safe in breastfeeding mothers though paracetamol may be prescribed as an alternative. Opioids like tramadol may be avoided as they may have a depressant effect on the newborn.

The patient should be asked to wear a properly fitting brassiere as it reduces the pain by causing relaxation of the stretched cooper's ligaments. Proper breast emptying is an integral part of the management of mastitis. The lactating mother should be encouraged to breastfeed frequently from the affected breast. After feeding, expressing milk manually or pump will help in good breast emptying and hasten healing. Hot compression with a hot pack or hot shower just before feeding can also facilitate milk let down and flow. Massaging of the painful area towards the nipple also helps to drain the breast more effectively. Lactation should be allowed to continue for proper drainage of the ducto-lobular system of the breast. Available literature does not support that there is any risk to the healthy and term newborn if breastfeeding is continued in the presence of mastitis. Drug-induced suppression of lactation is discouraged due to its negative impact on the immune system; furthermore, it can adversely affect the physical and mental development of the suckling baby. Rooming-in of the infant with the mother is encouraged to continue the breastfeeding uninterrupted.

Other supportive measures include adequate rest to the nursing mother, good nutrition and adequate hydration that can help in the healing process. Although most women with mastitis can be treated on an outpatient basis, hospital admission is required if there are features of sepsis, rapidly progressive infection, requiring intravenous antibiotic, immunocompromised state, and presence of an abscess.

If the mastitis progresses to form a breast abscess, it rarely resolves with antibiotics alone and requires drainage. Initially, percutaneous needle aspiration may be used to drain the breast abscess. At times, multiple aspirations may be

required to completely evacuate the abscess cavity. Ultrasound can be used to guide the aspiration if the collection is deep-seated or multiloculated. Percutaneous aspiration of the breast abscess has the potential benefits of better cosmesis, shorter healing time, and avoidance of anesthesia compared to surgical incision and drainage (I&D).

Presently, surgical I&D is contemplated if the abscess is large (>3 cm), the overlying skin of a small abscess is unhealthy (thin and shiny or necrotic), or multiloculated abscess which is unresponsive to repeated aspirations. During I&D, all the loculi must be broken and necrotic tissue needs to be excised. The abscess cavity should be thoroughly irrigated. Image-guided placement of a percutaneous catheter is another option for a large abscess if overlying skin is healthy. Antibiotic therapy should be decided based on pus culture sensitivity if the patient fails to respond to empirical antibiotic therapy.

35.3 Cellulitis and Abscess

Cellulitis is a common problem characterized by diffusely spreading and non-suppurative bacterial infection of the deeper dermis and subcutaneous tissue. The clinical presentation of cellulitis is often confused with other skin diseases like statis dermatitis, allergic/contact dermatitis, and panniculitis. If cellulitis is not treated properly, it can progress to suppuration and collection of pus—a condition known as an abscess. Though it is a common condition, there is no validated data on the true incidence of cellulitis in the pregnant population.

35.3.1 Etiology and Risk Factors

Cellulitis occurs de novo or following a breach in the continuity of skin due to trauma (insect bite, abrasion, penetrating wound, or drug injection), surgery, chronic inflammation (eczema, or radiation therapy), or higher tissue tension due to fluid stasis. Cellulitis is also common in patients with diabetes and weak immune response. Pregnancy is an additional risk factor for the development of cellulitis due to fluid retention as well as diminished immune response resulting from decreased neutrophilic chemotaxis, cell-mediated immunity, and natural killer activity. Infection during pregnancy may complicate to severe form when associated with a co-morbid condition.

35.3.2 Microbiology

Common organisms causing cellulitis are *Staphylococcus aureus* and streptococci. In a study of 179 patients with diffuse cellulitis, 73% of cases were found to be caused by Beta-hemolyticus streptococci [10]. Methicillin-resistant Staphylococcus aureus (MRSA) is being increasingly isolated from patients with cellulitis; it causes liquefaction of the infected tissue resulting in abscess formation.

35.3.3 Clinical Features

Cellulitis starts on broken, swollen, or traumatized skin. Typically, the infection is found on feet and legs but can start anywhere on the body like the arm, eye, breast, and abdomen. Cellulitis usually manifests as a painful and indurated area of subcutaneous tissue [11]. The overlying skin appears erythematous and shiny and is tender and warm. The skin surface may look like an orange peel (Peau'd orange). In contrast to erysipelas, cellulitis does not have distinct borders. The patient may also have systemic manifestations—fever, malaise, generalized weakness, headache, and tachycardia. The patient may also have toxic look depending upon the extent of sepsis. A fluctuant swelling signifies the collection of the pus in the underlying subcutaneous space.

35.3.4 Investigations

Diagnosis of cellulitis or superficial abscess is largely based on clinical assessment (history and physical examination). Needle aspiration and skin biopsy to identify the causative organism by

culture are not required in a typical case of cellulitis. However, laboratory investigations may be warranted in severe complicated cases, patients with any underlying comorbid condition, evidence of sepsis, or evidence of the underlying pathological condition. In the presence of systemic signs of infection, blood culture samples also should be drawn and sent. Radiological investigations may be required to assess the deeper extent of the infection.

35.3.5 Management

Treatment of cellulitis should be promptly started to prevent the spread of the infection. Antibiotics remain the most effective form of treatment in patients with cellulitis. Antibiotics should include empiric coverage against S. aureus and streptococci. Mild cases are treated with semisynthetic penicillin (cloxacillin), first and second-generation oral cephalosporins, erythromycin, or clindamycin. For severe cases, complicated with abscess require intravenous antibiotics as well as incision and drainage (I&D).

35.4 Necrotizing Fasciitis

Necrotizing fasciitis (NF) is an uncommon rapidly progressive life-threatening aggressive variant of a soft tissue infection that spreads quickly along the fascial planes causing widespread necrosis of subcutaneous tissue, superficial fascia, and other adjacent tissue [12]. It is a surgical emergency associated with significant morbidity and mortality. NF in the obstetric population is rare and has an ominous course. It is characterized by rapidly progressing acute onset infection involving the perineum, vulva, lower extremities, and abdominal wall of pregnant and postpartum women.

NF can involve any part of the body; however, it is usually commonly seen in the lower extremities. In obstetrical patients, necrotizing fasciitis usually involves an abdominal incision (post-cesarean section), episiotomy site, or other perineal laceration [13–15]. It is an important cause of postpartum hospitalization and intensive care unit admission. Because of its rarity, to date, necrotizing fasciitis in the obstetrical population is limited to case reports and small case series. In general, the mortality rates for necrotizing fasciitis varied from 6% to 76% in various reports [12].

35.4.1 Etiology and Risk Factors

Necrotizing fasciitis is seen mostly in patients with predisposing factors like advanced age, diabetes mellitus, hypertension, obesity, peripheral vascular disease, malnutrition, immunosuppressive state, trauma, and following surgical procedures [16]. In the majority of cases, NF is caused by a breach in the skin; the hematogenous spread is rarely seen. Pregnancy is an added risk factor because of its immunosuppressive state that may promote the occurrence of severe necrotic STIs. Diabetes mellitus is the most frequent co-morbid condition in patients with necrotizing fasciitis.

35.4.2 Pathogenesis

NF is a severe and potentially fatal infectious disease that rapidly extends from the subcutaneous tissues along the superficial and deep fascia causing vascular occlusion, ischemia, and necrosis of the tissue. Infection usually starts in the subcutaneous tissue and fascia and progresses further. The more superficial layers (dermis and epidermis) are usually spared initially. The infection progresses due to the synergistic action of the bacterial virulence (toxins and enzymes) and host-specific factors (age and co-morbidities) [17]. Bacterial endotoxins play an important role in the etiopathogenesis of the disease by causing the release of cytokines and mediators of rapid tissue destruction [18]. Vascular thrombosis is caused by invasive bacteria resulting in tissue ischemia which is further exacerbated by tissue edema [19]. Furthermore, the formation of an anaerobic environment helps the growth of anaerobic bacteria which can produce gas leading to crepitus. Necrosis of the tissue results due

to the lysis caused by the bacterial enzymes and secondarily to the vascular origin. Tissue ischemia further promotes the proliferation of the bacteria. The skin changes are usually disproportionate to the necrosis of the underlying subcutaneous tissue and fascia. Tissue ischemia and necrosis also explain the intense pain that these patients complain.

35.4.3 Microbiology

Several aerobic and anaerobic pathogens have been incriminated in the pathogenesis of NF. The infection can be either mono-microbial or polymicrobial. Recent studies have classified NF into four types based on the causative organisms involved (Table 35.2).

Type I NF is the most common type accounting for 70–90% of cases. It is a polymicrobial infection caused by the synergistic mixture of aerobic and anaerobic bacteria. It is usually seen in immunocompromised patients or with several comorbidities. It mostly occurs on the trunk and perineum.

Type II NF is usually a monomicrobial infection and caused by Gram-positive organisms. The most frequently isolated bacteria are Group A beta-hemolyticus streptococci (streptococcus pyogenes) and sometimes staph aureus. The infection usually occurs in individuals with no underlying medical condition/comorbidities and mainly involves extremities. The fulminant form may be caused by methicillin-resistant staph aureus (MRSA) and has an unfavorable outcome.

Type III NF is a monomicrobial infection and caused by Clostridium species or Gram-negative organisms including marine-related organisms. Clostridium perfringes is the most common anaerobic bacterium of clostridial species. Infection usually occurs at the site of external injuries (deep wound/crushing injuries or surgical wound. The commonest Gram-negative causes of NF remain Vibrio spp., such as V. damselae and V. vulnificus responsible for marine-related NF.

Type IV NF is very rare and is caused by fungi. It usually affects the immuno-compromised patients or those who have some other underlying pathology. Candida-related NF usually affects immunocompromised patients. Zygomycotic necrotizing infections (Mucor and Rhizopus spp.) affect immunocompetent patients after severe trauma. Fungal invasion is usually observed in traumatic wounds or burns; fungal staining and culture should be seriously deliberated in these patients.

Table 35.2 Microbiological types of necrotizing fasciitis

Type of NF	Organisms involved	Clinical characteristics
Type I	Polymicrobial	Indolent, good prognosis
Type II	Monomicrobial, Gram-positive organisms	Aggressive course, rapid progression, poor prognosis
Type III	Monomicrobial, Clostridium species and Gram-negative organisms (Vibrio spp)	Wounds contaminated with seawater or seafood ingestion.
Type IV	Fungal	Seen in immunocompromised patients or with underlying pathology, poor response to treatment, worst prognosis with high mortality

35.4.4 Clinical Features

Pregnancy-associated necrotizing fasciitis is usually seen in the postpartum period with a history of cesarean section or episiotomy wound. The infection in the postpartum period does not cause symptoms until 3 to 5 days after delivery or cesarean section. The clinical presentation may vary and is often characterized by persistent high-grade fever with chills, signs of systemic toxicity, severe pain in the affected area with local inflammatory skin changes; characteristically the pain is disproportionate to the physical findings. Early local signs are erythema, edema, and tenderness. Initial presentation of NF may

also be misjudged as cellulitis or wound hematoma. As the disease progresses, the overlying inflamed skin develops blebs, hemorrhagic bullae with extensive necrosis and sloughing leaving an ulcer with undermined edges and copious purulent discharge (Fig. 35.1). Sometimes gas formation in the wound can lead to crepitus in overlying skin, indicating anaerobic infection with Clostridium perfringes. In some cases, muscle is also involved causing myofascitis. The patients usually have features of sepsis. Systemic complications due to shock and metabolic abnormalities may occur in more advanced cases. In the absence of prompt treatment, NF rapidly progresses to septic shock, cyanosis, altered consciousness, multi-organ failure, and death.

Necrotizing fasciitis of the pelvis in puerperium may present with a classic triad of severe pelvic pain, unilateral pelvic edema, and features of septicemia.

35.4.5 Investigations

Diagnosis of necrotizing fasciitis is generally based on the clinical history and physical examination supplemented by radiological and laboratory findings.

Blood investigations are usually not specific. As these patients are resuscitated with a large volume of crystalloid fluids, the dilutional effect of these fluids should be kept in mind while interpreting the results of the hematological parameters. Although leucocytosis is a common feature in NF, leucopenia is also not uncommon especially in beta-hemolyticus streptococci associated NF, and is a bad prognostic factor [20]. Intravascular hemolysis should be suspected in the presence of rapidly falling hemoglobin and a stable hematocrit. Thrombocytopenia, deranged kidney function tests, electrolyte disturbances, and elevated C-reactive protein (CRP) are common in severe sepsis and should be monitored. Serum creatinine kinase is also elevated in patients with severe sepsis and MODS. Wong et al. [21] described a Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score as a diagnostic score to differentiate NF from other SSTIs based on six laboratory parameters (Total white cell count, hemoglobin, sodium, glucose, serum creatinine, and C-reactive protein). The minimum score can be zero while the maximum score can be 13 (Table 35.3). The authors highlighted a score of six or more as a strong predictor of NF with a positive predictive value of 92.0% and a negative predictive value of 96.0%.

Table 35.3 Laboratory risk indicators for necrotizing fasciitis

Variable	Score
C-reactive protein (mg/dL)	
<150	0
>150	4
TLC (/cubic mm)	
<15	0
15–25	1
>25	2
Hemoglobin (gm/dl)	
>13.5	0
11–13.5	1
<11	2
Sodium (mmol/l)	
>135	0
<135	2
*Creatinine (μmol/L)	
<141	0
>141	2
**Glucose (mmol/L)	
<10	0
>10	1

*Multiply by 0.01131 to convert to mg/dl
**Multiply by 18.015 to convert to mg/dl

Blood culture should be sent; though the yield is variable in different studies and varies from 11–60% depending upon the type of NF. Pus/toxic fluid can be aspirated percutaneously or collected during surgery in a sterile container and sent for bacterial culture and sensitivity. If it grows bacteria, the antibiotics can be selected based on sensitivity later if the patient does not respond to empirical antibiotic therapy.

Radiological imaging is used as an adjunct and helps in the early diagnosis of NF in equivocal cases. Plain radiography has low sensitivity and specificity and helps in detecting gas formation in the soft tissue strongly indicating infection with clostridial species. CT scan and MRI are more sensitive and specific than plain X-rays

in detecting the extent and severity of swelling and inflammation in the fascia, infective tissue necrosis, and can help guide the need for urgent surgical management.

Tissue biopsy obtained during surgical debridement/fasciotomy must be sent for microbiological and histopathological examination which is the gold standard for confirmation of the diagnosis (lobular and septal panniculitis, and fasciitis) [22]; moreover, an active search must be made to identify the invasive fungal infection which is otherwise missed.

35.4.6 Management

Treatment of NF involves early and aggressive surgical debridement, broad-spectrum antibiotic therapy, and supportive care by a multidisciplinary team of surgeons, emergency physicians, intensivists, and microbiologists.

The patient should be resuscitated with intravenous crystalloids, and vasopressors if required; pain should be adequately controlled with appropriate analgesia. The broad-spectrum intravenous antibiotics should be empirically started to provide coverage of Gram-positive cocci, Gram-negative rods and anaerobic organisms as most cases of NF are polymicrobial infections. Initial treatment usually consists of a combination of penicillinase-resistant penicillins, clindamycin/metronidazole with an aminoglycoside such as gentamicin or third or fourth-generation cephalosporins. Type II NF is treated with antibiotic against S.pyogenes and Staph aureus which coexist with the former. Methicillin-resistant staph aureus is covered by vancomycin, daptomycin, or linezolid. Penicillin and clindamycin are also effective against clostridium species responsible for Type III NF. Thereafter, antibiotics are tapered and changed according to initial blood, wound discharge and tissue culture, and clinical response of the patient. Acute renal failure is common in severe sepsis and creatinine clearance should be considered while deciding the antimicrobial therapy. Antibiotics are continued until the local and systemic infection is controlled and the patient is clinically and hemodynamically stable.

Emergency surgical exploration with debridement remains the mainstay of treatment for NF. The surgical debridement must remove all the necrotic and devitalized tissue to control the source of infection and toxins; removal of the necrosed tissue also improves the blood circulation and penetration of the antibiotics. Debridement of infected necrotic tissue is extended until healthy bleeding tissue is found. Sometimes post-cesarean necrotizing fasciitis may involve deeper pelvic organs like the uterus, adnexa, and uterine incision and thus require exploration of the abdominal cavity. After the initial debridement, daily dressing and evaluation of open surgical wounds are done to check tissue viability. Most of the time patients with NF require additional surgical debridement over several days to control infection. Postoperatively, the patient should be carefully monitored for fluid and electrolyte disturbances and nutritional support in the form of parenteral or enteral feeding. Depending on the extent of the defect the wound may be allowed to heal by secondary intention or a delayed primary closure. Reconstruction of the wound with a skin graft may be required in some cases. Needless to say, prompt and aggressive debridement is the key to optimize treatment outcomes. In the early NF, fasciotomy alone may be sufficient in removing the toxins and improving the perfusion. A retrospective study of 68 patients with the diagnosis of NF highlighted that aggressive surgical debridement was related to a mere 4.2% mortality compared to delayed surgical debridement that resulted in 38% mortality [23].

Hyperbaric oxygen (HBO) which comprises of therapeutic administration of 100% oxygen in high-pressure chambers (above one-atmosphere pressure) to increase the tissue oxygenation is used as an adjunctive treatment modality for NF; however, its role is not clearly defined. Though many case reports and case series have reported the beneficial effect of HBO in reducing NF-associated morbidity and mortality [24–26], well-designed clinical trials are warranted to generate high-level evidence to support or contradict

the therapeutic benefit of HBO [27]. Another adjunctive treatment is intravenous immunoglobulin (IVIG) which has been tried in streptococcal-associated NF. The therapeutic effect of IVIG is related to enhanced phagocytic killing, direct nullification of streptococcal superantigens, and anti-inflammatory effects facilitated through Fc-receptor interaction or soluble immune component [28–30]. The beneficial effects of IVIG in reducing NF-associated morbidity and mortality are reported in observational studies with a small sample size [29, 30].

35.5 Conclusion

Skin and soft tissue infections in pregnancy and puerperium range from mild to a moderate variety of infections including cellulitis, simple abscess, and mastitis to severe degrees of fulminant infections like necrotizing fasciitis. They are the result of an interplay between the clinical factors (duration of illness, severity, mechanisms of injury), microbiologic factors (virulence of the invasive micro-organism and drug susceptibility) and, the host factors (age, co-morbid conditions, metabolic disorders, fetal effects of the drugs, etc). Necrotizing fasciitis is a potentially life-threatening surgical emergency in pregnancy and a high index of suspicion and timely aggressive management can help to prevent the associated severe maternal morbidity and mortality.

Key Points

- Lactational mastitis is an inevitable condition in breastfeeding mothers caused due to faulty nursing techniques leading to milk stasis.
- Optimizing breastfeeding techniques is essential to prevent and treat mastitis.
- Early diagnosis and treatment with supportive therapy and antibiotics in mastitis can prevent the complication of breast abscess.
- Ultrasonography is of great value in the acutely inflamed breast for assessment of breast abscess, so unnecessary surgical intervention can be prevented.
- All breast abscesses should be managed with abscess drainage (percutaneous or open) and empirical antibiotic therapy.
- Cellulitis is a common problem characterized by diffusely spreading and non-suppurative bacterial infection of the deeper dermis and subcutaneous tissue commonly caused by *Staphylococcus aureus* and streptococci.
- Pregnancy is a risk factor for the development of cellulitis due to fluid retention as well as diminished immune response resulting from decreased neutrophilic chemotaxis, cell-mediated immunity, and natural killer activity.
- Successful management of necrotizing fasciitis includes high clinical suspicion for early diagnosis, timely aggressive surgical debridement, the institution of broad-spectrum antibiotics, and intensive supportive care.

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Part IX

Fetal Outcomes of Maternal Infection

Role of Maternal Infection in Miscarriages

36

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36.1 Introduction

Miscarriages are one of the commonest adverse pregnancy outcomes worldwide with an average of 36 miscarriages per year per 1000 women in the age group 15–44 years in developing nations and 27 in the developed nations and are classified as early and late depending upon the period of gestation when they occur [1, 2]. Although in the majority of cases, the effects of a miscarriage on women's health are not so serious but in some cases there can be both physical and mental repercussions. Physical symptoms include pain abdomen and bleeding per vaginum, which can be excessive at times, while mentally the woman can experience feeling of loss and grief. Miscarriage has been linked to post-traumatic stress depression (PTSD) symptoms such as flashbacks, anxiety, depression, which have an enormous effect on the psychology and mental health of the patient [3].

In majority of cases, a spontaneous single miscarriage is usually followed by a successful pregnancy. First-trimester pregnancy loss is termed as early miscarriage/miscarriage and is seen in up to one in five pregnancies. Second-trimester pregnancy loss is called late miscarriage and comprises 1–2% of pregnancies [4]. Excluding other causes, 15% of early miscarriages and 66% of late miscarriages are specifically due to infections and can be prevented by early diagnosis and treatment [5, 6].

36.2 Etiology of Miscarriage

There are many causes for miscarriage, of which the important identifiable causes are:

(a) Chromosomal aberrations
(b) Chemical pregnancy
(c) Placental, uterine and cervical causes
(d) Age of both parents
(e) Racial origin
(f) Psychosocial status of the woman
(g) Extremes of pre-pregnancy BMI
(h) Stressful environment
(i) Use of non-steroidal anti-inflammatory drugs
(j) Smoking
(k) Alcohol consumption,
(l) Numbers of infection
(m) Autoimmune diseases, such as diabetes mellitus or systemic lupus erythematosus

As mentioned earlier in the text 15% of early miscarriages and 66% of late miscarriages are due to infections [5, 6].

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36.3 Bacterial Infections and Miscarriages

36.3.1 Bacterial Vaginosis

During pregnancy, bacterial vaginosis (BV) is a notable risk factor for miscarriage, especially in the first trimester, being responsible for one extra miscarriage for every six pregnant women with bacterial vaginosis. The normal genital tract flora of a healthy woman consists mostly of Lactobacillus species [7]. It is when Lactobacillus species are replaced by other possible genital pathogens, such as group *B streptococci*, *Gardnerella vaginalis*, *Staphylococcus aureus*, *Ureaplasma urealyticum* or *Mycoplasma hominis* (M. hominis) that leads to a condition known as bacterial vaginosis (BV) [8, 9]. Gold standard method to diagnose BV is gram staining of vaginal smear. Clue cells, i.e., epithelial cells covered by adherent gram-negative rods are observed under microscopic examination. It results in a change of vaginal pH from the normal value of 3.8–4.2 up to 7.0. Switching to another sexual partner, not using barrier contraceptives, a recent pregnancy, use of an intrauterine contraceptive device and antibiotics treatment against lactobacillus are most likely the causes of BV [4, 10].

Premature delivery [11–14] and miscarriage [12, 15] have been associated with BV in various studies. In Albania, a retrospective case study was done on 150 women, who presented with infertility, and who had had a miscarriage or medically induced abortion. The study showed the presence of *U. urealyticum* and *M. hominis* in 54.3% and 30.4% of the patients, respectively [14]. Significantly higher prevalence of both pathogens was seen among women with a history of more than one miscarriage (P = 0.02 for both pathogen) and in women with history of single abortion (*U. urealyticum*: P = 0.04 and *M. hominis*: P = 0.02).

Another study from Turkey showed association of BV with abortion. In 101 abortion cases, the presence of Ureaplasma was found in products of conception (chorion, amnion, umbilical cord) in 25% of cases while *M. hominis* and group B streptococci were found to be the second most common pathogens present in11.1% cases, compared to non-infected controls [16]. Absent lactobacilli in vaginal flora was also associated with abortion (less than 25 weeks; OR 4.9; 95% CI 1.4–16.9) [12]. The treatment of infection includes metronidazole.

36.3.2 Brucellosis

Brucella are small, gram-negative, non-motile, non-spore-forming, rod-shaped bacteria. They cause a highly contagious zoonotic disease that infects domestic animals—cattle, dogs, sheep, goat, and pigs. Four species are found to infect humans: *B. abortus*, *B. canis*, *B. melitensis*, and *B. suis*. *B. abortus* mainly affects cattle while *B. melitensis* usually infects goats and sheep. *B. canis* affects dogs and pigs are the main hosts of *B. suis*. Intake of unpasteurized dairy products causes its transmission to humans. Isolation of bacteria from blood samples or serology confirms the infection. A case-control study which evaluated the miscarriage rate in 342 pregnant women with brucellosis compared with 33,936 uninfected women of similar socioeconomic status treated in the same hospital concluded that 24.14% of infected pregnant women aborted as compared to 7.59% of the controls [17]. In areas where brucellosis is endemic in farm animals, studies have documented that the disease is still considered a risk factor for miscarriages, especially in farmworkers.

36.3.3 Listeriosis

Listeriosis is a foodborne disease caused by a gram-positive bacterium *Listeria monocytogenes*. It usually infects people in the extremes of the age, i.e., newborns and elderly, immunosuppressed patients and pregnant women. Pregnant women are more susceptible to this infection and contribute to about one-fourth of all listeria infections worldwide. The bacteria are transmitted to humans by eating contaminated food like unpasteurized dairy products, contaminated vegetables, raw or reheated meats. This condition presents with flu-like symptoms such as raised body tem-

perature, weakness, and muscle aches. Listeriosis can be diagnosed by obtaining cultures from amniotic fluid, blood, or cerebrospinal fluid. Listeria infection in pregnant women can lead to miscarriage, premature birth or newborn affection, such as neonatal sepsis and meningitis [18]. Nucleic acids and antigens of *Listeria monocytogenes* are found in the placenta, fetal stomach contents or uterine discharges after a miscarriage [19]. High dose of Intravenous (IV) ampicillin (6–12 grams/day) for 14 days is the recommended treatment of choice.

36.3.4 Syphilis

Syphilis is bacterial infection caused by Treponema pallidum. The route of transmission is predominantly via sexual contact, vertical transmission from mother to fetus or by contact with the blood of an infected person. Congenital syphilis infection to the fetus can lead to miscarriages, stillbirth, prematurity, low birth weight babies or congenital infection of the neonate. The diagnosis is made by direct visualization of the treponeme on dark field microscopy or by antigen-antibody tests. Universal screening for syphilis is recommended for all pregnant women at the first antenatal visit. Penicillin is the treatment of choice for syphilis in pregnancy. A study conducted on Brazilian women concluded that syphilis is a risk factor associated with poor pregnancy outcomes. Testing done using a multiple regression model found a significant association between syphilis and history of miscarriage (OR 3.31; CI 2.20–4.99; $P < 0.0001$) [18]. A Chinese study concluded that when screening program was done aiming to prevent mother-to-child syphilis transmission, the adverse pregnancy outcomes, including miscarriage, were reduced from 27.3% in 2003 to 8.2% in 2011 [20].

36.3.5 *Coxiella burnetii*

Q fever caused by a bacterium *Coxiella burnetii* is transmitted to humans via inhalation of infectious aerosols from animal fluids. The disease is commonly seen in people who come in close contact with livestock. The infection is usually asymptomatic in most of the cases in adults, but when present, symptoms are very unspecific combined with pneumonia or hepatitis. Confirmation of the disease is done via PCR on blood sample. As per a recent report by the Centers for Disease Control and Prevention (CDC), Q fever infection is associated with adverse pregnancy outcomes [21]. But two studies conducted in 2012 and 2013 in Denmark could not find any association of *C. burnetii* with miscarriage [22]. Further studies are required to make a conclusive statement regarding the association. Treatment for the infection includes doxycycline.

36.3.6 *Mycoplasma genitalium*

Mycoplasma genitalium is a sexually transmitted disease caused by a small bacteria which inhabits the skin of the urethra and the external genitalia. It has been implicated as a cause of urethritis in both men and women, cervicitis and pelvic inflammatory disease in females. Increased association and transmission are seen with human immunodeficiency virus (HIV) infection. This infection is diagnosed via PCR on urine samples. So far there is only one published case-control study of this infection, from the USA on 392 women with miscarriage (upto 22 weeks of gestation) and 802 healthy pregnant controls. In 5.9% of cases *M. genitalia* was found, but there was no significant association between this infection and miscarriage [23]. Treatment for infection includes azithromycin and doxycycline.

36.3.7 *Chlamydia trachomatis*

Chlamydia trachomatis is an obligate intracellular gram-negative bacterium. It is classified into three human biovars: serovars Ab, B, Ba, or C, which cause trachoma; D–K, which cause urethritis, pelvic inflammatory disease, ectopic pregnancy, neonatal pneumonia, and conjunctivitis; and L1, L2, and L3, which cause lymphogranu-

loma venereum. It is one of the most common sexually transmitted bacterial disease worldwide. The infection is often asymptomatic in women. If left untreated, the infection is a risk factor for ectopic pregnancy and preterm birth. Diagnosis is carried out by PCR on vaginal swab samples. A case-control study published in 2011 reported a positive association between *C.trachomatis* and miscarriage [23]. IgG antibodies against the bacteria were significantly raised in the miscarriage group (15.2%) as compared to the controls (7.3%); P = 0.018). The microorganism was detected using PCR in 4.0% of the placenta from the cases with the infection as compared to 0.7% of controls (P = 0.026). In a Serbian study, 21.3% of 54 miscarriage cases were found to have persistent C. trachomatis infection. This association was established by sera levels of IgA against C. trachomatis major outer membrane protein [24]. A few contradicting studies have also been published which document conflicting evidence regarding the role of C. trachomatis in miscarriage [25]. Treatment for the infection includes tetracyclines, azithromycin, or erythromycin.

36.4 Viral Infections Implicated in Miscarriage

36.4.1 Cytomegalovirus

Cytomegalovirus (CMV) is a DNA virus belonging to the herpes virus family, Herpesviridae, with humans and monkeys as their natural hosts. The route of transmission of the virus is by contact with body fluids—blood, saliva, cervical mucus, breast milk, and genital secretions. It can also spread via blood transfusion and organ transplant. The clinical presentation ranges from asymptomatic to flu-like symptoms. These include fever, sore throat, myalgia, and swollen glands. It is associated with significant increased risk of miscarriage. In vitro studies have shown that CMV infects the placenta, multiplies in trophoblasts, initiating a cascade of reactions leading to placental dysfunction. This is postulated to be the cause of miscarriage.

36.4.2 Flavivirus

Flavivirus is a single-stranded positive RNA viruses of the Flaviviridae genus. There are four distinct serotypes—DENV-1, DENV-2, DENV-3, DENV-4, all capable of causing an illness called dengue fever. It is transmitted via bite of female mosquitoes, mainly of the species *Aedes aegypti*. Symptoms include rash, high-grade fever, headache, muscle, and joint pain. Severe infection is characterized by bleeding and shock, which can be life threatening. Diagnosis is made by direct DNA detection by PCR or antibody detection in serum by ELISA. A prospective study from Malaysia reported a notable association of recent dengue fever infection with miscarriage (5.3% in cases versus 1.7% in controls, adjusted OR 4.2, 95% CI 1.2–14, P = 0.023) [26]. But a systematic review of 30 studies concluded that it is unclear whether dengue fever is associated with adverse pregnancy outcomes [27]. However, relying on recent evidences, dengue fever appears to be a potential risk factor for miscarriage.

36.4.3 Human Immunodeficiency Virus

Human immunodeficiency virus (HIV) is a retrovirus. It is transmitted via contaminated blood transfusion, via sharing of needle, syringes, or other drug injection equipment and unprotected sexual intercourse or contaminated blood transfusion. The virus causes severe damage to the immune system of the infected person and eventually destroys it by using the DNA of CD4+ T lymphocytes, macrophages, and dendritic cells to replicate itself. It has been found that HIV infection has negative impact on pregnancy, but with the use of anti-retroviral treatment risk of adverse outcomes has been reduced [28, 29]. Moreover, HIV/AIDS (acquired immune deficiency syndrome) has been associated with BV and its association with adverse pregnancy outcomes is well established. The presence of multiple diseases could further compromise the pregnancy.

36.4.4 Rubella

Rubella belongs to the rubivirus family belonging to Matonaviridae genus. Rubella is an acute contagious disease affecting children and young adults. It causes mild symptoms like fever, rash, sore throat, nausea, and conjunctivitis. If contracted during the early weeks of pregnancy, it can result in miscarriage and serious fetal malformations [30]. According to latest WHO progress report, Rubella vaccine has been benchmark in reducing significant number of new cases [31].

36.4.5 Human Papillomavirus

Human papillomaviruses (HPV) is a group of more than 200 related viruses, of which more than 40 are directly sexually transmitted. Among these, many HPV types cause certain type of cancer like carcinoma of cervix, anal, oropharyngeal, penile, vulval, and vaginal. Untreated infection with high-risk types of HPV 16/18 specifically causes cervical cancer, and two viruses (HPV 6/11) cause genital warts. The studies on HPV infection causing miscarriage are contradictory. Studies by [32] Yang et al., 2013 and [33] Skoczyńskiet al., 2011 suggest that HPV infection has no negative impact on pregnancy outcomes. On the contrary, study done in Italy in 2011 study showed notable association between male partner HPV infection with miscarriage rate (66.7% in HPV infected couples versus 15% of controls with no HPV infection, $P < 0.01$) [34]. This study also reported that all pregnancies where both the partners were infected resulted in miscarriage. More well-planned studies need to be accomplished to understand the role of HPV infection in women as well as in both partners as a risk factor for miscarriage.

36.4.6 Herpes Simplex Virus

The Herpes simplex viruses are DNA viruses that are characterized by their ability to remain latent in the host and reactivate later. Two members of this family, HSV-1 (HHV1) and HSV-2 (HHV-2), establish latency in neuronal cells and, on reactivation, cause herpes genitalis or labialis. In most of the cases, HSV-1 causes sores around the mouth and lips, fever, blisters, or cold sores but it can also cause genital herpes. HSV-2 causes genital herpes, which usually present as sores around the genitals or rectum. The presence of the infection is confirmed by using PCR in sera samples. In a study done in Greece in 2009, DNA of HSV1 and/or HSV2 were detected in 43.5% of 95 frozen trophoblastic tissue samples from women who had miscarriage compared with 16.7% of women undergoing elective miscarriage ($n = 35$, $P = 0.03$, Fisher's exact test) [35]. The result concluded that HSV is capable of causing early miscarriage, though no differentiation was made between the two types of HSV. Similar results were interpreted in a study done in Korea in 2012 [36]. More studies and researches need to be done to accomplish convincing relationship between HSV1 and HSV2 with miscarriage.

36.4.7 Parvovirus B19

Parvovirus belongs to genus Erythroparvovirus. It causes a highly contagious childhood ailment with a distinct face rash, termed as "Slapped cheek syndrome." It spreads mainly through respiratory secretions such as saliva, sputum, or nasal mucosa and also through blood or blood products. Parvovirus B19 infection in pregnancy usually affects a small percentage of women who do not have antibodies against B19V, and it might cause a range of complications, including miscarriage, non-immune hydrops fetalis, fetal anemia, and fetal death. A study by Watt AP et al. in 2013 [37] reported a fetal loss in infected women with confirmed presence of the virus in aborted fetuses. In another study in 2011on 72 pregnant women with B19V infection, it was observed that if infection occurs prior to 20 weeks of gestation, the likelihood of vertical transmission is immense [38]. Brkic S et al., in a study (2011), reported a higher percentage of anti B19 IgM antibodies in women with pregnancy losses (22.72%, $n = 88$)

compared with 4.5% observed in 88 control healthy pregnant women [39]. But, surprisingly, anti B19V IgG antibodies were found to be higher in controls (70.5 and 53.4% respectively, $P = 0.046$). The pregnancy losses included miscarriage, non-immune hydrops fetalis and intrauterine fetal death, and this was the limiting factor in the study, and the relation between miscarriage and B19V could not be established properly. A Nigerian study done in 2011 reported prevalence of B19V in pregnant women was 40.7%. The study had appreciable levels of either IgG or IgM antibodies found in 111 out of 273 women under study. Nevertheless, these cases did not have a history of miscarriage [40]. Further studies are required to be carried to establish the correlation between B19V and miscarriage.

36.4.8 BK Virus

BK virus also known as Polyomavirus hominis 1, is a member of polyomavirus family. The mode of transmission is not defined, but it has been suggested that this virus may be transmitted through respiratory fluids or urine, since infected person periodically excretes the virus in the urine. Most of the times, the infection is asymptomatic, with the exception in immunocompromised persons. The infection is diagnosed by PCR on sera samples, urine cytology and viral immunostaining. Recently, a few studies have evaluated the potential role of BK virus infection on adverse pregnancy outcomes. A study done in 2011 on patients with infection of the placental villi associated with pregnancy loss detected no BK virus in the placenta from cases with miscarriage [41]. An Italian study in 2010 showed the presence of BK virus in fetal tissues from five aborted fetuses with chorioamnionitis and miscarriages due to chromosomal abnormalities (controls) [42]. This justified vertical transmission of the virus, but since the gestational ages were not matched and numbers of cases were small, the role of BK infection in miscarriage could not be established. More investigations are required to establish the association between BK virus and miscarriage.

36.4.9 Hepatitis B Virus and Hepatitis C Virus

Hepatitis B virus(HBV) is a partially double-stranded DNA virus, a member of the Hepadnavirus family and the Hepatitis C virus (HCV) is single-stranded RNA viruses, a member of the Flaviviridae genus. Both viruses are found in body fluids and both can cause liver inflammation. In the majority of adults, HepB is often self-limiting but in chronic infection the persistent viral replication in hepatocytes leads to immune-mediated hepatic damage. HCV infection leads to chronic hepatitis in majority of individuals. HBV is detected by the presence of surface antigen HBsAg in sera, and HCV is detected by presence of anti-HCV antibody. In a case-control study conducted in China, 75 assisted reproduction treatment received couples were studied. Study group consisted of one partner diagnosed with chronic HBV infection and in the control group both parents were seronegative for HBV [43]. Study group had an early miscarriage rate of 44% as compared with 9.1% in the control group ($P = 0.043$, Fisher's exact test). Miscarriage rates were higher (60%) when mothers were seropositive, and fathers were seronegative ($P = 0.03$). HBV DNA was detected in 6/62 fetal tissues from the case group, whereas no HBV DNA was detected in control group. These results put forward a positive association between chronic HBV infection in miscarriage. On contrary, a cross-sectional study from Yemen examined the association of miscarriage with HBV and HCV infection in pregnant women, concluded no association of the infections with miscarriage [44].

36.4.10 Covid 19 Virus

Severe acute respiratory syndrome coronavirus 2 (SARS- COV-2) infections are caused by a group of RNA viruses called coronaviruses. Due to paucity of data, no direct association has been established between maternal (SARS-CoV-2) infection during the first or second trimester of pregnancy and miscarriage. In a case report of miscarriage in a SARS-COV-2 positive woman with 19 weeks

pregnancy, the specimen of placental submembrane and placental cotyledon showed positive findings for SARS-COV-2 and negative results for other pathogens [45]. A few studies reported that the increased deposition of perivillous fibrin and the presence of multiple villous infarcts were found in the placenta of COVID-19 positive pregnant women. The infection may also result in placental deficiency and blockage of the transportation of nutrients to the fetus and can catalyze the process of preterm delivery, intrauterine growth restriction and miscarriage [46].

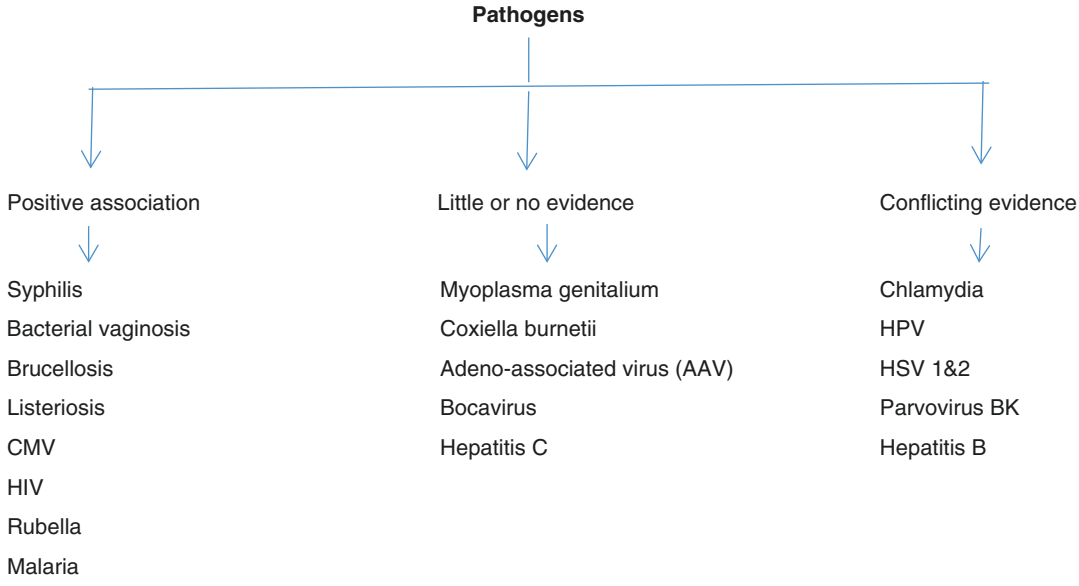
Various Pathogens Implicated in Causing Miscarriage and Their Sites of Detection [47]:

1. Fetus/placenta—Adeno-associated virus, Bacterial vaginosis, Bocavirus, *Chlamydia trachomatis*, Dengue fever
2. Vagina/cervix—Adeno-associated virus, Bacterial vaginosis
3. Maternal blood/urine—Bocavirus, Brucellosis, *Chlamydia trachomatis*, *Coxiella burnetii*, Cytomegalovirus, Dengue fever
4. Paternal semen sample—Adeno-associated virus. (Fig. 36.1)

36.5 Protozoal Infections

36.5.1 Malaria

Malaria is a febrile illness caused by the protozoa of the genus Plasmodium. Five species of Plasmodium (*P.falciparum*, *P.vivax, P. malariae*, *P.ovale*, *P.knowlesi*) can infect humans. The infection is transmitted by the bite of infected mosquitoes. It is endemic in many developing countries and exhibits as fever, chills, and flu-like illness. Diagnosis is made by identifying malaria parasites on microscopic examination of patients' peripheral blood smear samples. Depending on the species of the causative plasmodium, the disease is treated with different antimalarial drugs. Malaria in pregnancy results in the aggregation of erythrocytes infected by Plasmodium which can adhere to chondroitin sulphate A (CSA) on placental proteo-



*CMV-Cytomegalovirus, HIV- Human immune deficiency virus, AAV- Adeno associated virus, HPV- Human papilloma virus, HSV 1&2- Herpes simplex virus 1&2

Fig. 36.1 Infections associated with miscarriage [47]. Source: Sevi Giakoumelou, Nick Wheelhouse, Kate Cuschieri, Gary Entrican, Sarah E M Howie, Andrew W Horne. The role of infection in miscarriage. Hum Reprod Update 2016; 22 [1]: 116–133

glycans causing accumulation in the intervillous spaces which in turn results in blockage of crucial flow of nutrients from mother to embryo. Severity of the disease decreases with successive pregnancies, as immunity develops against the parasites which target the placenta. In a study conducted in Thailand on 3527 women with miscarriage and 14,087 women who gave birth to live newborns, it was observed that women who had malaria before 14 weeks of gestation, whether asymptomatic and symptomatic, were at a higher risk of miscarriage (adjusted OR 2.70, 95% CI 2.04–3.59 and 3.99, 95% CI 3.10–5.13, respectively). The risk ratios were same for both *P. falciparum* and *P. vivax* [48]. A study conducted in Uganda on 1218 pregnant women with malaria, no obvious association of malaria with adverse pregnancy outcome was found. The study did find a correlation between malaria and HIV [49].

Preventive measures, screening, and appropriate treatment must be taken to reduce the risk of malaria in pregnant women so as to decrease the associated rates of miscarriage.

36.5.2 Toxoplasmosis

Toxoplasmosis is caused by the parasite *Toxoplasma gondii* whose vertical transmission is well established. A cross-sectional study done in Mexico in the year 2014 reported that 6.7% of 326 women who had miscarriage were exposed and infected with *T.gondii* [50]. As per the report of a surveillance program carried out in England and Wales from 2008 and 2012, miscarriage or stillbirth was reported as a complication in 28 out of 190 antenatal women with toxoplasmosis [51]. A research study which tested serum of 100 cases of miscarriage, 86% of which were within 12 weeks of gestation, 55% of cases were seropositive for IgG against *T. gondii* [52]. The drawback of this study was that comparison with seronegative cases was not conducted. A meta-analysis of multiple Mexican studies also inferred that *T.gondii* infection rates were higher in women with miscarriage [53]. Seeing the notable worldwide prevalence of toxoplasmosis, screening must be done in pregnant women for the infection as it is identified as one of the major risk factors for adverse pregnancy outcomes.

36.6 Etiopathogenesis of Infections Leading to Miscarriage

During pregnancy, the immune system is remodeled to prevent rejection of fetal allograft carrying paternal antigen as foreign body. The fine balance between rejection and tolerance can be disrupted by any infection and the cascade of inflammatory changes can cause fetal rejection. Any disruption in the balanced maternofetal interaction can result in adverse pregnancy outcomes. Implantation at places other than the usual upper and posterior wall of the uterus, defective placentation or defective blood vessel transformation and disruption of immune balance are assumed to result in miscarriage.

Active infections can disrupt the balance of maternofetal interactions via an unknown mechanism that subsequently can lead to miscarriage. Each microorganism has its own mechanism by which it infects humans, crosses the placental barrier and triggers a series of circumstances that disrupt this interface. Only few mechanisms out of many have been identified till date. Most of the studies are done on animal and data from human studies are minimal.

Plasmodium falciparum crosses the placental barrier and infects trophoblast cells directly.

Listeria monocytogenes crosses the intestinal barrier to enter into the maternal circulation by using its bacterial surface proteins, internalin A and B and finally reach the placenta. There it infects and infests the trophoblast cells causing miscarriage.

The presence of CMV and AAV have been found in fetal tissues from women who had miscarriage [1]. The usual target cells of cytomegalovirus are epithelial cells, stromal cells and macrophages. But it has also been found that CMVs infect and multiply in trophoblast cells which results in a cascade of inflammatory events and also activates tumor necrosis factor alpha; both the processes cause cell destruction. It has been shown in the mouse model that TNF-α, which is usually expressed

in low levels in the placenta, activates Natural Killer cells, macrophages, and Th1-type cytokines causing increased fetal resorption. It also decreases the levels of implantation-associated matrix metalloproteinases 2 and 9 (MMP2 and MMP9) during the formation phase of primary villi in women infected with CMV, which in turn results in defective invasive capability of blood vessels. These findings establish that CMV infection can cause placental dysfunction and miscarriage [1, 5].

Bacterial infections lead to miscarriages by activating the innate immune system. Lipopolysaccharides (LPS) present in the cell wall of bacteria stimulate nitric oxide synthesis and prostaglandins synthesis, which are known to cause cell apoptosis and are associated with embryonic resorption. The effect can be reversed by inhibiting this pathway [1]. Another study on mouse models showed bacterial LPS causes poor uterine receptivity and implantation failure [5].

Above mentioned are only few elucidated mechanisms out of many unknown, by which pathogens can cause miscarriages.

Further research is required to develop association between infections and risk of miscarriage and understand the causes of pregnancy failure.

36.7 Conclusion

Infections, both systemic and local are an important cause of miscarriages. Fifteen percent of early and 66% of late miscarriages can be prevented by appropriate treatment of infections. Maternal infection causes abnormal implantation, faulty placentation or blood vessel transformation and disruption in immune balance, which subsequently results in miscarriage. Role of certain infections like Bacterial vaginosis, Brucellosis, Listeriosis, Syphilis, CMV and Toxoplasmosis has proven to cause miscarriages, while the associations of other infections like Chlamydia, HPV herpes simplex and parvovirus B19 is postulated and under research.

Key Points

- Fifteen percent first-trimester miscarriage and 66% second-trimester miscarriages are due to preventable infections.
- Bacterial vaginosis infection in the first trimester has a well-established association with early miscarriage.
- Brucellosis in humans is transmitted via the consumption of unpasteurized dairy products from infected livestock. It is a risk factor for miscarriage in area endemic for brucellosis.
- Syphilis, transmitted through unprotected sexual act, is also well associated with miscarriages.
- Viral infections which have been found to be associated with miscarriage include cytomegalovirus, flavivirus (Dengue fever), HIV, and rubella**.**
- Maternal infection causes abnormal implantation, placentation or blood vessel transformation and disruption in immune balance, which subsequently results in miscarriage.

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Infections and Preterm Labor

37

Krupa Shah

37.1 Introduction

Infection and inflammation have a critical role in the genesis of preterm labor and birth. Preterm labor (PTL) is defined as progressive cervical dilation and effacement resulting from uterine contractions before 37 completed weeks (259 days) of gestation but after 20 weeks leading to a birth of live fetus [1]. The definition varies depending on the age of viability across the countries, and so does the incidence. The lower limit of gestational age is 24 weeks, according to NICE guidelines [2]. The chances of survival of a fetus is exceedingly rare before 24 weeks and rare between 24 and 26 weeks, so currently, the age of viability is 26 weeks [3]**.** The age of viability also depends on the availability of neonatal care facilities in that country. The viability and maturity of a fetus are different as most preterm (PT) fetuses are viable but face the problem of immaturity. The delivery between 20 and 25+6 weeks of gestation is referred to as pre-viable births [4].

Every year, on a global note, nearly 15 million babies are born as preterm. The rate of preterm birth is in range of 5–18%; 9% for high-income countries and 12% for low-income countries [5]. India, China, and Nigeria are the top three countries facing maximum problem of preterm births. The preterm (PT) can be subdivided into moderate and late preterm (>32 weeks), early preterm (28–32 weeks) and very early/extreme preterms (<28 weeks) [6].

Preterm birth (PTB) has multiple immediate and future health challenges. The immaturity of lungs, infections and neurological consequences are the most commonly faced problems. It accounts for most of the infant deaths and nearly 20% for death among children under 5 years [6]. Hence, it is critical to identify risk and triggering factors for preterm delivery and to intervene timely. It is essential to prevent complications and to ensure survival without a disability. Such an intervention helps to reduce the global burden and cost arising from PTB.

The reasons for PTL are heterogeneous; Almost 50% are idiopathic. The most clearly identified etiology is infections, accounting for 30–40% of total PT birth. The preterm premature rupture of membrane (pPROM) accounts for 25–30% of PTB. In the genesis of PTB and pPROM, sterile inflammation and chorioamnionitis are important. The earlier is the onset of labor, the more likely is the presence of an infection and it is estimated that nearly 80% of extreme PTB are due to infection [7]. This chapter will focus on infection and inflammatory conditions resulting in PTB.

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37.2 Risk Factors for Infection

Any infection during pregnancy is a risk factor for PT labor. Poverty, social inequality, low education, poor hygiene (perineal importantly), immunocompromised status, extremes of age, bleeding in any of the trimester, poor nutrition and anemia, smoking, unsafe sex, uncontrolled diabetes, premature effacement and dilation of cervix, etc. are directly or indirectly associated with infection [8]. The list is not comprehensive and multiple other factors can increase the likelihood of infection like short cervix (<2.5 cm) and vaginal colonization with Group B Streptococcus (GBS), trichomonas vaginalis (TV) and bacterial vaginosis(BV) are important risk factors for PTL. Multiple vaginal examinations are another important reason for the ascent of microorganisms and, therefore, uterine infections.

37.2.1 Is Pregnancy a Risk Factor for Infection?

Immunosuppression during pregnancy is beneficial for fetal development, but such an immune alteration in adaptive immunity can reduce pathogenic organism clearance. There is evidence about boosted innate immunity and thus by compensating immunity, can protect the pregnancy and fetus without decreasing susceptibility to infection. It is clear that individual susceptibility and the extent of disease are important than pregnancy itself in determining the course and prognosis of the condition [9].

37.3 Mode of Transfer of Microorganisms

The most common pathway for entering microorganisms into uterus and amniotic fluid is through ascent from the cervix/vagina/perineum. There are four stages of ascending infection as depicted in Fig. 37.1, starting from cervicovaginal infection (I), decidual phase (II), intra-amniotic infection(III) and fetal infection (IV).

Fig. 37.1 Stages of ascending infection; (1) cervicovaginal infection (2) Intrauterine infection (3) Intra-amniotic infection (4) Fetal infection

In the first stage, there is excessive growth of facultative organisms or any pathological organisms like *Neisseria gonorrhoeae* in the cervix or the vagina. This stage leads to ascending infection into the uterine cavity. The organisms gain access to the decidua and produce an inflammatory reaction-decidualitis (second stage). The infection invades the chorionic fetal blood vessels-choriovasculitis and reaches the amnion. This is the third stage of infection. The integrity of the amniotic membrane is not a deciding factor in the transfer of organisms into the amniotic fluid. Amnionitis can lead to the fourth stage of fetal infection by multiple routes. Swallowing of infected amniotic fluid by the fetus leads to fetal pneumonia. Direct contact of the infected amniotic fluid leads to conjunctivitis, otitis, and omphalitis in the fetus. Systemic infection of the fetus results in bacteremia and sepsis. Other

routes of gaining access to uterine environment are hematogenous/ trans-placental dissemination, iatrogenic transmission (contamination due to invasive prenatal procedures), and antegrade seeding from peritoneal cavity via fallopian tubes [10].

37.4 Microbiology and Sites of Infections

The majority of infections are polymicrobial and at the concentration of $>10^5$ colony-forming bacteria. The common organisms are mentioned below.

Bacteria Gram-negative and positive, aerobic and anaerobic bacteria are associated with PTL. The route of transmission is usually ascending vaginal infection and iatrogenic in the majority. The organisms frequently cultured following PTD are [11]:

- *Ureaplasma urealyticum*
- *Mycoplasma hominus*
- Bacteroides
- *Gardnerella vaginalis*
- Group B Streptococcus (GBS)
- *Chlamydia trachomatis*
- *Neisseria gonorrhoeae*
- Enterococci
- *Listeria monocytogenes*

The microorganisms associated with PTD may be population specific. For example, GBS is more common in western countries, whereas *E. coli*, klebsiella, and peptostreptococcus are more common in India. If abovementioned organisms are found from the amniotic cavity before 20 weeks, pregnancy is likely to end within weeks (4–8 weeks) [12].

Viruses Viral infection is generally associated with systemic infection and Covid 19, influenza, Hepatitis E and Herpes simplex virus are all known to produce systemic infection [13–15]. There are reports of increased severity of infection associated with pregnancy. The viral intra-amniotic infection is not found commonly. However, cytomegalovirus, enterovirus, and adenoviral DNA have been isolated through molecular techniques (Polymerase chain reaction identifying a specific sequence of these microorganisms) from the amniotic fluid.

Parasites Malaria and amoeba, through systemic infection, result in PTL. Malarial parasites have been isolated from the placenta and have an impact on fetal development.

Protozoa Vaginal trichomonas infection is a frequently reported condition and almost exclusively transmitted by sexual route. It is significantly associated with PTL and pPROM. It often acts as a transporter of pathogenic flora.

Fungal It is less frequently associated with PTL and rarely with chorioamnionitis.

37.4.1 Sites of Infection

1. *Cervicovaginal Infection*: The cervicovaginal ecosystem has various flora in an either symbiotic or commensal relationship, with lactobacillus dominancy (up to 95%) and anaerobic-aerobic bacteria ratio 2:1–5:1. Change in richness and amount of vaginal microflora is associated with pregnancy. Pregnancy having risk factors results in the development of cervicovaginal infection, the most common being bacterial vaginosis (BV), trichomonas infection and candida infection. Gonorrhea and chlamydia are associated with cervical/urethral infection. Vaginal GBS is strongly associated with PTD and pPROM.
2. *Periodontal Infection*: There is a well-established relationship between periodontal infection and PTL. The common bacteria found are *F. nucleatum* and *P. gingivalis*. However, the treatment of periodontal infection is not found to treat preterm labor. It elicits intrauterine infection through hematogenous spread (trans-placental bacterial transfer).

3. *Systemic Infection*: Maternal infections like typhoid, malaria, pneumonia, tuberculosis, and pyelonephritis can elicit PTL [7].
4. *Urinary Tract Infection*: Asymptomatic bacteriuria is common during pregnancy and *E. coli* is frequently isolated in the culture. Other gram-negative bacteria associated are *Proteus mirabilis* and *Klebsiella pneumoniae*.

37.5 Pathology

The sequence of events emerging from infection, inflammation or both leading to PTD has been delineated. Up to 40% of preterm labor has an etiology of infection. An infection is the only etiology that can be intervened, so that a double hit of prematurity and infection can be prevented.

Inflammation The role of an inflammatory cascade leading to preterm labor is well established. Even with the intact membranes, changes suggestive of sterile inflammation (SI) /microbial inflammation have been reported in cases of PTB and in normal delivery [16–18]. It is found that sterile intra-amniotic inflammation is more common with an intact membrane in cases of PTL. In reality, an inflammation labeled as sterile may not be sterile as there may be pathological microorganisms, which are either fastidious bacteria or some viruses (*Fusobacterium nucleatum*, Sneathia, peptostreptococcus sp, bacteroids, clostridiales and bergeyella, etc.). The reporting of SI depends on the culturing method employed by laboratories. The bacterial colonization of intra-amniotic space has been found even in uncomplicated pregnancies [11].

Inflammation, on one aspect, is essential for the success of reproduction and, on the other hand, leads to many pathological consequences. It is vital for each step of reproduction, i.e., menstrual cycle, implantation, and later during labor. Any damage signal (cellular death/stressors) causes activation of inflammatory processes (flow chart 1 given in Fig. 37.2) and any dysregulation of the inflammatory system results in PTL. Preterm labor without infection is more prevalent, and antibiotics do not help in these conditions [19].

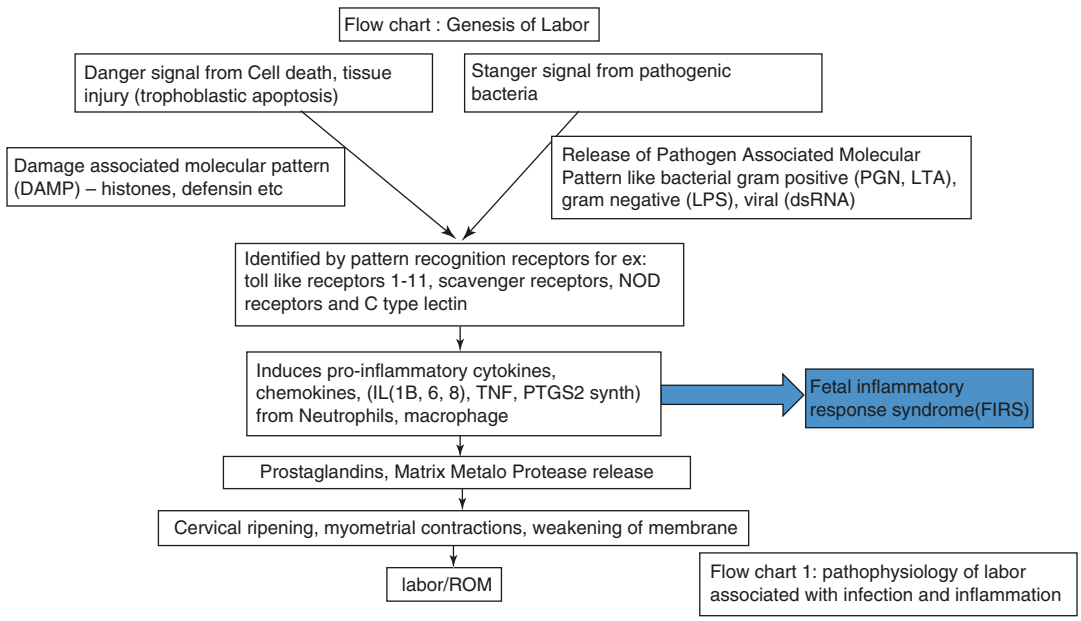

Fig. 37.2 Genesis of labor. NOD, nucleotide-binding oligomerization domain-like receptors; dsRNA, double-stranded ribonucleic acid; TNF, tumor necrosis factor; PGN, peptidoglycan; LTA, lipoteichoic acid; LPS, lipopolysaccharide; IL, interleukin; ROM, rupture of membrane; PTGS2 prostaglandin endoperoxide synthase 2

Infection The intra-amniotic infection and chorioamnionitis (CA) usually occur after ascending infection. The vagina is a host for many microorganisms, and this environment is termed as vaginal microbiota. Healthy microbiota is dominated by lactobacilli or lactic acid-producing bacteria. Other bacterial species present in vagina are streptococcus sp., staphylococcus, Bacteroides, fusobacterium, Gardnerella, Mobiluncus, Prevotella (gram-positive) *E. coli* (gram-negative), mycoplasma and ureaplasma, etc. Pregnancy alters the microbiota with a reduction in diversity and richness along with a decrease in pathogenic organisms [20]. The change in vaginal microflora or vaginal infections with pathogens like *N. gonorrhoeae*, trichomonas, candida can trigger PT labor. The propensity of microorganism to ascend is mentioned in various studies [21, 22]. In particular, to GBS, not all bacteria can ascend, but those who ascend are found to be of high virulence. GBS depends on hyaluronidase activity to avert the uterine immune responses and promote ascending infection leading to PTB [22].

Naturally, amniotic fluid has antibacterial activity. The intra-amniotic infection occurs when the antibacterial activity of AF diminishes or bacterial virulence is more. Genetic polymorphism in tumor necrosis factor, interleukin 1, interleukin 6 plays a vital role in PTD [23, 24]. Maternal and fetal polymorphisms of the toll-like receptor gene have also been implicated.

Chorioamnionitis: It is characterized by heterogeneous signs and symptoms occurring due to an infection, inflammation or both in a pregnant woman with increasing maternal and neonatal complications. An intrauterine infection or inflammation or both is newly coined as triple I [25]. It is frequently associated with acute intra-amniotic inflammation and infection involving chorion, amnion, decidua, placenta and/or fetus, usually due to ascending infection. There is a clinical or subclinical variety of chorioamnionitis (CA). The clinical symptoms are mentioned in Table 37.1. The subclinical variety shows no or very mild infection symptoms and is identified by either

Table 37.1 Diagnosis of preterm labor and chorioamnionitis

Preterm labor (PT)	Chorioamnionitis
• *Threatened PT*: cervical length <2.5 cm, <80% effaced, <1 cm dilation • *Early PTL* : 4–6 uterine contraction/hour, cervix >1 but <3 cm dilated • *Advance PTL*: ≥6 contraction/hour cervix dilatation ≥3 cm, ≥80% effacement	• Fever >38 °C/100.4 °F • Maternal tachycardia (>100/bpm for 5 min or longer) • Uterine tenderness • Foul-smelling amniotic fluid in cases of ROM or discharge • Fetal tachycardia (>160 bpm for 10 min or longer) • Complete blood count with WBC counts >15,000/mm^3 without the usage of corticosteroids • Immature neutrophils often support CA

1. Histology suggestive of infection/inflammation of placenta, membrane, decidua and/or umbilical cord.
2. Positive amniotic fluid culture after amniocentesis or following pPROM/PTD [26].

PTL occurred in nearly 40–70% of these pPROM subjects. A Study by Agrawal V found that up to 32.4% of subjects showed intra-amniotic microbial infection before labor started and it reached 75% at the time of labor. CA is just around 12% in patients with PTL and intact membranes [15].

Infection and Inflammation Both Here, the findings are suggestive of both infection and inflammation.

37.6 Pathophysiology of Preterm Labor

Ascending infection or inflammation causes the release of endogenous substance/specific agents from intracellular and extracellular compartments. These substances are Damage Associated Molecular Pattern (DAMP) and Pathogen Associated Molecular Pattern (PAMP). DAMP is vital for tissue repair after injury, thus having physiological benefits. But when the process is chronic, a large volume of DAMP causes persis-

tent inflammation, which is harmful. Infective organisms activate PAMP which is recognized by toll-like receptors on the cells of fetal membrane, placental trophoblast, endo-cervix, and prominently on uterine NK cells, with macrophage and neutrophils with the release of cytokines. As depicted in flow chart 1 given in Fig. 37.2, it results in the activation of crucial components of labor [27] (Fig. 37.2). Elevated levels of IL-6 in fetal cord blood is termed as fetal inflammatory response syndrome (FIRS), which is associated with a high incidence of neonatal morbidity and mortality.

37.7 Diagnosis of Preterm Labor

Timely diagnosis is vital for intervention and delivery. A high index of suspicion is essential for early diagnosis, as in the majority, symptoms appear late.

Clinical symptoms at presentation of women with PTL include uterine contractions, pelvic pressure, menstrual-like cramps/regular painful hardening of the uterus, vaginal discharge, and lower back pain. The diagnostic features of PTL and CA are mentioned in Table 37.1. Diagnosis of chorioamnionitis needs the presence of fever and two of the abovementioned features (one clinical feature according to ACOG).

37.7.1 Laboratory Tests

1. Tests for Systemic Infection
   (a) C-reactive protein (CRP): The value of less than 0.8 mg/dl rules out subclinical chorioamnionitis. The value of 0.8–1.6 needs repeat evaluation after 12–24 h. The rising trend in CRP or value of >1.6 mg/dl suggests a high probability of chorioamnionitis. (some studies mention a normal range of 5.6–16.4 g/ml in the early second trimester) [28].
   (b) Neutrophil Lymphocyte Ratio: It is a simple inflammatory marker suggesting increased neutrophils and decreased lymphocytes. It can be cost-effective in predicting neonatal sepsis in pPROM cases, and the cutoff is taken as 5.14 [29].
2. Test for infective microorganisms
   (a) Vaginal Discharge Examination: For BV—the clinical criteria are homogenous discharge, amine odor, clue cells and elevated pH (Amsel's criteria). Here, gram staining can identify almost 77% of BV and gram stain is a gold standard with Nugent's score. Greenish to yellow vaginal discharge with froth is pathognomic of Trichomoniasis (wet mount and gram stain 950 sensitive). Similarly, curdy white adherent discharge suggests candidial infection (wet mount is 70% sensitive, and culture is not generally needed).
   (b) Urine Analysis and Culture: The yield of test increases in pregnancies with specific urinary complaints. It helps in obtaining pathologic bacteria in the asymptomatic and symptomatic women.
   (c) Vaginal Swab: High vaginal swab (HVS) and endocervical swab are often used to diagnose the cause of vaginal discharge, but it has a limited value. It identifies the microbiome in the cervix and vagina. Gram stain, culture and molecular tests can determine organisms like gonorrhea and chlamydia (endocervical NAAT test), while TV, BV, candida and streptococci infection can be diagnosed with HVS. The absence of H_2O_2 producing lactobacillus and abnormal gram stain is strongly associated with intra-amniotic infection.
   (d) Rectovaginal Swab: Swab from the lower third of vagina and rectum helps in diagnosing GBS and *E. coli*.
   (e) Blood Culture: Nearly 10% of women with CA have a positive blood culture. It is useful in patients with fever suggestive of systemic bacteremia to isolate the organism and provide a guide to appropriate treatment.

3. Confirmatory Diagnosis of Intra-Amniotic Infection
   (a) Amniocentesis: It proves infection through gram stain or molecular tests. It is not routinely performed due to its invasive nature and a long time to result (up to 3 days).
      (I) Indications are
         (i) Clinically suspected cases to have confirmed diagnosis before inducing for PTL.
         (ii) To diagnose subclinical intra-amniotic infection in patients with PTL/PPROM.
      (II) Biochemical/microbiologic evidence of infection in amniotic fluid is low glucose or positive amniotic fluid culture and high WBC counts in the absence of bloody tap. Other markers are levels of matrix metalloproteinases, high Interleukin 6, and Leukocyte esterase test with varying sensitivity and specificity for detection of infection [10]. It has limited predictive value for maternal and neonatal outcomes. The main drawback is that it does not explain fetal infection/ inflammation.
   (b) Fetal Cordocentesis: It can diagnose fetal infection through microbiological study and inflammatory markers. This is a technically demanding procedure with uncertain clinical relevance.
   (c) Placental pathology revealing infection (histopathological evidence of infection/ inflammation in the placenta, membranes, or umbilical cord) may help confirm the suspected diagnosis, but again it does not suggest fetal infection. As it is a post-delivery diagnosis, it does not really of help in intrapartum management.
4. Biomarkers

Markers that assess the risk for early neonatal sepsis are of utmost importance to prevent morbidity and mortality. It is of value in patients in whom steroids and tocolysis are being planned. No ideal, accurate biomarker yet exists.

1. Fetal Fibronectin—It is a glycoprotein produced by amniocytes and cytotrophoblasts. It is found in the amniotic fluid up to 22 weeks. Its presence between 24 and 32 weeks was earlier correlated with preterm birth. In 2016, a meta-analysis, disapproved of its association in the prediction of preterm birth [30].
2. Interleukin levels—Increased levels of IL-6 and IL-8 levels in cervicovaginal fluid in association with cervical length could predict preterm birth within 7 days with a specificity of 92.8%. But a low sensitivity of the test of about 56.4% limits its use [31].
3. Placental alpha macroglobulin-1 (PAMG-1)—It is a bedside test that has a sensitivity of 80% and specificity of 95%. This test has greater use in decreased cervical length [32].
4. Insulin-like growth factor binding protein-1 (IGFBP-1)—Various studies have tested IGDBP-1 alone or in combination of interleukin 6. It has been found to have sensitivity of more than 85% and a specificity of more than 90%. It has been suggested as a more reliable alternative to fetal fibronectin. Various bedside tests which are available commercially are being used [33–35].

Maternal Serum Markers

Maternal salivary estriol, measured at 25–34 weeks, had 82% negative predictive value on identifying women who will not deliver preterm, which could be used for avoiding unnecessary interventions to prevent preterm birth [36].

Certain other markers in maternal serum are being considered and researched but need further validation. These include maternal serum calponin 1, ratio of maternal serum alpha-fetoprotein (AFP)/amniotic fluid AFP , maternal serum progesterone-induced blocking factor (PIBF) and maternal plateletcrit count(markedly higher in patients who delivered preterm; cutoff value of 0.201%, with a sensitivity of 95.6% and specificity of 87.5%).

5. pPROM Diagnosis

Sterile speculum examination for visualization of amniotic fluid, fern test of dried vaginal fluid, pH of amniotic fluid (7.1–7.3) by nitrazine test, pad test along with dye instillation (not used routinely) and detection of placental alpha macroglobulin test are some of the tests for diagnosis of pPROM.

6. Fetal Test for Diagnosis and Prognosis

Antenatal scan: It is indicated to assess the amount of liquor (confirm ROM), growth normalcy, cervical length (CL) and biophysical profile. It provides critical information in the management of the pregnancy. The risk of PTD is inversely proportionate to CL. It is studied that the presence of abnormal vaginal flora is directly associated with cervical shortening and shorter cervix at 20–24 weeks and 30–34 weeks [37].

Non-stress test: It is not a recommended test for confirmation/exclusion of the diagnosis of intra-amniotic infection in pPROM. Fetal tachycardia (>160 bpm for 10 min or longer), cardiotocography with diminished/absent variability, sinusoidal pattern) suggests the possibility of fetal ill health.

Repetition of investigations like Total WBC count, C-reactive protein, and fetal surveillance is recommended during conservative treatment for the lung maturity period.

37.8 Management

Aim of the management includes:

1. To control and treat an infection
2. Deliver the fetus with optimum fetal lung maturity
3. Optimize neonatal and maternal outcome

37.8.1 Tocolysis

Tocolysis in a woman with infection is ***usually contraindicated***. However, it may be of value in selected cases without overt chorioamnionitis. It can be considered on case to case basis in low gestational age. The role of atosiban, calcium channel blockers, and magnesium sulfate are well evaluated and found to be effective in delaying the labor. It is recommended only to prolong gestational age by 48 h until the effect of steroids takes place and to make a transfer to the tertiary care facility. It is recommended in patients with a viable fetus, threatened preterm, and cervical dilation of <2 cm. Tocolytic drugs are of benefit for a woman presenting with contractions which are otherwise likely to deliver before receiving the benefit of steroids. The drug of choice is Nifedipine (20–30 mg initial dose followed by 10–20 mg every 6 h). MgSO4 is not better than nifedipine, and side effects may be severe. Atosiban is preferred for a woman with contraindication to nifedipine. Beta-adrenergic agents are not preferred by the majority to arrest uterine contractions in these situations. Aggressive tocolysis may not prolong the pregnancy or reduce neonatal mortality, and hence, not advised beyond 48 h. If the effect of the tocolytic agent lasts for a shorter time in successive doses, it is interpreted as failed tocolysis and it is better to stop the tocolytic agent and allow delivery.

37.8.2 Antibiotics

Depending on culture report, antibiotic which is specific to the organism isolated is recommended. Empirical use of antibiotics for PTL with intact membranes is not recommended. As most infections are polymicrobial, broad-spectrum antibiotics are preferred for short-term therapy (three injections in 24 h). According to WHO [6], the antibiotic of choice is erythromycin in cases of pPROM (moderate-quality evidence). ACOG recommends a 2 day course of intravenous ampicillin and erythromycin followed by oral tablets for 5 days. This is recommended to prolong pregnancy and decrease short-term neonatal complications [38]. Table 37.2 mentions the various regimes of antibiotics.

37.8.3 Steroids

Steroids are recommended to improve fetal lung maturity between 24 and 34 weeks of gestation, who are at risk of PTD within 7 days. It is effective in reducing neurological and bowel morbidity and neonatal mortality. It is recommended for its beneficial effect on intraventricular hemorrhage rather than on respiratory

Table 37.2 Antibiotics in chorioamnionitis

Recommendation	Gram positive	Gram negative	Anaerobic coverage	Duration
ACOG	Ampicillin 2 g 6 hourly or (penicillin 5 million units IV) *If allergy to penicillin*, Cefazolin 2 g IV 8 hourly *if severe allergy*, clindamycin 900 mg IV every 8 h or vancomycin 1 g IV every 12 h	Gentamycin 5 mg/kg 24 hourly or loading dose of 2 mg/kg followed by 1.5 mg/kg 8 hourly until delivery	For LSCS Clindamycin 900 mg IV /Metro 500 mg IV 8 hourly for anaerobic coverage	If risk factors for Postpartum infection present (bacteremia± fever) short course (3 doses) is advisable Can be given as single dose/standard dose depending on clinical status
RCOG	Amoxicillin 2 g IV then amoxicillin 1 g IV 3 times daily if penicillin allergy, clindamycin 900 mg IV 3 times daily until delivery	If severe sepsis then gentamycin as dosed above	Metronidazole 500 mg IV 3 times daily	Postpartum up to 5 days depending on clinical status

distress syndrome. Standard dose treatment is recommended in PTL and pPROM [39, 40]. There is always a concern of infection associated with corticosteroid administration [2]. Studies have proven that antenatal steroids may be safe even with CA and that adverse neonatal outcomes are more than the risk associated with steroids [41]. It is not absolutely contraindicated even in cases of maternal sepsis. It is noteworthy that dexamethasone regime (6 mg 6 hourly for 4 doses) was associated with a significant increase in WBC counts compared with betamethasone (2 doses of 12 mg 24 h apart) in cases of pPROM [27].

37.8.4 Magnesium Sulfate and Neuroprotection

Periventricular white matter injury is the pathological lesion found with cerebral palsy in PTL. Magnesium sulfate is found beneficial for neuroprotection. It is given in the recommended regimen, including a loading dose of 4 g over 20–30 min followed by 1–2 g infusion for 24 h or up to delivery to prevent neuronal injury. Ideally, the infusion is recommended for at least 4 h before delivery, but there may still be a benefit if given for less than 4 h. It is recommended before 32 weeks of gestation [42].

37.8.5 Acetaminophen

Antipyretics have shown beneficial effects in cases of intra-amniotic infection as they reduce neonatal encephalopathy and fetal tachycardia (may help to avoid LSCS in cases of non-reassuring NST).

37.9 Delivery

Routine LSCS for improving the outcome of PTD is not recommended regardless of breech or cephalic presentation [6]. The preterm cesarean is technically difficult as the lower segment would need classical incision, future to that, scar dehiscence and uterine rupture, placental adherence and maternal death should be anticipated in successive pregnancies. LSCS is not recommended for less than 26 weeks of GA. After 26 weeks, vaginal birth is recommended unless there are maternal or fetal contraindications. The cesarean section may be helpful in delivering very low weight preterm, very preterm, and extreme preterm unless delivery is imminent as it is associated with low perinatal mortality across all ages. Forceps may be applied for controlled head delivery, and vacuum is generally contraindicated for PTD. Maternal understanding and physician discretion on case to case base is critical regarding the mode of delivery.

The essential steps like partograph, continuous, or intermittent auscultation of fetal heart for early detection of fetal distress, artificial rupture of the membrane in intact membrane cases and, oxytocin administration should be followed if vaginal delivery is decided. Multiple P/V examinations (>3) should be restricted. Epidural analgesia, scalp electrode and intrauterine pressure catheters should be used judicially. Appropriate resuscitative measures, surfactant, and CPAP, should be planned beforehand.

37.10 Complications

37.10.1 Maternal

Labor dystocia/increase in LSCS rate, bacteremia, PPH, wound abscess, postpartum endometritis, pelvic abscess, thromboembolism, septic shock, ARDS, DIC, death is associated with infection.

37.10.2 Neonatal

Fetal Inflammatory Response Syndrome (FIRS), pneumonia (10–21%), neonatal meningitis, respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), cerebral palsy (CP), periventricular leukomalacia are the commonly found adverse effects on a neonate with infections and PTB.

37.11 Prevention

1. Nutritious diet from the beginning of pregnancy. Assisting the pregnant woman in food supplement program, giving her instructions about preparing nutritious food containing a good amount of protein, zinc, and antioxidants will go a long way in the prevention of PTB.
2. Cleanliness also helps to decrease the risk of infection; daily bathing and wiping of perineum from front to back is an important perineal instruction.
3. Attempt to facilitate increased immunity by hydration, exercising daily and rest.
4. Sterile speculum and hygienic speculum and vaginal examination.
5. Assessment for vaginal discharge.
6. Assessment of urinary tract infection.
7. Urethral and vaginal culture for GBS or other microorganism and treatment accordingly.
8. Antiseptic precautions during internal examination.

Key Points

- Seventeenth November is world prematurity day. It addresses global crisis of prematurity; purple is the color representing the cause.
- Preterm birth has multiple immediate and future health challenges. The immaturity of lungs, infections and neurological consequences are the most commonly faced problems.
- Infection, inflammation, and lowered immunity of amniotic fluid have a significant role in the genesis of pPROM and preterm labor.
- Infection-mediated PTL is the only etiology that is well studied. Hence, proper education of women regarding prevention, early detection and treatment of infection is a strategy to reduce complications associated with PTD and pPROM.
- Screen and treat program should be implemented to identify a woman at risk of infection-mediated PTL.
- The goal of treatment is to allow for fetal maturity till the uterine environment is healthy.
- If fetal infection or compromise is apparent, the delivery of the premature fetus is the way to improve the outcome of the fetus.

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38 Fetal Manifestations of Infections in Pregnancy

Chanchal Singh

38.1 Introduction

Infection in pregnancy is common and majority will not have any adverse effect on the fetus. However, it is important to recognize those infections which can be transmitted to the fetus and cause fetal and/or neonatal adverse sequelae. The mainstay of diagnosing fetal manifestations of infection in pregnancy is ultrasound. Since there is no recommendation for routine testing for congenital infections in pregnancy (except syphilis), it is usually fetal findings on ultrasound that prompt maternal testing and maternal infection is diagnosed retrospectively.

38.2 Fetal Manifestations of Congenital Infections

Most ultrasound findings in an infected fetus are nonspecific and do not provide a diagnostic clue to the causative agent, e.g., fetal growth restriction, oligohydramnios, polyhydramnios, placentomegaly, etc. (Table 38.1) though some are unique to the disease-causing virus, e.g., fetal anemia in Human Parvovirus.

Table 38.1 Ultrasound findings suggestive of fetal infection

Extracranial findings	Cranial findings
• Fetal growth restriction (especially early onset) • Oligohydramnios • Polyhydramnios • Placentomegaly • Hyperechogenic bowel • Liver calcifications • Ascites • Pericardial effusion • Subcutaneous edema • Nonimmune hydrops	• Microcephaly • Ventriculomegaly • Paraventricular calcifications • Intraventricular synechiae • Periventricular pseudocysts • Intracranial hemorrhage • Vermian hypoplasia • Cerebellar calcifications and/or cysts • Lissencephaly-pachygyria • Polymicrogyria

Table 38.2 lists the findings specific to the causative agent though there remains a considerable overlap amongst various infections.

38.3 Diagnosis of Maternal Infection

Since the commoner ultrasound findings suggestive of fetal infection are nonspecific, a thorough history should be taken from the mother if a specific etiology is to be established. This includes the history of fever with rash, lymphadenopathy and/or exposure to an infected person. History of travel for both the pregnant woman and her husband/partner is important when fetal Zika virus is being suspected. The diagnosis of maternal infection should be based on seroconversion by testing

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Table 38.2 Ultrasound findings specific to infectious agent [1, 2]

	CNS	Craniofacial	CVS	GIT	Musculoskeletal
CMV	Ventriculomegaly, Intracranial calcifications, Microcephaly	Eye abnormalities	Supraventricular tachycardia, pericardial effusion, Myocardial calcifications	Echogenic bowel, Hepatic calcification, Ascites	–
Rubella	Microcephaly	Microphthalmia Cataract	ASD, VSD	Hepatomegaly	–
HPV B19	–	–	Cardiomegaly, Pericardial effusion, Hydrops Fetal anemia (MCA PSV > 1.5 MoM)	Meconium peritonitis, Ascites	–
Chickenpox	Ventriculomegaly, Hydrocephalus, porencephaly, polymicrogyria	Microphthalmia Cataract	–	Echogenic bowel, Hepatic calcification, Hepatomegaly	Limb hypoplasia, contractures, clubbed feet, decreased mobility
Zika virus	Microcephaly, Periventricular cysts, Cerebral and cerebellar atrophy	Cataracts, microphthalmia, optic-nerve abnormalities, Craniofacial disproportion	–	–	Talipes, Contractures

paired samples for both IgM and IgG. IgM testing alone is inconclusive and may be false positive in many cases due to chronic persistence of the IgM antibody, cross-reactivity with other viral infections and/or nonspecific polyclonal stimulation of the immune system in response to other infections [1]. Since the timing of infection is important in determining the risk of transmission and affectation of the fetus, IgG avidity (available for Rubella, CMV, and toxoplasma) should be done. Low avidity (<30%) is suggestive of recent infection within last 3 months. A high avidity (>60%) suggests past infection that has occurred more than 3 months ago or secondary infection. Comparison with prior reports, even from a previous pregnancy or in the interpregnancy period, can help in differentiating between primary and secondary infection. History of past immunization should be taken.

Ultrasound features may take up to 4–6 weeks from suspected maternal infection to appear. When maternal serology is suggestive of infection in pregnancy, but there are no ultrasound features suggestive of infection, the fetus should still be followed up by serial ultrasound as signs of fetal infection may appear even up to 12 weeks following maternal infection [3].

38.4 Cytomegalovirus (CMV)

CMV is the most common viral cause of congenital infection in pregnancy, with a reported incidence of 0.2–2.2% of live births [4, 5]. It is the most common non-genetic cause of sensorineural hearing loss (SNHL) in children. Since there is no recommendation for routine testing for CMV, maternal serology testing is usually done after finding fetal manifestations. Fetal manifestations of CMV include ventriculomegaly, intracranial calcifications (Fig. 38.1), periventricular cysts, intracranial hemorrhage, cerebellar hypoplasia, cortical abnormalities, echogenic bowel, apart from any of the nonspecific findings listed in Table 38.1 [3, 6].

The risk of vertical transmission in case of a maternal infection is about 30–40% and increases with advancing gestation ranging from 25 to 45% in the periconceptional period (1 week before and 5 weeks after the LMP) and first trimester to

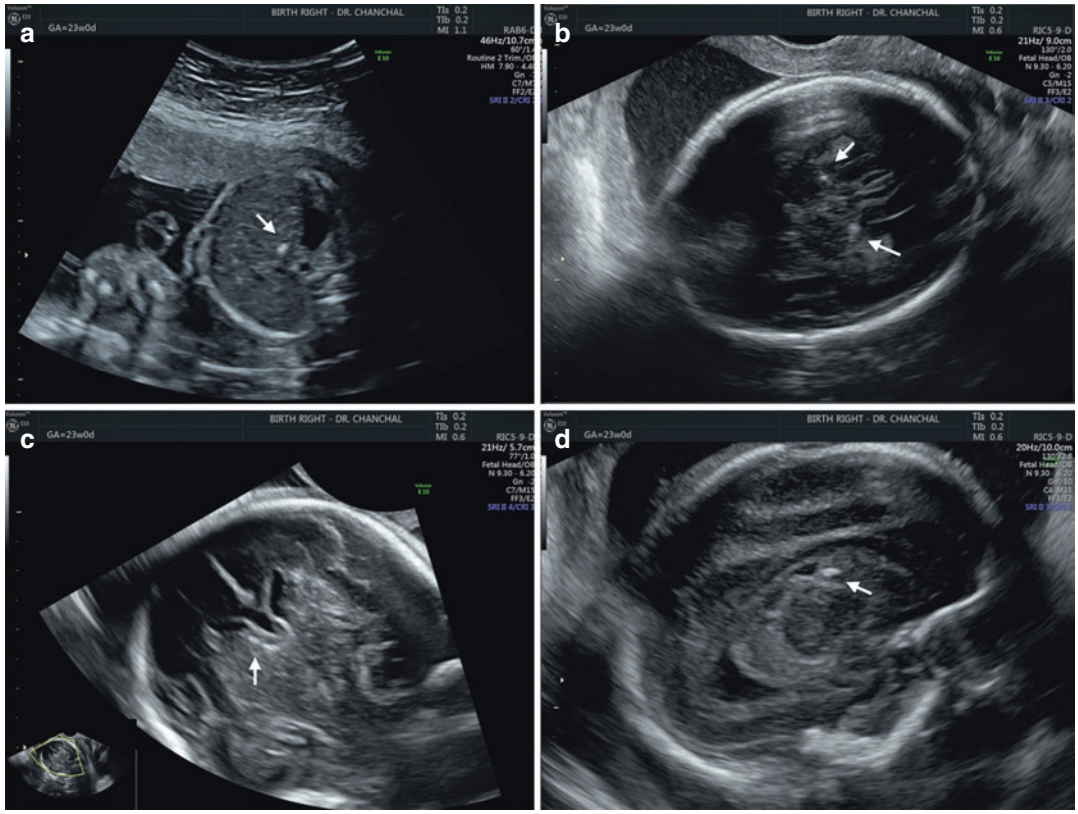

Fig. 38.1 (**a**) Transabdominal 2D ultrasound showing hepatic calcification (**b–d**) Transvaginal 2D ultrasound images intracerebral and periventricular calcifications in a fetus with CMV infection (CMV PCR positive on amniotic fluid)

47–78% in the third trimester [1]. The risk of severe symptoms in an infected fetus is as high as 70% when maternal primary infection occurs in the periconceptional period. This risk is 20% when infection occurs in the first trimester, 5% in the second trimester and it is almost negligible when infection occurs in the third trimester.

38.4.1 Diagnosis of Fetal Infection

Once fetal manifestations are seen on the ultrasound, amniocentesis should be offered for CMV PCR on amniotic fluid. In cases where maternal infection is suspected but there are no ultrasound features, amniocentesis should be delayed up to 6–8 weeks following maternal infection, or after 20 weeks whichever is later, to minimize the risk of a false-negative report. Since the virus is excreted in fetal urine, time should be given for fetal diuresis to get established, which is by 18 weeks. This is true for fetal diagnosis for all infections.

It is difficult to predict the long-term outcomes of infected fetuses; however, the timing of infection in terms of gestation, the presence and type of fetal abnormalities and laboratory parameters such as fetal platelet count and CMV IgM have been reported to be prognostic indicators. The absence of ultrasound features in an infected fetus (amniotic fluid PCR positive) has a negative predictive value (NPV) of 93% for the birth of an asymptomatic neonate [7]. Fetal MRI in the third trimester (performed after 30 weeks), when normal, improves this prediction to 95% [8]. It is important to highlight that there remains a residual risk of SNHL despite the absence of fetal manifestations on ultrasound and MRI. Adding viral load in amniotic fluid and fetal blood parameters increases the NPV to 95% and 100%,

Table 38.3 Ultrasound criteria to define "moderately"' CMV infected fetus [10]

At least one extracerebral abnormality consistent with fetal CMV infection	And/or one isolated cerebral abnormality	And/or laboratory finding on fetal blood sampling
• Fetal growth restriction • Abnormal amniotic fluid volume • Ascites/pleural effusion/subcutaneous edema/hydrops • Placentomegaly (>4 cm) • Echogenic bowel • Liver calcifications • Hepatomegaly (>4 cm) • Splenomegaly (>3 cm)	• Mild isolated ventriculomegaly (<15 mm) • Isolated cerebral calcification • Isolated intraventricular adhesion • Vasculopathy of lenticulostriate vessels	Fetal viral load >3000 copies/mL Fetal platelet count < 100,000/mm^3

respectively [7]. However, current guidelines do not recommend routine fetal blood sampling in these fetuses [1]. The positive predictive value (PPV) of ultrasound alone in fetuses with non-severe ultrasound features is 60%; when combined with amniotic fluid viral load and fetal blood parameters, the PPV increases to 78% and 79%, respectively [7].

Recent studies have shown a significant neonatal benefit from maternal oral high-dose valacyclovir when given to mothers carrying moderately infected fetuses as characterized by ultrasound findings (Table 38.3) [9, 10]. 82% of neonates born to women in the treated group were asymptomatic as compared to 43% of those in the historical cohort. There were no adverse maternal or neonatal effects with the use of high-dose valacyclovir. Current guidance is to use valacyclovir only in research settings [1]. Data regarding the use of CMV human immunoglobulin (HIG) therapy in preventing fetal/neonatal infection and adverse sequelae are conflicting and this therapy is not currently recommended [11, 12].

The residual risk of SNHL and less severe adverse neurodevelopmental sequalae, which may become evident only later in asymptomatic newborns, mandates long-term paediatric follow-up for all infected fetuses/neonates.

38.5 Rubella

Rubella or German measles is a common childhood viral disease caused by a single-stranded RNA virus belonging to the Togaviridae family. Infection in adults, including pregnant women, may be asymptomatic or cause a mild flu-like illness with diffuse maculopapular rash and lymphadenopathy. Infection in pregnancy, especially in the first trimester, can result in miscarriage, intrauterine fetal death, stillbirth, or congenital Rubella syndrome (CRS) [13]. CRS remains a huge burden in South-East Asia, with an estimated 46% of 103,000 infants with CRS in 2010 being born in this region [14]. The risk is highest in countries where women in the child-bearing age group are nonimmune to Rubella. This infection has virtually been eliminated from the West due to widespread Rubella immunization. In fact, routine testing for Rubella at booking has been discontinued in the UK given the high levels of herd immunity following widespread implementation of immunization. India introduced the measles, mumps, and Rubella (MMR) vaccine in 2017 and launched a mass vaccination program targeting children from 9 months to 14 years of age [15].

The diagnosis of primary maternal infection in Rubella should be based on "seroconversion" and in the context of clinical symptoms as the false positive rate of Rubella IgM is as high as 15–50%. Thus the history of exposure, fever with rash, prior vaccination and pre-pregnancy immunization, pre-pregnancy test results should be taken into account while interpreting these reports. The risk of fetal infection is 90% when maternal infection occurs prior to 12 weeks. The risk of fetal affection at this gestation is as high as 97%, and if primary maternal infection is proven to have occurred in the first trimester, termination may be considered even without invasive testing [1]. The risk of fetal infection is 55% when

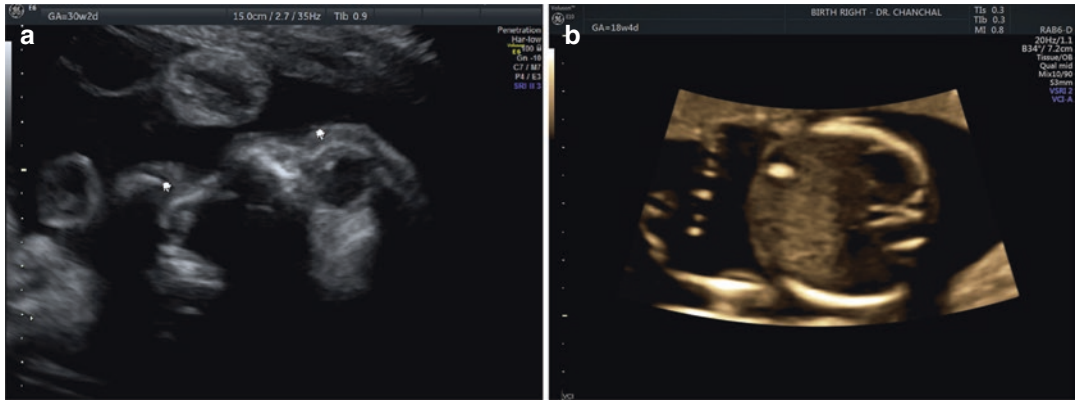

Fig. 38.2 (**a**) 2D ultrasound showing bilateral cataract in a fetus diagnosed with Rubella infection. (**b**) Hepatic calcification in a fetus with CRS

maternal primary infection occurs between 12 and 16 weeks and 45% after 16 weeks. The risk of fetal affectation is 20% at 12–16 weeks. There is a small risk of hearing loss in the newborn when maternal infection occurs at 16–20 weeks. The fetal risk is minimal when primary maternal infection occurs after 20 weeks. The risk of fetal infection following maternal secondary infection is less than 5%.

If primary maternal infection is suspected between 11 and 18 weeks, amniocentesis should be offered to the patient. Diagnosis of fetal infection is based on the detection of Rubella viral RTPCR in amniotic fluid. The specificity of viral PCR on amniotic fluid is 100%, and sensitivity is more than 90%, presuming that the procedure is timed correctly [16]. The most common reason for false-negative results on amniocentesis is the wrong timing of the procedure; amniocentesis should be performed minimum 6 weeks following suspected maternal infection or after 20 weeks of gestation, whichever is later. It is also suggested that the sample should be processed as soon as possible and transported frozen if that is needed [16]. If the amniotic fluid is positive for Rubella viral PCR, fetal infection is presumed. There is currently no therapy for fetal Rubella infection.

Amniocentesis should also be offered if there are ultrasound features suggestive of fetal infection, e.g., early-onset fetal growth restriction, microcephaly, ventriculomegaly, intracerebral calcifications, fetal cataract (Fig 38.2a), echogenic bowel, hepatic calcifications (Fig. 38.2b), placentomegaly, etc. [17–19] The specificity of ultrasound in diagnosing congenital Rubella syndrome is 100% though the sensitivity is only 11% given the nonspecific nature of the findings and overlap with other fetal infections [20].

38.6 Varicella Zoster Virus

Varicella Zoster virus (VZV) is a highly contagious DNA virus of the herpes family that causes "varicella" or chickenpox in seronegative or susceptible individuals ("primary" infection), but once infection occurs, it confers lifelong immunity. The virus remains dormant in sensory ganglia and may get reactivated to cause vesicular erythematous skin lesions in dermatomal distribution, which has been termed as "zoster" or "shingles." Chickenpox is a relatively benign and self-limiting illness in childhood; however, in pregnant women, it may be associated with high risk of maternal morbidity and mortality.

Varicella infection in early pregnancy does not increase the risk of miscarriage, but the virus can cross the placenta and may result in fetal infection, causing the fetal varicella syndrome (FVS) [21]. It is postulated to be caused by a reactivation of the virus in utero rather than by primary infection. The risk of fetal varicella syndrome (FVS) is 0.5% when maternal infection occurs in

Table 38.4 Diagnostic criteria for congenital varicella syndrome [26]

1. Appearance of maternal chickenpox in pregnancy
2. Presence of congenital skin lesions in dermatomal distribution and/or neurologic defects, eye disease, limb hypoplasia
3. Proven intrauterine infection by detection of viral DNA in the infant
4. Presence of specific IgM
5. Persistent IgG in the infant beyond 7 months of age
6. Appearance of zoster during early infancy

Table 38.5 Treatment for confirmed maternal/fetal toxoplasma infection [1]

Confirmed maternal infection	Confirmed fetal infection
• Spiramycin 1 g oral, TDS *to be started within 3 weeks following maternal seroconversion and to be continued till the end of pregnancy if no fetal infection (amniotic fluid negative for Toxoplasma DNA PCR)*	• Spiramycin 1 gram, TDS × 1 week *followed by* – Pyrimethamine 50 mg OD – Sulfadiazine 1 g, TDS – Folinic acid 50 mg weekly *to be taken throughout pregnancy and infant till 1 year of age*

the first 13 weeks of pregnancy, 2% when it occurs between 13 and 20 weeks and minimal when maternal infection occurs after 20 weeks of gestation [22, 23]. When varicella occurs in the third trimester and delivery occurs within 5 days of maternal infection, there is a high risk of neonatal varicella with high risk of neonatal morbidity and mortality.

The diagnosis of FVS is mainly based on ultrasound findings that appear about 5 weeks after maternal primary infection. Ultrasound features include limb defects, fetal cataract, microcephaly, hyperechoic foci in the liver or bowel, fetal growth restriction, polyhydramnios and/or nonimmune hydrops [1]. Amniocentesis and viral PCR on amniotic fluid confirm fetal infection, but all affected fetuses may not develop the syndrome, nor does a negative result rule out fetal varicella syndrome [24]. Thus, the diagnosis is based mainly on ultrasound, which should be done by an appropriately trained fetal medicine expert at least 5–6 weeks after maternal infection [21, 25].

The diagnostic criteria and clinical features of congenital varicella syndrome are given in Table 38.4 [26]. The affected children have long-term learning difficulties and neurodevelopmental problems. However, no long-term neurodevelopmental delay has been reported in asymptomatic children [27].

38.7 Toxoplasma

Toxoplasmosis in a parasitic infection caused by ingestion of tissue cysts in undercooked meat, processed meat, or from contaminated soil or water infected by oocytes excreted by cats. Improvement in hygiene leads to decrease in incidence; however, the reported incidence from western country like UK is still 2–5 per 1000 pregnancies [28]. A recent study from North India reported a seroprevalence of 44.9% on antenatal screening [29]. Primary maternal infection is asymptomatic in two-thirds of women or may present with mild fever, malaise, headache, lymphadenopathy, and coryza. The risk of vertical transmission increases from less than 1% at gestation less than 4 weeks, 4–15% in the first trimester, to more than 60% after 36 weeks. The risk and severity of fetal adverse effects are inversely proportional to the gestational age at infection. Thus, the risk of congenital toxoplasmosis following primary maternal infection is highest in mid-gestation, i.e., from 13 to 28 weeks. This risk is estimated to be 20–50% without treatment [30, 31].

Fetal manifestations are nonspecific and include microcephaly, ventriculomegaly, hydrocephalus, intracranial hemorrhage, intracranial calcifications, ascites, hepatosplenomegaly, hydrops, and fetal growth restriction. Neonatal and later sequelae include developmental delay, epilepsy, and blindness due to chorioretinitis. Infected newborns also have hepatosplenomegaly, anemia, rash, jaundice, and pneumonitis [32, 33].

Toxoplasmosis is one congenital infection that is amenable to drug therapy (Table 38.5). However, since the sensitivity of amniocentesis for diagnosing fetal infection is less than 90% [34], 4 weekly ultrasound surveillance especially

focusing on fetal growth, eyes, and brain, is recommended for the rest of the pregnancy [1]. Fetal MRI should be considered a complimentary imaging modality due to its ability to pick up subtle intracranial abnormalities. The parents should be counseled that even if there is no abnormality on USG and MRI, there remains a 30% risk of long-term sequalae of chorioretinitis and vision loss in an infected fetus [35, 36].

38.8 Human Parvovirus B 19

Human Parvovirus B 19 is a DNA virus belonging to the Parvoviridae family and a common cause of mild childhood disease characterized by a typical "slapped cheek appaearance." Although 60–75% of pregnant women are immune to it, the reported incidence of acute parvovirus infection in pregnancy is 1–2% [37]. Infection in adults is mostly asymptomatic but may present as erythema infectiosum, "fifth disease," characterized by transient malaise, fever, and arthralgia. The risk of vertical transmission in infected women is 15% before 15 weeks of gestation, 25% between 15 and 20 weeks and 70% towards term [38, 39]. The virus has a predilection for rapidly dividing erythroid precursor cells, thereby inhibing erythropoiesis leading to aplastic crisis in the infected fetus. It causes severe hemolytic anemia in the fetus leading to hepatosplenomegaly, cardiac failure, nonimmune hydrops and intrauterine fetal demise. MCA PSV is typically elevated in infected fetuses (Fig. 38.3). These fetal manifestations may present on ultrasound up to 3 weeks following maternal infection. Since it is a self-limiting disease that resolves spontaneously over 1–7 weeks, treatment consists of ultarsound sur-

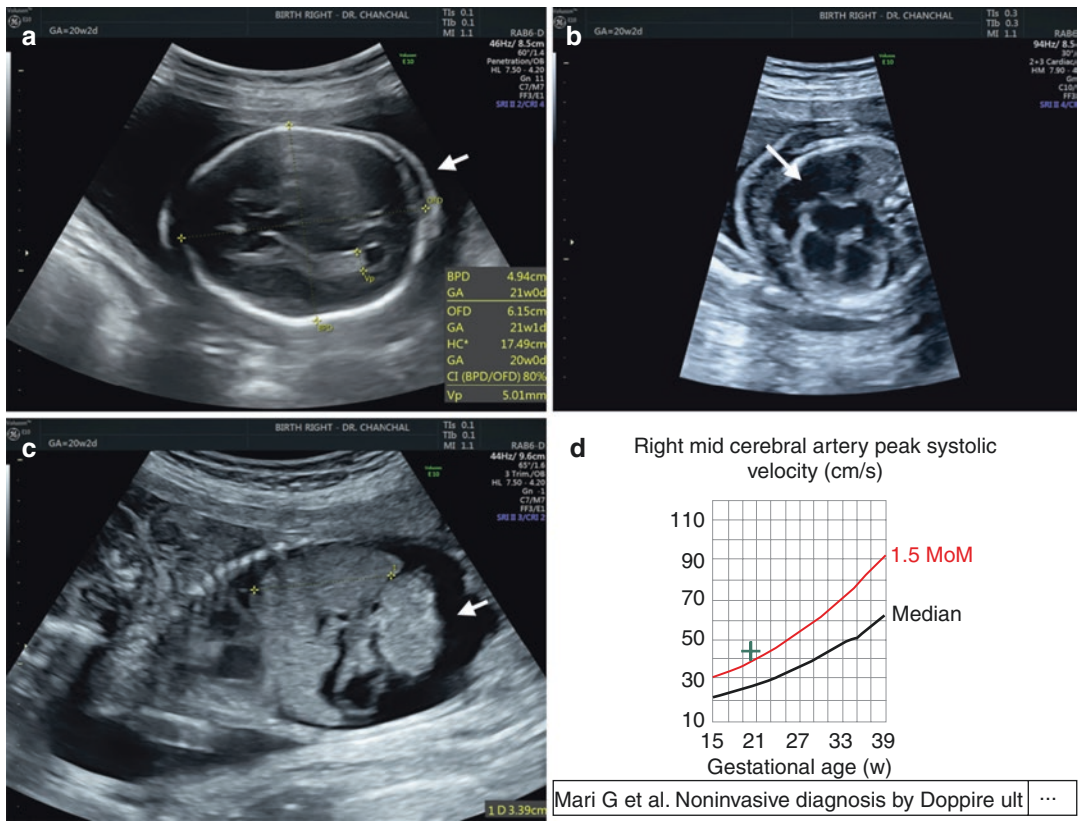

Fig. 38.3 Fetal manifestations of HPV B19 infection: 2D ultrasound images showing subcutaneous edema (**a**), cardiomegaly and pericardial effusion (**b**), fetal ascites (**c**) and fetal MCA PSV above 1.5 MoM suggestive of fetal anemia (**d**)

veillance for fetal anemia by MCA PSV Doppler monitoring and intrauterine transfusion if it rises above 1.5 MoM. The presence of hydrops is a poor prognostic indicator with a 50% risk of intrauterine demise [39, 40]. The virus does not cause any teratogenicity, and if the fetus survives the acute episode of infection, long-term neurodevelopmental outcome is good.

38.9 COVID-19

No discourse on infection in pregnancy in current times can be complete without the mention of COVID-19. As per current evidence, there is no significant increase in the incidence of congenital abnormalities, stillbirth, or neonatal death among women with COVID-19, although data on the risk of miscarriage is inadequate [41, 42]. Although a recent paper from Wuhan reported two-thirds of pregnancies with SARS to be affected by fetal growth restriction (FGR), there is no evidence yet that FGR is a direct consequence of maternal COVID-19 infection [43]. Current guidance recommends that an ultrasound following a minimum of 14 days after resolution of acute illness of COVID-19 that required hospitalization should be done [44]. There is evidence for lack of vertical transmission: the virus has not been found in the amniotic fluid, cord blood, or maternal milk [45, 46]. High fevers in pregnancy, especially in the first trimester, can increase the risk of birth defects which remains true for COVID-19 as well. Data on long-term health effects of SARS-CoV-2 infection on pregnant women and their children is lacking at present.

38.10 Summary

Fetal manifestations of congenital infection can present with various specific and nonspecific ultrasound findings. These findings should prompt a thorough history taking and targeted investigations. Amniocentesis remains the mainstay for diagnosing fetal infection.

Key Points

- The risk of fetal infection in pregnancy is highly dependent on the causative organism and the gestation at which maternal infection occurs.
- Most maternal infections are asymptomatic or associated with mild nonspecific symptoms. Thus, it is usually ultrasound findings that prompt maternal investigations and a retrospective diagnosis of maternal infection.
- In cases where the maternal infection is suspected, but there are no ultrasound abnormalities (or it is too early to detect ultrasound abnormalities), diagnosis of maternal infection should not be based on IgM alone but on "seroconversion" based on paired samples at least 2 weeks apart along with IgG avidity.
- When maternal infection is suspected, ultrasound surveillance remains the primary modality for detection of an affected fetus, and it should be done by a maternal-fetal medicine specialist at least 6 weeks following the maternal infection.
- Amniocentesis remains the mainstay for diagnosing fetal infection. It should be performed at least 6 weeks following maternal infection or after 18–19 weeks of gestation whichever is later, to avoid "false-negative" results.
- Therapeutic options for treating an infected fetus are limited at present.

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39 Maternal Infections and Allergic Disorders in Offspring

Neha Gami and Kotni Gayatri

39.1 Introduction

Allergic diseases are affecting more and more children in recent years. Allergic disorders in children include Atopic dermatitis (AD), IgE-mediated food allergies, asthma, and allergic rhinitis and they are believed to affect about 30% to 35% of all children [1]. These diseases are a significant cause of morbidity among children and substantial loss to the society due to the cost of medical care, missing school days and absence from work by parents [2, 3].

In order to prevent these disorders, there is a lot of attention being paid to the causes behind these conditions. A complex interaction between genetic and environmental factors is most likely responsible for their development. Recently more attention has been paid to environmental factors as they are modifiable and may play a role in the prevention of these diseases. These environmental factors can be prenatal, intrapartum, postnatal, and during early childhood.

Maternal infections have attracted a lot of attention as they may be an important preventable cause of childhood allergic disorders. Some of the other prenatal factors are the use of antibiotics, obesity, dietary factors like lack of exposure to allergens, deficiency of zinc, vitamin D and vitamin E. The mode of delivery and breastfeeding may be other pregnancy-related factors involved.

In this chapter, we will discuss the following

1. Etiology of allergic disorders in children.
2. Possible link to environmental factors in antenatal and early neonatal period.
3. Normal and abnormal immune development in prenatal and early childhood.
4. Specific factors during pregnancy and lactation that may impact the incidence of allergic disorders in children.

As this area of research is still evolving there is no strong evidence about prevention strategies but we will summarize some recommendations at the end of the chapter.

39.2 Pathogenesis and Etiology of Allergic Disorders in Children

Allergic disorders have recently become very common among children affecting 30% to 35% of all children [1]. It is estimated that 14% of children all over the world have asthma, 7.9% have eczema, and 20.7% have allergic rhinitis (hay fever) [4, 5]. Food allergies are also rising in the pediatric population.

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39.2.1 Pathogenesis

Asthma is a disease marked by an increased reactiveness of the airway and airway obstruction in response to allergens which is partially or completely reversible [6]. Eczema is characterized by epidermal dryness and itchiness that causes typical relapsing lesions and plaques [7].

The pathophysiology of asthma involves the infiltration of the airways by inflammatory cells like neutrophils, eosinophils, and lymphocytes, and mast cell activation leading to damage to the epithelial cells. These immune-mediated inflammatory responses lead to swelling of the airway, increase in mucus production, and bronchial muscle dysfunction, which reduce airway flow leading to symptoms of asthma [8–10].

Atopic dermatitis has a complex and multifactorial pathophysiology. It involves barrier dysfunction, alterations in cell-mediated immune responses, IgE-mediated hypersensitivity, and environmental factors. The imbalance of Th2 to Th1 cytokines creates alterations in the cell-mediated immune responses and can promote IgE-mediated hypersensitivity, both of which appear to play a role in the development of atopic dermatitis [11].

39.2.2 Etiology

Genetic factors like allergic reactions in either parent have been linked to the development of allergic disorders in children. Of the children with allergic disease, 12% had no family history of allergy, 30% to 50% had a single parent with allergies, and 60% to 80% of the children had a history of allergies in both parents [12]. Environmental factors like allergen exposure are also gaining importance. This is mainly because they are modifiable and hence may play a role in the prevention of these disorders.

Certain observations led researchers to try and evaluate the link between childhood allergic conditions and prenatal factors. Allergic reactions occurring even with the first known ingestion of food suggested that sensitization with food allergy may occur during pregnancy and/or through the breastfeeding [13]. Evidence from research into the development of the fetal immune system showed that the first 1000 days of a child's life, that is, from conception to the second birthday, is the time of development and programming of the immune system [14]. Prenatal and early postnatal influences may interfere with normal lung and immune system maturation, resulting in an increased susceptibility to asthma and other allergic disorders in the child. This has further brought the focus of preventing childhood allergic disorders to the prenatal period.

39.2.2.1 Normal and Abnormal Immune Development

Let us try and understand the development of the immune system to understand how its development may be influenced by maternal infections.

The immune system has two types of T lymphocytes—CD4 and CD8. The CD4 or T helper cells are prolific cytokine producers and are further of two kinds—Th1 and Th2. The cytokines produced by them are Th1-type cytokines and Th2-type cytokines [15].

The Th1 type cells mainly produce cytokines that are pro-inflammatory and play a role in destroying intracellular parasites and are involved in autoimmune responses of the body. The main Th1 cytokine is Interferon gamma. This response however needs to be under check as uncontrolled Th1 response can lead to tissue damage of the host.

The Th2 cells mainly produce interleukins (IL) 4,5,10, and 13. While IL 4, 5, and 13 are involved in IgE medicated atopic reactions and in eosinophil activation, IL 10 has an anti-inflammatory role. Th2 counteracts the microbicidal and autoimmune responses mediated by Th1 cytokines. Hence a balance between Th1 and Th2 is best suited for a good immune response [15]. People with atopy have a Th2 skewed response when exposed to certain antigens. They tend to produce more IgE when exposed to spe-

cific antigens, leading to manifestations of allergic reactions.

Pregnancy and early postnatal life are chiefly viewed as Th2 dominant states. In order to reduce the risk of miscarriage, a strong Th2 response is necessary to alter the Th1 cellular response in utero. Since pregnancy is chiefly a Th2 skewed state, fetuses tend to be born with Th2 biased immune responses. These can be switched off rapidly postnatally under the influence of microbiological exposure or can be enhanced by early exposure to allergens [15].

Hence any influence on the fetal immune system from conception till full maturity that interferes with normal development or leads to an imbalance between Th1 and Th2 response can lead to the development of allergic disorders in these children in the future.

39.3 Environmental Factors in Antenatal and Early Neonatal Period as a Cause of Allergic Disorders in Children

39.3.1 Antenatal Environmental Factors

It is now believed that the first 1000 days of a child's life, that is, from conception to the second birthday, is the time of development and programming of the immune system. This has brought the focus of preventing childhood allergic disorders to the prenatal period.

Recent evidence from both animal and human studies suggests that fetal exposure in the prenatal period to certain adverse stimuli or influences may impact the normal development of the fetal immune system, thus impacting the subsequent development and immune responses of the neonate and even as a child [16, 17].

Some of the other prenatal factors are the use of antibiotics, obesity, intrapartum factors like cesarean delivery, dietary factors like lack of exposure to allergens, Zinc, Vitamin D, and Vitamin E deficiency.

39.4 How Maternal Infections Cause Allergic Disorders in Offspring

39.4.1 Fetal Programming

The biological mechanism that explains how maternal infections may be linked with allergic disorders in their children is called *fetal programming* [18]. It refers to the programming of the immune system that starts in the prenatal period and continues till the first 1000 days of a child's life.

Pregnancy is a Th2 dominant state with increased IL-4, IL-5, IL-10, and IL-13.levels. Th1 type cell-mediated immune response is undesirable for the maintenance of pregnancy. (Interferon gamma and IL12). To reduce the risk of miscarriage, a strong Th2 response is necessary to modify the Th1 cellular response in utero [15].

The fetus has the ability to switch on an immune response, and because pregnancy is chiefly a Th2 dominant environment, babies tend to be born with Th2 biased immune responses. As a part of the maturation process after birth, there is a gradual development of the Th1 type immune system over the first 12–18 months of a child's life. A slower maturation of the TH1 immune response during these first months of a child's life is what predisposes a child to the development of allergy and asthma in the future [19]. In children with asthma and allergic disorders, Th2 polarized immune deviation has been noticed. This imbalance in the circulating levels of Th1 and Th2 associated chemokines may precede the onset of wheeze.

The Th2 response is usually switched off after birth quite quickly due to the exposure of the neonate to microbes. The persistence of Th2 and a slower maturation of Th1 immune response may be genetically determined but is also influenced by environmental factors in the prenatal and early neonatal, and infancy period.

To summarise, there is a complex interaction between maternal, placental, and fetal cytokine production, which normally works to prevent

rejection of fetus. If unbalanced, it can result in persistent Th2 type response instead of transient Th2 response in newborn and a slower development of the Th1 immune system. This imbalance of Th2/Th1 response can lead to allergic conditions in a child.

39.4.1.1 How Maternal Infections Influence Fetal Immune Programming

During certain maternal infections, there is a strong pro-inflammatory response. This causes an increase in production of inflammatory cytokines in the uterus. These cytokines are then released into the amniotic fluid through the placenta. The fetal skin and lungs are thus exposed to these cytokines affecting the development of the fetal immune system. This then leads to allergic responses to certain antigens in future life. Also, early neonatal infections resulting from exposure to bacteria during delivery may predispose the children to asthma.

During chorioamnionitis, there is an increase of the production of cytokines like interleukin (IL)-6, Tumor necrosis factor (TNF)-a, Interferon (IFN)-b, monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-1b, and IL-8 inside the uterus [20–22]. This exposure of fetal lungs to IL-6, IL-8, and TNF—a has been linked to chronic lung disease [23]. Exposure to TNF—a has been shown to have a negative impact on the forced expiratory volume in 1 s (FEV1) in children with asthma [24]. In rhinovirus infections the children who developed wheezing were found to have high IL-8 levels [25].

It has been proposed that pro-inflammatory responses stimulated by infections during pregnancy may contribute to allergic disorders in children.

39.4.2 Specific Maternal Infections

There is an association between maternal infections during pregnancy and allergic disorders like asthma and Atopic eczema in infants (pooled OR: 1.55; 95% CI: 1.24–1.92) [26]. As discussed above, there is a biological mechanism that can explain how maternal infections can influence the developing fetal immune system and hence predispose a newborn to an imbalance between a Th1 and Th2 immune response, thus leading to asthma and other allergic disorders.

Table 39.1 Odds ratio of developing allergic disorders in children with specific maternal infections [26]

Maternal infection	Pooled OR	95% CI
Fever	1.73	1.35–2.23
Chorioamnionitis	1.42	0.96–2.11
Respiratory infection	1.49	0.94–2.36
Urogenital infection	1.39	1.18–1.64
All infections	1.55	1.24–1.92

Based on the type of maternal infection, a strong association was found between fever, urogenital infections and the chances of developing asthma and other allergic disorders in the offspring [26]. Less significant association was seen with chorioamnionitis and respiratory infections, as shown in Table 39.1.

In another study by Collier et al., it was shown that maternal urinary tract infections were associated with a 60% increase in the odds of childhood asthma while other common antepartum infections like gynecologic infections and respiratory infections were not associated with a similar increased risk [27]. However, there was no clear explanation for this link.

39.4.3 Gestational Age at Maternal Infection and Risk of Childhood Allergies

Another question that is crucial for the practical application of this knowledge is the "sensitive period" or vulnerable period during the pregnancy. This refers to the time during the antenatal period when these infections may have the maximum impact on the developing immune system.

This has evaded most researchers till now due to significant variation among studies in design, exposure, and outcome measurements [26]. Few authors have found an association between the

risk of childhood allergies and the trimester of maternal infections. Hughes et al. [28] found that respiratory infection during the first trimester resulted in a higher incidence of childhood asthma as compared with infections in the second or third trimesters. Another study conducted by Algert et al. [29] showed that gestational age at the time of first antenatal urinary tract infection had no effect on the risk of childhood asthma, while Pesce et al. [7] reported that the risk of eczema was significantly higher in children born to mothers who reported infections with fever during the first trimester or gynecological infections during the third trimester of pregnancy.

A similar relationship between specific maternal infections and eczema was not seen in the study by Zhu et al. [26]. However, there was a statistically significant association of maternal infection overall with eczema (OR: 1.36; 95% CI: 1.13–1.64; $P < 0.01$) [26]

The authors adjusted for most major confounding factors, but they were unable to remove potential confounding factors such as antibiotic exposure, birth weight, and breastfeeding [26].

The prenatal infections and use of antibiotics are modifiable and can thus prevent childhood allergic disorders. Awareness of this association, prevention, and appropriate management of antenatal infections may play a significant role in preventing childhood asthma and eczema.

39.5 Impact of Special Factors During Pregnancy on Allergic Disorders in Children

39.5.1 Antibiotic Use in Pregnancy

The Centers for Disease Control and Prevention (CDC) has reported that at least 30% of all outpatient antibiotics are incorrectly prescribed for the management of viral infections. Inappropriate antibiotic use, especially during pregnancy, increases the risk of short-term and long-term complications, including alteration of the fetal microbiome [30].

A meta-analysis by Zhao et al. [31] showed that use of antibiotics in the antenatal period was associated with asthma or wheezing in childhood and this relationship was shown to be significant. They found that the risk of antibiotic use and pooled ORs of developing wheezing or asthma were 1.09 (95% CI, 0.92–1.29) if antibiotics were used in the first trimester, 1.14 (95% CI, 1.01–1.29) for use in the second trimester, and 1.33 (95% CI, 1.11–1.60) for use in the third trimester, respectively. This analysis showed that the risk was highest if antibiotics were used in the last trimester; however, further studies will be needed to confirm this trend.

It has been reported that during pregnancy, bacteria from the maternal gut can actually be transmitted to the fetus through the placenta and amniotic fluid. Thus, the first bacteria to colonize human beings are most likely transmitted antenatally [32, 33]. In a study by Stokholm et al. in 2014 [34] found that women who had received antibiotics for any reason during pregnancy had increased colonization in the vagina by staphylococcus bacteria as compared to those women who had not received any antibiotics. This increased staphylococcal colonization has been found to be associated with asthma in later childhood [35].

The large number of studies finding significant causal relationships, as well as dose-related increased risk of childhood asthma due to prenatal or childhood antibiotics [35] relationships, has been corroborated by experimental animal and human microbial studies. More studies are still needed addressing the impact of antibiotics used intrapartum, genetic factors, and possible confounding by maternal and childhood infections to be able to confirm this relationship. Use of multiple, broad-spectrum antibiotics early in life (prenatal and during early infancy) appears to have an increased risk of allergies, especially asthma in later life of the child.

Even after adjusting for antibiotic use, maternal infection was found to be associated with childhood asthma and eczema. Thus infections can be considered an independent risk factor as the association was statistically significant [6, 7].

39.5.2 Fetal Gut Microbiota

Recently there has been a lot of attention on the topic of microbiota. The intestine is home to the largest population of microorganisms in the human body which is known as gut microbiota. There is a theory linking microbiota with allergic disorders and the immune system. The microbiota hypothesis proposes that disruptions to the microbial composition during a crucial period in early life can have long-lasting effects on the immune system [36]. A neonate's immune system is biased towards a Th2 dominance which allows microbial colonization and thus helps to avoid inflammatory responses to harmless microorganisms. When the immune system encounters pathogenic organisms, there is a slow shift from the Th2 to Th1 response, thus "training" the immune system and educating it about when to elicit an inflammatory response and when not to. Any disturbance to this process by the use of antibiotics in prenatal or early neonatal life or maternal infections (causing a Th2/Th1 imbalance) can disturb this shift between Th2 and Th1 response, potentially leading to allergic disorders in the future [37].

Dysbiosis, or a derangement in the composition of commensal bacteria, can be induced by several environmental factors, including cesarean birth, antibiotic use, and dietary changes. Pre- and postnatal antibiotic exposure is similarly associated with reduced diversity of the newborn intestinal flora. The clinical relevance of dysbiosis is illustrated by the hygiene hypothesis, which postulates that a lack of early life exposure to a microbe-rich environment favors the development of asthma [38].

Studies on children born on farms showed that consumption of unpasteurized milk-containing high lactobacilli load may have been protective [39, 40] against allergic diseases. This early microbial exposure may lead to an early switch from TH2 to TH1 biased response soon after birth. However, children with a predominance of Th2 response at birth, due to antenatal factors as described above, will not be able to make this switch easily and may persist with TH2 response to lead to allergic disorders. This is an additional mechanism by which maternal infections may be responsible for allergic disorders in offspring.

Another pregnancy-related factor that may play a role in the composition of gut microbiota in children is the mode of delivery. Abdominal delivery by cesarean has been associated with increased incidence of atopy and allergic diseases like atopic dermatitis, rhinitis, asthma, and eosinophilic esophagitis in children [37, 39–41]. During vaginal delivery, the fetus ingests maternal vaginal and colonic microbiota while passing through the birth canal. This is probably a crucial phase of initial gut colonization. This exposure of neonates to maternal bacteria results in stimulation of toll-like receptor (TLR) and production of interleukin (IL)-12 and interferon (IFN)-g. These cytokines promote the differentiation of naïve helper T (Th) cells into Th1 effector cells [37]. Thus, children born by cesarean section are more susceptible to the development of allergies as appropriate exposure to microbiome of newborn through natural birth may be required for maturation of their immune system in early life [42].

39.5.3 Mode of Delivery

Cesarean section is probably linked to allergic disorders in the neonates in two ways. First, cesarean birth is associated with reduced pro-inflammatory cytokine responses to TLR stimulation and secondly, there is an increased abundance of bacterial colonization in the airway later during infancy, increasing the risk of infantile wheezing [43].

Another difference seen on the basis of mode of delivery was in the levels of transforming growth factor (TGF)-b1. These levels were lower in newborns following cesarean section [44]. Thus, newborns born vaginally were exposed to higher levels of TGF-b1 and exhibited more protection towards atopy in later life [45].

However, the data is inconclusive and more long-term studies looking at maternal microbiota and its impact on infant microbiota, as well as the development of infant allergies, are needed.

39.5.4 Breast Feeding and Use of Antibiotics in Early Postnatal Life

Overall breastfeeding is beneficial on the health of the offspring; however, the effect on the prevention of allergic diseases is controversial. A review by American Academy of Pediatrics [46] found that breastfeeding till 3–4 months of age reduces risk of developing eczema, and more than 4 months, reduced chances of atopic disorder in the first 2 years of the child's life [46]. Longer duration of partial or exclusive breastfeeding reduces the risk of asthma even after 5 years of age [46]. Another study from Taiwan of 186 children showed that partial or exclusive breastfeeding for longer than 6 months reduces milk sensitization in children at 1.5 years of age [47]. A Canadian study showed that direct exclusive breastfeeding was more effective than any other mode of breastfeeding in preventing childhood asthma, possibly due to efficient transfer of protective factors like microbiota and alternation in milk factors such as immune cells and cytokines [48].

Antibiotic use prenatally and during first 2 years of life significantly increases the risk of developing atopic and metabolic disorders. Microbiota is most susceptible to irreversible disturbances at this time. Thus antibiotic use during breastfeeding can also impact the neonatal microbiota and thus predispose the child to allergic disorders.

39.5.5 Maternal Diet

Maternal diet is certainly an important determinant of the fetal growth, but recent evidence suggests that it also has an influence on the development of neonatal immune responses and thus determines the proneness of neonate to infectious diseases and allergies [49].

Recent studies have shown a possible role of a *decline in consumption of fresh fruits and vegetables* in the increase of allergic disorders in children [50]. As these foods are rich in antioxidant activity, consumption by the pregnant woman could prevent the development of inflammation, specifically the IL4 dependent IgE production by B cells.

39.5.5.1 Role of Polyunsaturated Fatty Acids (PUFA)

Increased consumption of PUFA by expecting mother promotes the production of Prostaglandin E2, which in turn increases the IL4 production, which is pro-inflammatory. Diets rich in fish oil decrease the production of pro-inflammatory mediators such at TNf alfa and leukotrienes [50]. Hence a diet rich in fish oils and fruits and vegetables and comparatively less in PUFA can reduce the inflammatory response in fetuses [50].

39.5.6 Maternal Allergen Exposure

Contrary to popular belief of allergen avoidance during pregnancy, prenatal consumption of potentially allergenic food items has actually been shown to reduce allergic sensitization in offspring of these women [13].

Various studies have shown that maternal consumption of allergens like peanuts [13], milk [13], egg yolk, wheat, soy, tree nuts, crustaceans, shellfish in non-allergic women reduces allergic reactions, asthma, and allergic rhinitis in their offspring. Consumption of peanuts in the first trimester was associated with reduction of allergic reaction to peanut in offspring [14, 15], milk in the first trimester reduced allergic rhinitis and asthma, and wheat exposure during the second trimester reduced atopic dermatitis in their offspring [13].

To summarize, maternal infection has an important role in the development of childhood asthma and other allergic disorders as an independent risk factor as well as indirectly by the use of antibiotics, which in turn by effecting gut microbiota.

39.6 Prevention Strategies

39.6.1 Recommendations for Clinical Practice

1. Prevent infections during pregnancy by promoting healthy diet and lifestyle.
2. Avoid antibiotic use in pregnancy, including the intrapartum period, as much as feasible. If unavoidable, then restrict antibiotic use to narrow-spectrum antibiotics using only minimal effective dosages.
3. Support vaginal birth as much as feasible to allow for natural exposure to commensals.
4. Encourage breastfeeding.
5. Avoid antibiotic use in children, especially in first 2 years of life; specially avoid broad-spectrum antibiotics.

Key Points

1. Allergic disorders in children have a complex etiology with interplay between genetic and environmental factors.
2. People with atopy have a Th2 skewed response when exposed to certain antigens. They tend to produce more IgE antibodies when exposed to specific antigens, leading to manifestations of allergic reactions.
3. Pregnancy and early postnatal life are chiefly viewed as Th2 dominant states.
4. Any influence on the fetal immune system from conception till full maturity that interferes with normal development or leads to an imbalance between Th1 and Th2 response can lead to the development of allergic disorders in these children in the future.
5. Maternal infection, especially fever and urogenital infections, has been found to be associated with childhood asthma and eczema.
6. Use of multiple, broad-spectrum antibiotic early in life (prenatal and during early infancy) appears to have an increased risk of allergies, especially asthma in later life of the child.
7. Children born by cesarean section are more susceptible to the development of allergies as appropriate exposure to microbiome of newborn through natural birth may be required for maturation of their immune system in early life.
8. Antibiotic use during breastfeeding can also impact the neonatal microbiota and thus predispose the child to allergic disorders.

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40 Genetic Syndromes Mimicking Congenital Infections

Shagun Aggarwal

40.1 Introduction

Many genetic disorders can mimic disease states of environmental etiology due to underlying common pathophysiological mechanisms. One such category of genetic diseases is the pseudo-TORCH syndromes, which closely mimic the perinatal TORCH group of infections. These disorders present in the prenatal or early postnatal period with cardinal findings reminiscent of TORCH infections in the absence of any evidence of an infection [1–3]. It is important for the obstetrician to be aware of these conditions and seek timely genetic opinion, as, unlike TORCH infections, these conditions have a high recurrence risk, and timely recognition and intervention can prevent this.

40.2 What Are Pseudo-Torch Syndromes?

Every practicing obstetrician would have come across a rare case scenario of a woman who appears to have a child affected with TORCH infection in more than one pregnancy or a fetus with a TORCH infection but the virus being unidentifiable despite all possible testing endeavors. These case scenarios are illustrative of a unique group of genetic disorders known as Pseudo-TORCH syndromes. These conditions show clinical and imaging findings of a TORCH infection, but are not due to a viral infection but rather due to an underlying genetic defect [1–3].

At least seven different clinical and imaging phenotypes have been clubbed under the blanket term of Pseudo-TORCH syndromes. Many of these phenotypes show genetic heterogeneity, i.e., mutations in more than one gene can result in that particular genetic syndrome. The common clinical and imaging findings [1–3] in this group are:

1. Microcephaly—usually of prenatal onset
2. Presence of intracranial calcification—this may vary in distribution and density in the different disorders
3. Developmental arrest/delay—this may vary in severity, but is usually significant
4. Seizures

Besides these consistent findings shared by all disorders grouped into Pseudo-TORCH syndromes, various other findings are variably present, which mimic congenital TORCH infections. These are as follows:

1. Ventriculomegaly

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2. Hepatosplenomegaly
3. Lissencephaly, polymicrogyria, and other migration abnormalities
4. White matter abnormalities
5. Thrombocytopenia
6. Retinal abnormalities, cataract
7. Complex neurological abnormalities-spasticity, choreoathetosis, dystonia
8. Intracranial cyst formation.

Table 40.1 depicts the various Pseudo-TORCH syndromes along with their clinical and imaging findings.

40.3 Types of Pseudo-Torch Syndromes

Although the Pseudo-TORCH syndromes resemble each other and the congenital TORCH infections, there are certain distinctive findings in each of these conditions, which can be recognized and used to perform targeted genetic evaluation. The various different syndromes/phenotypes are as follows:

40.3.1 Aicardi Goutières Syndrome

This is the most common disorder mimicking congenital TORCH infections. It presents as an early onset encephalopathy with significant intellectual and physical disability.

40.3.1.1 Clinical Presentation

The onset can be in perinatal period or early infancy. Twenty percent of patients show calcifications in-utero. Individuals with neonatal onset present at birth with abnormal neurologic findings, hepatosplenomegaly, elevated liver enzymes, and thrombocytopenia. Those presenting later usually are symptomatic within the first few weeks of life after a period of normalcy. These infants develop irritability, sterile pyrexias, regression of milestones, focal neurological signs like spasticity, dystonia, and progressive microcephaly. These symptoms have a subacute course lasting few months, usually followed by a static encephalopathy with severe microcephaly and significant intellectual, physical disability. Seizures and exaggerated startle have been reported in some children, and mortality may occur due to severe neurological involvement. Skin lesions in form of chilblains on fingers and toes, and occasionally pressure points can be seen in 40% of individuals and these are characteristic of this condition. Hearing is normal, however varying degrees of cortical blindness may occur with unremarkable ocular findings [4–7].

40.3.1.2 Neuroimaging

Intracranial calcifications in the basal ganglia especially involving putamen, globus pallidus and thalamus; also extending into the white matter, sometimes in a para-ventricular distribution. These findings can be best appreciated on a CT imaging. In addition, MRI reveals white matter abnormalities involving frontotemporal lobes, appearing as T1 hypointensity and T2 hyperintensity. Occasionally, temporal lobe cysts can be seen. Cerebral, cerebellar, and brainstem atrophy can also be appreciated [4–7].

40.3.1.3 Laboratory Findings

CSF leukocytosis and increased interferon-alpha levels are characteristic of Aicardi Goutières syndrome. Peripheral blood shows thrombocytopenia, transaminitis, and positive interferon signature by quantitative PCR [4–7].

40.3.1.4 Molecular Diagnosis

Mutation in at least seven different genes (including *TREX1, RNASEH2A, RNASEH2B, RNASEH2C, ADAR, IFIH1, SMAHD1)* [4–7] can result in this phenotype, and confirmation of diagnosis can be done by multi-gene panel testing/clinical exome sequencing. Some of the genes show an autosomal recessive inheritance, and others depicting autosomal dominant pattern. Families with autosomal recessive inheritance have a recurrence risk of 25% in every pregnancy, while those with autosomal dominant inheritance are usually due to de-novo mutations, with consequent low recurrence risk.

Table 40.1 Disorders initially described as Pseudo-TORCH syndromes or with phenotypic overlap

Disorder	OMIM ID	Distinctive clinical features	Distinctive radiologic findings	Distinctive laboratory findings	Molecular basis	Inheritance pattern
Aicardi Goutieres syndrome	#225750 #610181 #610329 #610333 #615010 #615846 #612952	Hepatosplenomegaly Chilblains, thrombocytopenia, other autoimmune phenomenon, dystonia	Leukodystrophy Calcification in basal ganglia	Increased cerebrospinal fluid interferon levels and leukocytosis	*TREX1* *RNASEH2ARNASEH2BRNASEH2C* *SAMHD1 ADAR* *IFIH1*	Both autosomal recessive and autosomal dominant as per the gene involved
Band-like calcification with simplified gyration and polymicrogyria/ Pseudo TORCH syndrome 1	251290	Seizures, renal dysfunction	Band-like dense cortical calcification, polymicrogyria predominantly fronto-parietal	Autopsy-calcification in pericytes/ astrocytes around blood vessels and polymicrogyria	*OCLN*	Autosomal recessive
Pseudo TORCH syndrome 2	617397	Intracranial hemorrhage, hepatic dysfunction, thrombocytopenia, seizures	Lissencephaly, pachygyria, cerebellar hypoplasia, cortical necrosis, calcification involving basal ganglia, subcortex, periventricular	Cardiac defect, bradycardia, extracranial calcification, metaphyseal changes, hepatomegaly, Increased interferon type 1 signalling	*USP18*	Autosomal recessive
Pseudo TORCH syndrome 3	618886	Episodes of fever and multisystemic illness with respiratory insufficiency, hepatosplenomegaly, thrombotic renal angiopathy, and neuroregression, thrombocytopenia	Cortical atrophy, cerebellar atrophy, hemorrhage, white matter abnormalities	Increased interferon type 1 signalling, evidence of increased IFN stimulated gene expression, features of hemophagocytic lymphocytosis, low NK cells	*STAT2*	Autosomal recessive

(contniued)

Table 40.1 (continued)

Disorder	OMIM ID	Distinctive clinical features	Distinctive radiologic findings	Distinctive laboratory findings	Molecular basis	Inheritance pattern
Hemorrhagic destruction of the brain, subependymal calcification, and Cataracts	#613730	Congenital cataract, seizures	Multifocal parenchymal hemorrhage, cystic degenerative lesions brain, subependymal calcification	Renal cystic dysplasia, ectopia, altered cortico-medullary differentiation, pelvicalyceal dilatation	*JAM3*	Autosomal recessive
Leukoencephalopathy, cystic, without megalencephaly	#612951	Hearing loss, seizures, dystonia, athetosis, doll-like facies	Leukoencephalopathy, Anterior temporal lobe subcortical cysts, periventricular, basal ganglia calcification	–	*RNASET2*	Autosomal recessive
Idiopathic basal ganglia calcification	%114100	Choreoathetosis, seizures, retinitis pigmentosa, retinal calcification	Calcification basal ganglia, dentate nuclei, cortex, subcortical white matter	Autopsy-extensive brain calcium deposits, calcification of vessels, iron deposits	Not known	Not known
Encephalopathy with intracranial calcification, growth hormone deficiency, microcephaly, and Retinal degeneration	225755	Dwarfism, ataxia, retinal degeneration	Basal ganglia calcification White matter changes	Growth hormone deficiency	Not known	Not known

Common features: Microcephaly, developmental arrest, intracranial calcification, and spasticity

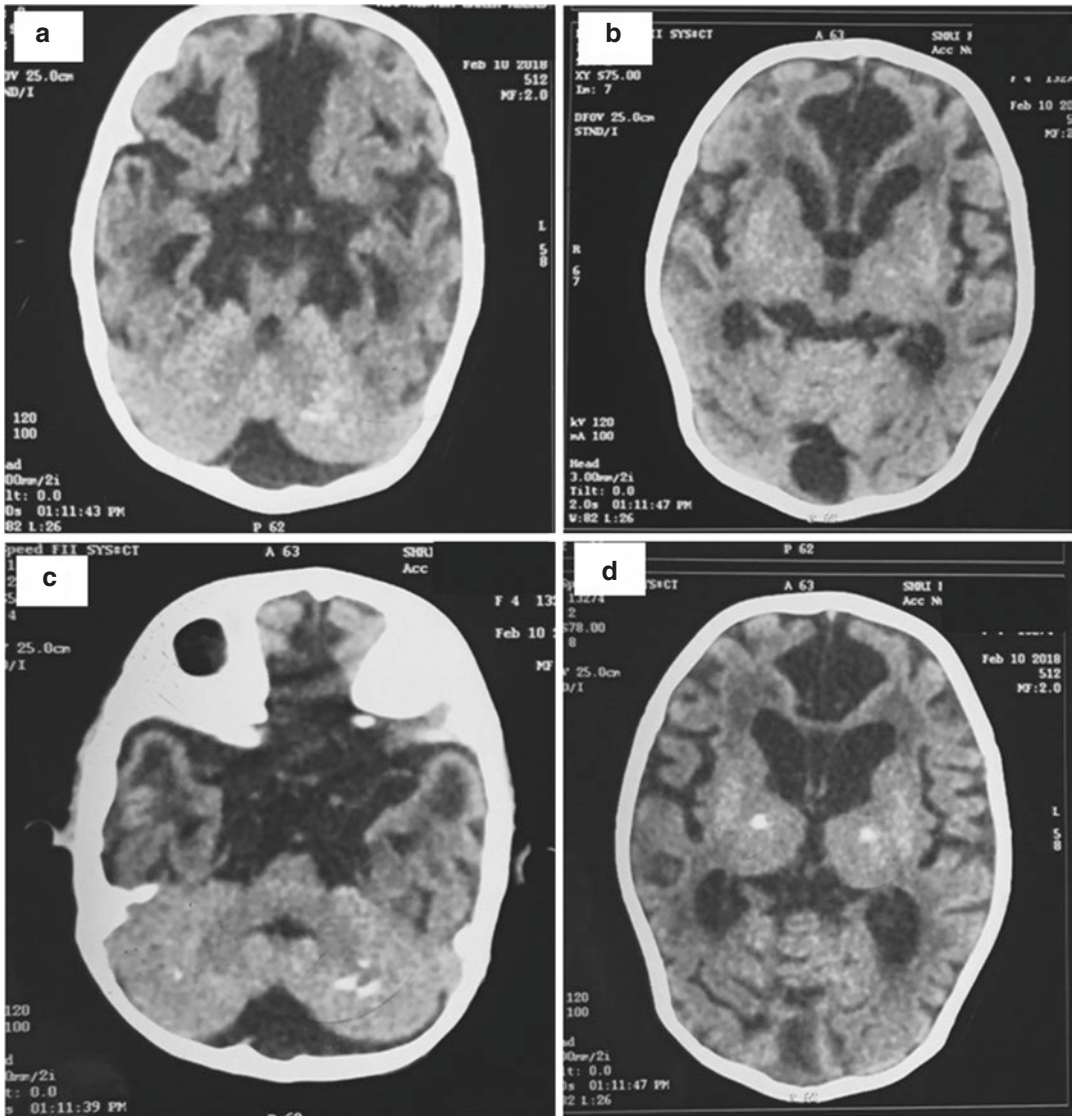

Fig. 40.1 CT brain images of a patient with *TREX1* mutation related to Aicardi Goutières syndrome: (**a**) Marked cerebral atrophy, white matter abnormalities in temporal lobe; (**b**) Marked cerebral atrophy, white matter abnormalities in the frontal lobe, basal ganglia calcification; (**c**) Temporal lobe cysts, cerebellar calcification; (**d**) Basal ganglia calcification, cerebral atrophy (Acknowledgment to Dr. Deepti Saxena and Dr. Kausik Mandal, Faculty at Department of Medical Genetics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow for sharing these images)

Figure 40.1 depicts the CT findings of a patient with Aicardi Goutières syndrome due to *TREX1* mutation. Characteristic findings of basal ganglia and cerebellum calcification, cerebral atrophy and white matter abnormality along with temporal lobe cysts can be appreciated.

40.3.2 Band-Like Calcification with Simplified Gyration and Polymicrogyria

This condition is caused by biallelic mutations in *OCLN* gene.

40.3.2.1 Clinical Presentation

Disease onset is appreciated at birth or within the first few months of life. Clinical course is characterized by microcephaly, facial dysmorphism, severe developmental delay, seizures, spasticity, failure to thrive and early death. Systemic findings like those seen in Aicardi Goutières syndrome are usually not present, and there is no evidence of immune dysregulation. On the other hand, some individuals may develop renal dysfunction. Other rare findings like diabetes insipidus have also been reported [8–10].

40.3.2.2 Neuroimaging

Calcification is usually dense and extensive, involving cortical grey matter (band-like calcification), basal ganglia, brainstem, and cerebellum. In addition, bilateral symmetrical polymicrogyria in a perisylvian and temporal distribution with severe loss of cerebral volume, simplified gyration, and wide Sylvian fissures can be appreciated in MRI [8–10].

40.3.2.3 Laboratory Findings

No specific hematological or biochemical findings in peripheral blood are seen. CSF shows increased protein, but normal leucocytes, glucose, and interferon levels. Brain histology also shows distinctive findings in form of calcification in pericytes/astrocytes around blood vessels along with polymicrogyria [8].

40.3.2.4 Molecular Diagnosis

This is an autosomal recessive condition and all individuals harbor mutations in the *OCLN* gene. Confirmation of diagnosis can be done by Sequencing of this gene. Recurrence risk is 25% for all pregnancies of a couple with previous child with this condition. Figure 40.2 depicts the imaging findings of a patient with *OCLN* mutations with characteristic features of dense calcifications (band-like) in frontoparietal cortex, pachygyria, and cerebral atrophy.

40.3.3 Pseudo-TORCH Syndrome 2

This is a recently described condition caused by biallelic mutations in *USP18* gene.

40.3.3.1 Clinical Presentation

Onset may be in the prenatal or neonatal period. It is characterized by intracerebral hemorrhage,

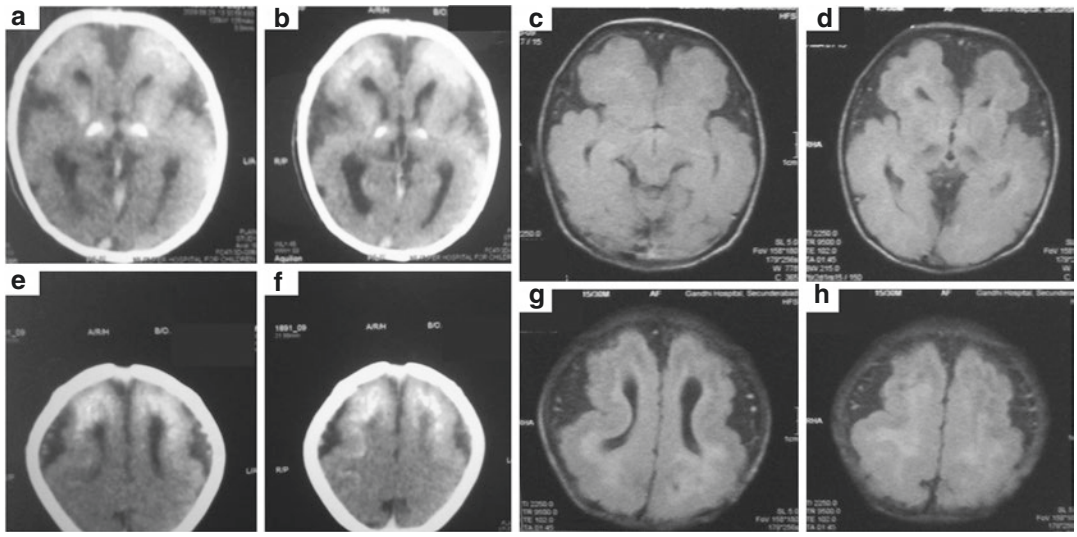

Fig. 40.2 CT and MRI brain images of child with *OCLN* mutation related Band-like calcification-simplified gyration: (**a**) Basal ganglia calcification; (**b**) Basal ganglia and frontal lobe calcification; (**e**, **f**) Bilateral dense frontoparietal cortex calcification; (**c**, **d**) Perisylvian polymicrogyria-pachygyria with deep Sylvian fissures; (**g**, **h**) Polymicrogyria-pachygyria generalized

cortical destruction, intracranial calcifications and microcephaly. Systemic findings like hepatomegaly, deranged liver function, ascites, extracranial calcifications and thrombocytopenia are seen and associated with interferon pathway activation. Extracranial calcifications involving the musculoskeletal system have been reported in few patients. Lactic acidosis and bradycardia have also been reported. Prognosis is poor with infantile demise [11].

40.3.3.2 Neuroimaging

Characteristic finding in this condition is the presence of intracerebral hemorrhage, which can manifest in the prenatal period as early as second trimester. This is accompanied by migrational abnormalities, cerebellar hypoplasia and calcification involving basal ganglia, subcortex, periventricular regions [11].

40.3.3.3 Laboratory Findings

Peripheral blood shows thrombocytopenia, transaminitis, and lactic acidosis [11].

40.3.3.4 Molecular Diagnosis

This is an autosomal recessive condition, and all individuals harbor mutations in the *USP18* gene. Confirmation of diagnosis can be done by Sequencing of this gene. Recurrence risk is 25% for all pregnancies of a couple with a previous child with this condition.

40.3.4 Pseudo-TORCH Syndrome 3

This rare condition is caused by biallelic mutations in *STAT2* gene and is characterized by interferon pathway activation.

40.3.4.1 Clinical Presentation

Episodes of fever accompanied by hepatosplenomegaly, respiratory insufficiency, renal thrombotic angiopathy presenting with proteinuria, thrombocytopenia and neuro-regression. Some individuals develop hemophagocytic lymphohistiocytosis like picture. Prognosis is poor, leading to early lethality. Prognosis is poor with early infantile death [12, 13].

40.3.4.2 Neuroimaging

Intracerebral hemorrhage**, c**ortical and cerebellar atrophy and white matter changes, along with diffuse calcification, are seen [12, 13].

40.3.4.3 Laboratory Findings

Findings of thrombocytopenia, hemophagocytic lymphohistiocytosis and low NK cells, along with elevated liver enzymes and nephrotic range proteinuria, are seen. Transcript analysis shows activation of Interferon stimulated genes [12, 13].

40.3.4.4 Molecular Diagnosis

This is an autosomal recessive condition, and all individuals harbor mutations in the *STAT2* gene. Confirmation of diagnosis can be done by Sequencing of this gene. Recurrence risk is 25% for all pregnancies of a couple with previous child with this condition.

40.3.5 Hemorrhagic Destruction of the Brain, Subependymal Calcification, and Cataracts

Biallelic mutations in the *JAM3* gene result in this autosomal recessive disorder.

40.3.5.1 Clinical Presentation

As the name suggests, this is characterized by massive intracerebral hemorrhage resulting in brain matter liquefaction and cystic degeneration, calcification in the subependymal region and congenital cataracts. Clinically severe developmental delays, microcephaly, seizures and spasticity is present, and death occurs in early infancy. Some patients may also have renal and cardiac malformations, along with hepatomegaly [14, 15].

40.3.5.2 Neuroimaging

Intracerebral hemorrhage, cystic degeneration of brain, porencephalic cysts, calcification in subependymal region, basal ganglia and white matter are the findings appreciated on neuroimaging. Some patients may also show posterior fossa abnormalities [14, 15].

40.3.5.3 Laboratory Findings

Thrombocytopenia and abnormal neutrophil counts have been reported [14, 15].

40.3.5.4 Molecular Diagnosis

This is an autosomal recessive condition and all individuals harbor mutations in the *JAM3* gene. Confirmation of diagnosis can be done by Sequencing of this gene. Recurrence risk is 25% for all pregnancies of a couple with previous child with this condition.

40.3.6 Leukoencephalopathy, Cystic, Without Megalencephaly

This is an autosomal recessive disease caused by mutations in *RNASET2* gene.

40.3.6.1 Clinical Presentation

This condition has a variable severity and closely mimics congenital CMV infection in clinical as well as neuroimaging aspects. Onset is in the first year of life with developmental delay, poor speech development, hearing loss, seizures, and extrapyramidal features like dystonia and choreoathetosis. Most patients achieve ambulation with support and clinical course is of a stable encephalopathy [16–18].

40.3.6.2 Neuroimaging

Multifocal leukoencephalopathy in periventricular and frontotemporal regions, temporal and frontal lobe cysts, ventriculomegaly and intracranial calcification in basal ganglia and cerebellum can be appreciated [16–18].

40.3.6.3 Laboratory Findings

No significant hematological or biochemical finding.

40.3.6.4 Molecular Diagnosis

This is an autosomal recessive condition and all individuals harbor mutations in the *RNASET2* gene. Confirmation of diagnosis can be done by Sequencing of this gene. Recurrence risk is 25% for all pregnancies of a couple with previous child with this condition.

Figure 40.3 shows the imaging findings in a patient with suspected *RNASET2* mutations. Characteristic features of temporal lobe cysts, small foci of calcification in frontal white matter and patchy white matter abnormalities can be appreciated.

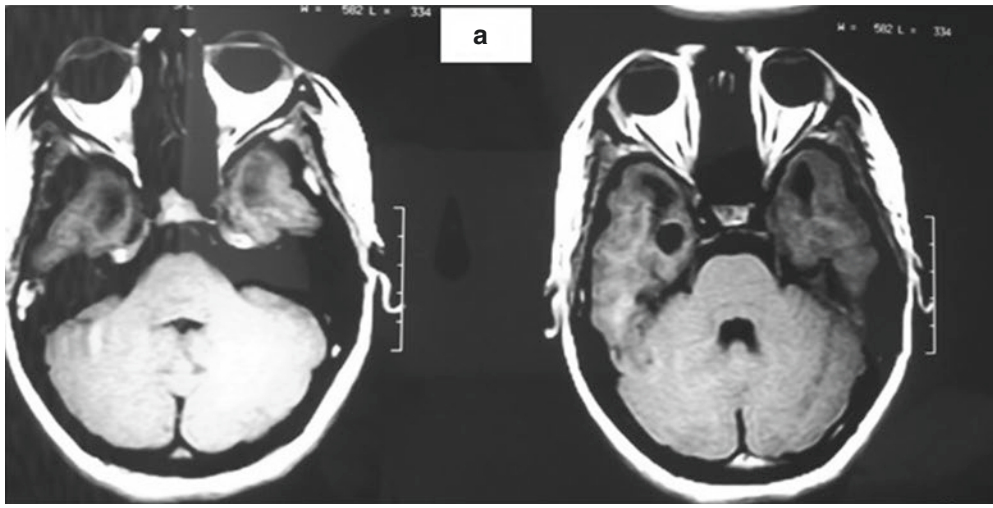

Fig. 40.3 MRI findings of patient with *RNASET2* mutation: (**a**) Bilateral temporal lobe cysts; (**b**) Few fine calcification in bilateral frontal region; (**c**) T2 images showing white matter changes in bilateral frontal regions

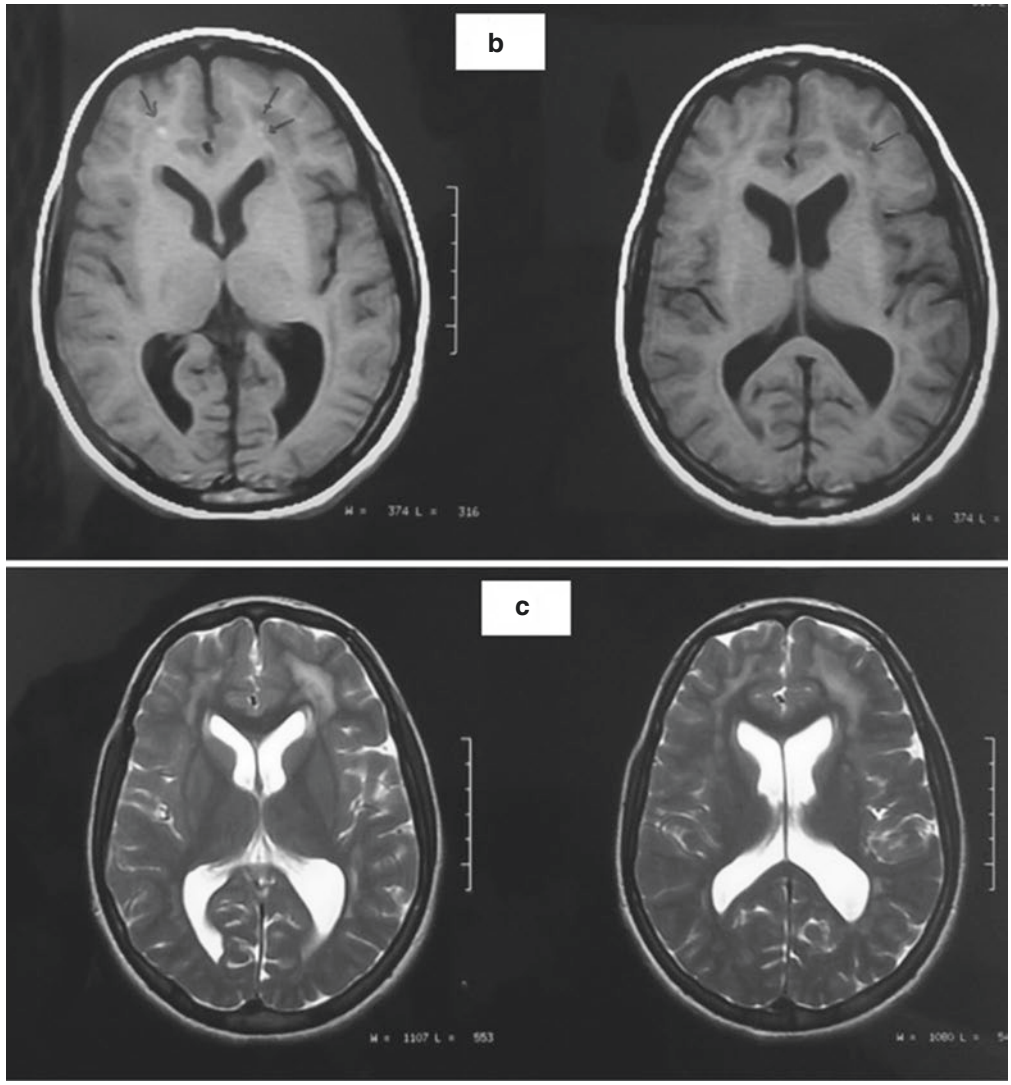

Fig. 40.3 (continued)

40.3.7 Conditions with Unknown Genetic Loci

Two different clinical phenotypes have been described, but their genetic basis is not defined yet. These include the Idiopathic Basal Ganglia calcification childhood type (#114100) [19] and Encephalopathy with intracranial calcification, Growth hormone deficiency, Microcephaly, and Retinal degeneration (225755) [20]. Both conditions show a variable severity of clinical presentation and autosomal recessive inheritance.

40.4 Shared Pathophysiology of Torch Infection and Pseudo-Torch Syndromes

A shared pathophysiological mechanism underlies the phenotypic similarity between many of the conditions included under Pseudo-TORCH syndromes and the congenital TORCH infections. This mechanism has been well studied in Aicardi Goutières syndrome, where high CSF interferon levels is one of the cardinal diagnostic

criterion. The mutations in various genes, including *TREX1, RNASEH2A, RNASEH2B, RNASEH2C, ADAR, IFIH1, USP18, STAT2,* have been shown to result in an activation of the interferon 1 signaling pathway. These disorders are now called the Type 1 Interferonopathies, a group that also includes other autoinflammatory phenotypes like SLE and familial chilblain lupus. TORCH infections also evoke a similar interferon response as part of innate immunity. Many of the sequelae of the infection, especially in the growing fetus, are believed to be secondary to the interferon pathway activation. This shared pathophysiology is likely responsible for the clinical and imaging overlap [21, 22].

40.5 Recognition of Pseudo-Torch Syndromes in the Clinic

1. Clinical and neuroimaging findings of congenital TORCH infection in the absence of any evidence of infection, i.e., normal TORCH serology and/or negative viral PCR and cultures indicates the possibility of a Pseudo-TORCH syndrome. Rarely some cases may show a positive serology, but this is akin to an anamnestic response and should not be taken as confirmation of infection. Infection can be ruled out by performing RT-PCR or culture for the corresponding organism.
2. Recurrence of congenital TORCH infection in more than one pregnancy of a woman. Although secondary reactivation of TORCH infections has been rarely reported, recurrence is more likely to be due to an underlying genetic etiology. In all such cases, an attempt should be made to perform a genetic evaluation.

40.6 Confirmation of Diagnosis of Pseudo-Torch Syndrome

Confirmation of diagnosis is done by performing a DNA-based molecular diagnostic test. All the Pseudo-TORCH syndromes belong to a group of genetic diseases called *Monogenic/Single-gene/Mendelian disorders*. The genetic defect in single-gene disorders lies at the level of DNA and can be as small as change in a single base of the DNA molecule. These defects cannot be picked up using tests like karyotype or chromosomal microarray. A molecular diagnostic test that involves sequencing of the genes involved is required for definitive diagnosis. As mutations in many different genes can present as a Pseudo-TORCH syndrome phenotype, and due to clinical overlap, it is difficult to distinguish the individual conditions, sequencing of all the involved genes in one step provides more timely and cost-effective diagnosis. The test which is employed for such a single-step diagnostics is called *Clinical Exome sequencing*. This test is based on the technology of Next generation sequencing and is able to perform sequencing of all known disease-causing Mendelian genes (6000–8000 genes). The cost for this test is between INR 15,000–20,000, and it is easily available in various genetic laboratories across India. In case this test cannot be performed or clinical diagnosis is strongly indicative of a specific Pseudo-TORCH syndrome, sequencing of a specific gene can also be done using conventional methods like Sanger sequencing. A molecular diagnosis helps in confirmation of clinical suspicion and is mandatory for performing invasive prenatal diagnosis in subsequent at risk pregnancies.

40.7 Significance and Practical Implications

It is important to distinguish Pseudo-TORCH syndromes from congenital TORCH infections due to the following reasons-

(a) Unnecessary treatment targeted to an infective etiology can be avoided.
(b) Recurrence risk for subsequent pregnancies of the woman would be 25% in most Pseudo-TORCH syndromes, in contrast to a negligible recurrence risk for congenital TORCH infections. This helps in accurate counseling of the couple and discussion of preventive strategies.

(c) Genetic testing is important for confirmation of diagnosis of Pseudo-TORCH syndrome.
(d) Prenatal diagnosis can be provided for Pseudo-TORCH syndromes in subsequent pregnancies of the woman as early as 11–12 weeks by chorionic villus sampling. This testing is possible only if the causative mutation in the affected child has been identified prior to the pregnancy planning.
(e) Various drugs like ruxolitinib, baricitinib, tofacitinib which are JAK inhibitors are known to downregulate the interferon 1 stimulated genes (ISG). ISGs are believed to be responsible for the organ damage in majority of Pseudo-TORCH syndromes as well as congenital TORCH infections. Downregulation of ISGs by JAK inhibitors has shown clinical benefit in patients with Aicardi Goutieres syndrome and *USP18* associated Pseudo-TORCH syndrome2. However, this treatment is shown to have maximal benefit when started presymptomatically [23–25].

40.8 Conclusion

Pseudo-TORCH syndromes are a group of genetic diseases that closely mimic the congenital TORCH infections. Recognition of these conditions is important for appropriate management, counseling, and prevention in subsequent pregnancies. A genetic consultation and molecular genetic testing can help in the diagnosis of these syndromes, thereby optimizing patient care.

Key Points

1. Pseudo-TORCH syndromes show intracranial calcification along with clinical and neuroimaging overlap with congenital TORCH infections.
2. Pseudo-TORCH syndromes should be suspected in cases with negative viral workup and those families showing a recurrence.
3. Genetic testing is now easily available and not very expensive. This testing is mandatory to confirm the diagnosis as well as to provide prenatal diagnosis.
4. Identifying the genetic etiology in the index patient enables early, definitive prenatal diagnosis at 11–12 weeks by chorionic villus sampling, and hence prevents recurrence.
5. Identification of genetic etiology also helps in appropriate management of affected individual.

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Part X

Infection Prevention Strategies in Obstetrics

Vaccination in Pregnancy

41

Anshuja Singla and Nasrin Fatima

41.1 Introduction

The development of vaccines has been one of the greatest achievements in the field of modern medicine which has revolutionized the field of public health. It is not only cost effective but also has eradicated some dreadful diseases such as smallpox and provided protection against diseases which were responsible for high morbidity and mortality in the past centuries. It has been one of the most successful public health campaigns launched worldwide.

Centers for Disease Control and Prevention surveyed nearly 2100 women aged 18–49 years who were pregnant any time, only 54% of pregnant reported getting a flu vaccine before or during pregnancy and 55% of the pregnant women reported receiving tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) during pregnancy [1]. According to a statistical report, in the year 2017, approximately 29 million pregnant women across India were vaccinated.

Vaccination in pregnancy carries more significance as it not only protects the mother but also the baby from certain vaccine preventable diseases. The various vaccinations recommended during pregnancy will be discussed in the chapter.

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41.2 Innate and Adaptive Immunity

Immunity is the ability of a human host to resist foreign micro-organisms. It is mainly divided into two broad categories: innate immunity and adaptive immunity [2]. It can also be classified as active immunity and passive immunity. Active immunization is the administration of an antigen to stimulate antibody production and passive immunization is administration of an antibody to provide short-term protection [3]. The type of immune response that is present since birth is innate immunity, also known as natural or native immunity [4]. It comprises epithelial barrier and various phagocytes including neutrophils, monocytes, and macrophages, whereas adaptive immune response is acquired during the lifetime when an individual is exposed to a specific micro-organism and includes B and T lymphocytes.

Certain specific features of innate immunity and adaptive immunity are enlisted in Table 41.1 [3].

41.3 Immunology of Pregnancy

During pregnancy, maternal immune system adapts to accommodate the semi-allogenic fetal graft. This is necessary for the acceptance of the fetus and also for the development of the placenta without affecting the maternal host.

S. Mehta, A. Grover (eds.), *Infections and Pregnancy*, https://doi.org/10.1007/978-981-16-7865-3_41

Table 41.1 Different types of immune responses

Innate immunity	Adaptive immunity
Present since birth	Acquired after birth
First line of defense	Subsequent line of defense
Poor specificity, antigen nonspecific	High specificity, antigen specific
Rapid response, within minutes	Slow response, takes days
Does not react against the host	Can react against the host
No memory	Memory present

Various local and systemic modifications are now suggested to be involved in protecting the fetus from the maternal immune response, mainly:

- Cytokine shift—Successful pregnancy is associated with a dominance of Th2-type immunity, and induction of Th1-type responses considered potentially dangerous for the continuation of pregnancy [5].
- Hormonal effects—Estrogen and progesterones are massively upregulated during pregnancy, and both of these hormones have immunomodulatory functions [5].
- HLA expressions—Trophoblasts are the main cell type of the placenta, and exhibit unique Major Histocompatibilty Complex (MHC) expression compared to mother and baby [5]. MHC class II molecules are not expressed by trophoblasts rather non-classical MHC gene encoding HLA-G are expressed which downregulate natural killer (NK) cell function [6].

Ideally, women should be completely vaccinated before pregnancy. The benefits of vaccination in pregnancy should outweigh the risk to the mother and fetus.

Inactivated or killed vaccines, toxoids, and immunoglobulins are usually safe during pregnancy. There is no evidence of any harmful effects of such vaccines on the fetus or on the pregnancy.

41.4 Vaccination

It is the method of inducing adaptive immune response against microbes by exposure to non-pathogenic forms or various components of the microbes [2]. Vaccines are produced from non-pathogenic or purified components of the microbes. They provide protection against infection by inducing active immunity and producing immunological memory which provides protection even in subsequent exposures.

There are three different kinds of vaccines—live attenuated vaccines, killed vaccines, and purified macromolecules derived from the microbes [3].

41.4.1 Live Attenuated Vacccines

Live attenuated vaccines are created by reducing the virulence of a pathogen but keeping it viable [3]. Though the infectivity and pathogenicity are abolished but the antigenicity of the pathogen still remains. These vaccines stimulate a strong and effective immune response that is long lasting. Since they are live attenuated, less number of doses is required to produce an adequate immune response. When administered, these vaccines stimulate the host immune response to produce antibodies and memory cells against that pathogen.

In very rare cases, natural mutation may convert this less virulent pathogen to a more virulent form or may get incorporated into the host genome resulting in infection. Also they carry great risks to the fetus and thus *live attenuated vaccines are contraindicated in pregnancy.*

41.4.2 Killed Vaccines

Inactivated or killed vaccines are produced from pathogens that have lost their disease producing ability or virulence through physical or chemical

methods [3]. Immune response produced requires multiple dosing and is not long lasting. There is no risk of inducing infection as in live vaccines, safety profiles are favorable, and are more safe and stable than live vaccines [3]. Killed vaccines include inactivated polio vaccine, whole cell pertussis vaccine, rabies vaccine, and hepatitis A vaccine.

41.4.3 Purified Macromolecules

Three types of purified macromolecules are in current use [3]:

- Subunit vaccines—These vaccines contain only the antigen that stimulates immune response and not the entire pathogen such as Hepatitis B vaccine.
- Conjugate vaccines—These vaccines are produced from the poorly immunogenic polysaccharides that are conjugated with a carrier protein to increase their immunogenicity. Examples are Haemophilus influenzae vaccine, Neisseria meningitidis, and Streptococcus pneumoniae vaccine.
- Toxoids—These are produced by treating bacterial toxins with formaldehyde and include diphtheria toxoid and tetanus toxoid.

Table 41.2 enumerates the vaccines that are indicated, recommended in certain conditions, and contraindicated in pregnancy [7]:

41.5 Specific Vaccines and Their Use in Pregnancy

41.5.1 Bacillus-Calmette–Guerin (BCG)

It is contraindicated in pregnancy due to the risk to the fetus associated with live vaccines [8]. It falls into the category C and no well controlled studies have been done in pregnant women.

Table 41.2 Recommendation of vaccines in pregnancy

Indicated during pregnancy	Recommended only under specific conditions	Contraindicated in pregnancy
Inactivated influenza vaccine	Hepatitis A	BCG vaccine
Pertussis vaccine	Hepatitis B	Measles vaccine
Inactivated polio vaccine	Meningococcal vaccine	Mumps vaccine
Diphtheria toxoid	Pneumococcal vaccine	Rubella vaccine
Tetanus toxoid	Rabies vaccine	Varicella vaccine
	Typhoid vaccine	Human papilloma virus vaccine
	Yellow fever vaccine	Vaccinia vaccine

41.5.2 Measles, Mumps, and Rubella (MMR)

MMR vaccine should not be administered to a woman who is pregnant or is planning to get pregnant because of the risk associated with live vaccines [9]. Woman who received MMR vaccine should avoid conception for 28 days [3]. If a woman gets vaccinated with MMR vaccine during pregnancy, she should be explained about the risks. But MMR vaccination during pregnancy is not an indication for termination of pregnancy [10].

41.5.3 Varicella Vaccine

Pregnant women who develop varicella can have more severe illness and have a 1–2% risk of transmitting the virus to the fetus causing congenital varicella syndrome [11, 12]. Women who are susceptible and planning to conceive should receive two dose schedule of varicella vaccine and avoid conception for 28 days [13].

If woman gets inadvertently vaccinated during pregnancy, she should be counseled about the risk but it is not an indication to terminate pregnancy [14]. No adverse outcomes have been associated with inadvertent varicella vaccination during pregnancy [14].

41.5.4 Human Papillomavirus Vaccine

CDC recommends routine vaccination at 11 or 12 years of age. It can be given as early as 9 years of age. Vaccination is also recommended for females aged 13 through 26 years and for males aged 13 through 21 years if not vaccinated previously or completed the three dose schedule. The recommended three dose schedule is 0, 1–2 months, and 6 months [15]. HPV vaccination is not recommended in pregnancy as the effect on the fetus is still not known. If a woman is found to be pregnant, she should delay the initiation of the vaccination series [15]. If a woman becomes pregnant after first dose of the vaccine, the subsequent doses can be delayed till postpartum [15].

41.5.5 Influenza Vaccine

Influenza vaccination is an important component of prepregnancy, antenatal, and postpartum period. Influenza infection in second and third trimester can result in increased risk of progression to pneumonia, intensive care unit admission [16], and adverse perinatal and neonatal outcomes such as preterm birth, small for gestational age (SGA), or still birth [17]. According to the recommendations of the American College of Obstetricians and Gynecologists and CDC guidelines, all adults should receive one single dose of influenza vaccine annually [18].

Women who are pregnant or are planning to conceive during the influenza season should receive inactivated influenza vaccine as soon as it is available [18] and it can be given during any trimester [18].

41.5.6 Tetanus, Diphtheria, and Pertussis Vaccine (Tdap)

On June 10, 2005, Tdap vaccine was formulated for use in adults and adolescents in the United States between the age group 11–64 years to reduce the pertussis associated morbidity in adults and maintain the standard of care for tetanus and diphtheria [19]. The majority of morbidity and mortality attributable to pertussis infection occurs in infants who are 3 months and younger [20] but the vaccination series in infants usually begins by 2 month of age [21]. This leaves a window of significant vulnerability for infants [22]. Thus, in 2013, tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccination during pregnancy was introduced to protect the infant passively in the first few months of life [23]. Vaccination is done between 27 and 36 weeks of gestation, in order to maximize the transplacental transfer of pertussis antibodies, irrespective of previous status of vaccination. If not administered during pregnancy, Tdap should be given immediately postpartum, if the woman has never received prior vaccination [23]. If vaccinated before 27–36 weeks, no further vaccination is required. Tdap can be administered outside the window of 27–36 weeks in case of wound management or pertussis outbreak. Partners, family members, and infant caregivers should be vaccinated, ideally 2 weeks before coming in contact with the newborn, if not vaccinated earlier [24].

41.5.7 Tetanus Toxoid (TT)

Tetanus kills an estimated 180,000 neonates (about 5% of all neonatal deaths) and up to 30,000 women (about 5% of maternal deaths) annually [25]. The use of Tetanus and adult diphtheria (Td) rather than TT is recommended during pregnancy and in women of childbearing age to prevent maternal and neonatal tetanus and diphtheria since 1989.

If a woman has never been vaccinated against tetanus or the status is unknown, three doses of tetanus vaccination are recommended at 0 weeks,

4 weeks, and 6–12 months. The Tdap vaccine should replace one dose of Td, ideally between 27 and 36 weeks of gestation. Two more additional doses after the third dose should be given to women who are being vaccinated against tetanus for the first time during pregnancy; fourth dose to be given 1 year after third dose and fifth dose to be given 1 year after the fourth dose or these doses can be given in subsequent two pregnancies after the third dose to provide protection throughout the childbearing age.

If a woman has had 1–4 doses of TT/Td in the past, she should receive one dose of TT/Td during each subsequent pregnancy to a total of five doses.

Under the Ministry of Health and Family Welfare of India, Td vaccine is given during pregnancy as two doses, first dose to be given as early as possible and the next dose to be given after 4 weeks. If the woman has received two doses of Td in her previous pregnancy and if it was within 3 years, then a single booster dose of Td will be sufficient [26].

41.5.8 Hepatitis A

Inactivated Hepatitis A is recommended if an associated high-risk condition [27] is present.

Indications for Hepatitis A vaccination in pregnancy are:

- Chronic liver disorder
- Hemophilia
- Intravenous drugs users
- Working with or near sewage
- Women working in institutions (mental asylums) where levels of personal hygiene may be poor
- Working with primates [28].

41.5.9 Hepatitis B

Infection during pregnancy causes severe maternal morbidity such as severe hepatic infection and increases the risk of preterm birth. The risk of vertical transmission of infection is around 70%–90%. It increases the risk of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma in the child later in life.

The safety and efficacy of Hepatitis B vaccine in preventing the infection is around 90%–100%. The recombinant vaccine is recommended in pregnant woman with high-risk factors.

Indications for Hepatitis B vaccination during pregnancy are:

- Intravenous drug user
- Multiple sexual partners
- Partner having Hepatitis B infection
- Received blood transfusions or blood products
- Liver disease or chronic kidney disease
- Women traveling to high risk countries
- Female sex workers
- Exposure to body fluids at work places such as hospitals [29].

41.5.10 Meningococcal Vaccine

Routine vaccination with single dose of meningococcal vaccine is recommended for all adolescents and particularly those women with high-risk conditions such as asplenia, immunosuppressed, complement deficiency, traveling to high-risk endemic areas, history of contact with an infected individual, or a university student under 25 years [30].

The two available vaccines are Meningococcal Group C conjugated vaccine (MenC) and quadrivalent (ACW135Y) polysaccharide vaccine.

Usually their use is not recommended during pregnancy, but single dose may be given only for abovementioned high-risk conditions [31]. Conjugate vaccine is preferred to polysaccharide vaccine as it provides better and long lasting protection. But in pregnancy polysaccharide vaccine is safe and immunogenic.

41.5.11 Pneumococcal Vaccine

Ideally vaccination should be done prior to conception. Unimmunized pregnant women with

medical conditions such as asplenia, complement deficiencies, immunosuppression, cardiopulmonary disease, renal and other metabolic diseases should receive single dose of the 23-valent pneumococcal purified capsular polysaccharide vaccine [32].

41.5.12 Typhoid

Pregnant woman should be advised to avoid travel to typhoid endemic areas [33]. If indicated, single dose of inactivated parenteral vaccine can be given at least 2 weeks before travel [34].

41.5.13 Rabies Vaccination

The fatality rate of rabies infection is around 100% [35]. It is associated with increased risk for maternal death and indeterminate risk to the fetus.

Rabies post-exposure prophylaxis is the method of choice for preventing rabies infection [36]. Rabies vaccine is not contraindicated in pregnancy and breastfeeding and can be given in woman at risk of infection [3]. Post-exposure prophylaxis includes one dose of rabies vaccine given intramuscularly on the day of exposure and then a dose of vaccine given again on days 3, 7, and 14. Women who have not been previously immunized should also receive a dose of human rabies immune globulin along with the rabies vaccine.

41.5.14 Yellow Fever Vaccine

As with all other live vaccines, yellow fever vaccine is also avoided in pregnancy. Pregnant women should be advised to avoid travel to an endemic area. If unavoidable, vaccine can be given after consulting an infectious disease specialist [37].

If a woman received yellow fever vaccine, she should delay conception by at least 2 weeks; however, avoidance for a month is more desirable. If a woman gets vaccinated during pregnancy, she should be counseled about the minimal chance of the baby being affected.

41.6 Breastfeeding and Vaccination

Neither inactivated nor live attenuated vaccines are contraindicated during breastfeeding. It poses no risk to the mother or the infant. Live viruses in the vaccines can replicate in the mother but have been demonstrated not to be excreted in human milk.

The vaccines that are contraindicated during lactation are:

- Smallpox vaccine—There is risk of contact transmission from the mother to the child [14].
- Yellow fever vaccine—Breast feeding is avoided as a precaution after yellow fever vaccination because of the risk of vaccine associated neurologic disease in infants whose mothers were recently vaccinated [38]. Until specific research data are available, vaccination is to be avoided during lactation. However, if travel to an endemic area cannot be postponed, vaccination should not be withheld [14].

41.7 Summary

Vaccination has certainly revolutionized the field of public health**.** It is not only cost effective but also has eradicated some dreadful diseases such as smallpox and provided protection against diseases which were responsible for high morbidity and mortality in the past centuries. Vaccination during pregnancy provides us an opportunity not only to protect the mother but also to provide protection to the newborn from certain vaccine preventable diseases. Live vaccines are usually contraindicated in pregnancy due to the theoretical risks to the fetus. Inactivated or killed vaccines, toxoids, and immunoglobulins are usually safe during pregnancy. Breastfeeding and postpartum period is not a contraindication to vaccination.

Key Points

- Live attenuated viral and bacterial vaccines are contraindicated during pregnancy because of the theoretical risk to the fetus.
- There are no reports of fetal risks from vaccinating the pregnant women with inactivated vaccines or toxoids.
- Vaccines such as inactivated influenza vaccine should be given in pregnancy as soon as possible.
- Tdap should be given between 27 and 36 weeks of gestation.
- Vaccines such as Hepatitis A and B, pneumococcal, meningococcal, and rabies can be given only under specific conditions and the usual dosing schedule is followed.
- Breastfeeding is not a contraindication to vaccination except for smallpox and yellow fever vaccines.

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42 Prevention of Post-Cesarean Infection

Patrick Duff

42.1 Introduction

Cesarean delivery is now the most frequently performed major operation in the United States. In most US medical centers, the cesarean delivery rate ranges from 25 to 30%. The total number of cesareans in the country now exceeds one million per year. Internationally, the World Health Organization (WHO) estimates that 18.5 million cesareans are performed each year. Approximately 40% of countries have cesarean delivery rates <10%. About 10% have cesarean delivery rates of 10–15%, and approximately 50% of countries have rates that exceed 15% (https://www.who.int>healthreport>30C-sectioncosts).

Infection is the most common postoperative complication of cesarean delivery. Infection typically takes three forms: endometritis (organ space infection), wound infection (surgical site/incisional infection), and urinary tract infection. Although most of these infections are straightforward to diagnose and treat, some may evolve into more serious, and even life-threatening conditions such as sepsis, pelvic abscess, septic pelvic vein thrombophlebitis, or wound dehiscence. This chapter will provide an evidence-based review of the key preventive measures that reduce the risk of postoperative infection. The principal focus will be on measures that help prevent endometritis and wound infection.

42.2 Endometritis (Organ Space Infection)

The frequency of post-cesarean endometritis depends upon the socioeconomic characteristics of the patient population, the indication for the cesarean (scheduled versus urgent versus emergent), and the use of antibiotic prophylaxis. In essence, the highest rates of infection occur in women of low socioeconomic status, who have been in labor and who may not have received adequate antibiotic prophylaxis. In the past, when widespread use of prophylactic antibiotics was not a trend, the rates of endometritis exceeded 50% in highly indigent patient populations. Today, the frequency is significantly lower, <10% in most populations [1].

The principal microorganisms that cause endometritis are anaerobic Gram-negative bacilli such as *Bacteroides species* and *Prevotella species*, anaerobic Gram-positive cocci such as *Peptococcus* species and *Peptostreptococci* species, and aerobic Gram-positive cocci such as group B streptococci, enterococci, and staphylococci (Fig. 42.1). The major risk factors for post-cesarean delivery are summarized in Table 42.1.

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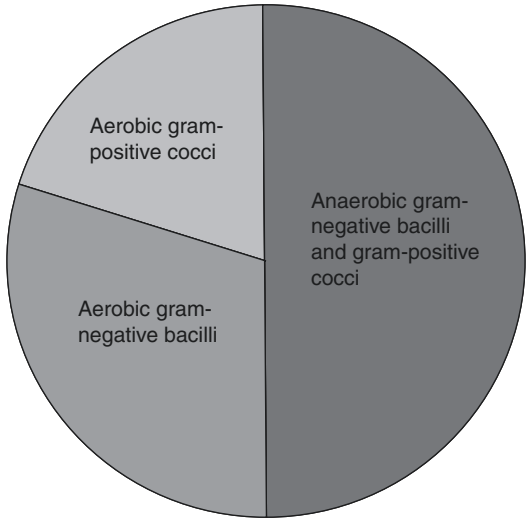

Fig. 42.1 Principal microorganisms responsible for post-cesarean endometritis

Table 42.1 Principal risk factors for post-cesarean endometritis

• Low socioeconomic status
• Nulliparity
• Prolonged labor with ruptured membranes
• Multiple internal vaginal examinations
• Internal fetal monitoring
• Group B streptococcal colonization
• Bacterial vaginosis

Three steps are of critical importance in reducing the frequency of endometritis: cleansing of the vagina with antiseptic prior to surgery, use of prophylactic antibiotics prior to surgery, and removal of the placenta by umbilical cord traction rather than by manual extraction.

42.2.1 Vaginal Cleansing Prior to Surgery

There is mention of various studies in literature that have sought to determine the benefits of cleansing of the vagina with antiseptic solution in addition to administration of prophylactic systemic antibiotics to reduce the incidence of post-cesarean infection. Starr and colleagues [2] conducted a randomized, placebo-controlled trial of 308 women who underwent a non-emergency cesarean delivery. They demonstrated that the practice of a 30-second vaginal scrub with povidone-iodine as compared to only an abdominal scrub, decreased the incidence of postoperative endometritis in the women (7% versus 14.5%, $p < 0.05$). The groups did not differ in the frequency of wound infection.

Haas and colleagues [3] in another randomized controlled trial evaluated composite postoperative morbidity which included fever, endometritis, sepsis, readmission, and wound infection in women receiving preoperative vaginal cleansing. They found that vaginal cleansing with povidone-iodine preoperatively, compared with an abdominal scrub alone, was associated with a decreased incidence of the composite postoperative morbidity(6.5% versus 11.7%; relative risk, 0.55; 95% CI, 0.26–1.11; $p = 0.11$).

Subsequently, Asghania and associates [4] conducted a double-blind, non-randomized study of 568 women undergoing cesarean delivery. They were divided into two groups—one which received an abdominal scrub plus a 30-second vaginal scrub with povidone-iodine and the second which received an abdominal scrub alone. They reported a reduction in the incidence of postoperative endometritis in women who received the combined scrub (1.4% versus 2.5%; $p = 0.03$, adjusted odds ratio, 0.03; 95% CI, 0.008–0.7).

In another study by Yildririm and colleagues [5], a randomized controlled trial was conducted to evaluate infection rates in 334 women who, in addition to an abdominal scrub, received vaginal cleansing with povidone-iodine in comparison to 336 patients who were given the standard abdominal scrub only. They documented a decreased incidence of endometritis in women who received the combined abdominal and vaginal scrub (6.9% versus 11.6%; $p = 0.04$; RR, 1.69; 95% CI, 1.03–2.76).

Haas and colleagues [6] published a Cochrane review evaluating seven studies, which studied the effectiveness of preoperative vaginal cleansing with povidone-iodine. The total study population included 2635 women. They concluded that vaginal preparation with povidone-iodine at the time of cesarean delivery significantly decreased the rate of postoperative endometritis compared with the control group (4.3% versus

8.3%, RR, 0.45; 95% CI, 0.25–0.81.) with the most significant impact in women who were in labor before delivery.

In the most recent systematic review and meta-analysis, 16 randomized controlled trials with 4837 patients were reviewed by Caissutti et al. [7] The frequency of postoperative endometritis was the primary endpoint of their study. Six trials considered only patients undergoing a scheduled cesarean delivery, nine studies included both scheduled and unscheduled cesareans, and one included only unscheduled cesareans. In 11 studies, the antiseptic solution was povidone-iodine, while two trials used chlorhexidine-diacetate 0.2%; one used the 0.4% version of this solution. Another trial used metronidazole, 0.5% gel, and the other used the antiseptic cetrimide, a mixture of different quaternary ammonium salts. Systemic antibiotics were administered prior to the surgical incision in six of the trials, while in another six, antibiotics were given after the umbilical cord was clamped. In two trials, systemic antibiotics were given at varying times, and, in the two final trials, the timing of antibiotic administration was not reported.

The review concluded that, in 15 trials, women in the treatment group reported a significantly lower rate of endometritis (4.5% compared to 8.8%, RR, 0.52, 95% CI, 0.37–0.72). The beneficial effect of vaginal cleansing was statistically significant only in the group of women who were in labor (8.1% versus 13.8%, RR, 0.52, 95% CI, 0.28–0.97.) In the subgroup analysis of the ten trials that used povidone-iodine, the reduction in the frequency of post-cesarean endometritis was statistically significant (2.8% versus 6.3%, RR, 0.42, 95% CI, 0.25–0.71). However, this same protective effect was not observed in women treated with chlorhexidine.

42.2.2 Administration of Prophylactic Antibiotics

More than 50 years ago, the classic sequence of basic science experiments that forms the foundation for use of prophylactic antibiotics were performed on guinea pigs by Burke [8]. He conclusively demonstrated that prophylactic antibiotics are most effective when they are administered prior to the surgical incision and prior to the time that bacterial contamination occurs. In Burke's studies, it was observed that when prophylaxis was delayed more than 4 h after the start of surgery, no beneficial effect occurred.

Interestingly, when prophylactic antibiotics began to be used for cesarean delivery, concerns were raised about the possible exposure of the neonate to antibiotics just prior to delivery. Specifically, the obstetricians questioned whether this exposure would lead to an increased frequency of evaluations for suspected sepsis and would select for resistant organisms that would make neonatal sepsis more difficult to treat [9, 10]. Accordingly, for almost two decades, the standard of care was to administer prophylaxis after the umbilical cord was clamped.

This long-standing practice was challenged in 2007 by Sullivan and colleagues [11]. Using a carefully designed, prospective, randomized, double-blind trial, they showed that patients who received preoperative cefazolin had a significant reduction in the frequency of endometritis compared to women who received the same antibiotic after cord clamping (1% versus 5%, RR 0.2, 95% CI, 0.2–0.94). Though the rate of wound infection was lower in the preoperative antibiotic group (3% versus 5%), this difference did not reach statistical significance. The most significant finding recorded was that there was no increase in the frequency of proven or suspected neonatal infection in infants exposed to antibiotics prior to delivery. Subsequent to the publication by Sullivan et al., other reports [12, 13] have confirmed that administration of antibiotics prior to surgery is more effective in preventing endometritis and wound infection compared to administration after umbilical cord clamping. Moreover, preoperative administration of antibiotics does not increase the frequency of proven or suspected neonatal sepsis.

In an older review, the present author [14] reviewed the evidence regarding choice of antibiotics and number of antibiotic doses and concluded that a single dose of a first-generation cephalosporin such as cefazolin was the preferred

regimen. The effectiveness of a single dose of first-generation cephalosporin was comparable to two and three-dose regimens and to single or multiple-dose regimens of broader-spectrum agents. As of today, the recommendation for antibiotic prophylaxis is to use a single 2 g dose of cefazolin.

In the recent past, four papers have raised the possibility that the prophylactic effect of antibiotics can be increased if the spectrum of activity of the antibiotic regimen is broadened to include an agent that is effective against *ureaplasms*. In the first report, Tita et al. [15] evaluated an indigent patient population with an inherently high rate of postoperative infection and showed that the addition of azithromycin, 500 mg, to cefazolin significantly reduced the rate of post-cesarean endometritis. Tita and coworkers [16], further presented a follow-up report from the same institution, and demonstrated that the addition of azithromycin also resulted in a significant decline in the frequency of wound infection. In both of these studies, the antibiotics were administered after cord clamping. In a subsequent report, Ward and Duff [17] showed that the combination of azithromycin plus cefazolin administered preoperatively resulted in a very low rate of endometritis (1.3%, 95% CI, 1.0–1.78) in an indigent population similar to that of Tita et al. [15, 16]. In a subsequent investigation, Tita et al. [18] reported the results of the Cesarean Section Optimal Antibiotic Prophylaxis (C/SOAP) trial. This was a multicentric trial conducted at 14 centers in the United States and included 2013 women who had undergone cesarean delivery during labor or after membrane rupture. The study groups were randomly assigned to two groups—1119 women to receive 500 mg of azithromycin plus conventional single-agent prophylaxis (usually cefazolin) and 994 women to receive a placebo plus conventional prophylaxis. The primary outcome measured were the development of endometritis, wound infection, or other infection occurring within 6 weeks of surgery.

The authors observed the primary outcome in 62 women (6.1%) who received azithromycin plus conventional prophylaxis and in 119 women (12%) who received only single-agent prophylaxis. The relative risk of developing a postoperative infection was 0.51 in women who received the combined therapy. There were significant differences between the two groups in both the rates of endometritis (3.8% versus 6.1%, $p = 0.02$) and wound infection (2.4% versus 6.6%, $p < 0.001$).

Harper and associates [19] subsequently validated the cost-effectiveness of the cefazolin-azithromycin protocol using a decision analytic model. When balancing the added cost of the second antibiotic against the reduced number of infections in women who received combined therapy, the cost savings in women having an unscheduled cesarean was $360 (95% CI $98–157), while the cost savings was $143 (95% CI $98–157) in those having a scheduled cesarean delivery.

All women, regardless of weight, should receive a 2-g dose of cefazolin [20]. The drug azithromycin, in a dose of 500 mg, achieves adequate concentrations in serum and the myometrium but the concentration in adipose tissue is more problematic [21].

42.2.3 Removal of the Placenta

Researchers have proven that the risk of postcesarean endometritis is reduced by avoiding manual removal of the placenta. Instead, it is recommended to apply traction to the umbilical cord after placental separation to remove the placenta. Yancey and associates [22] demonstrated that, in women who labored prior to surgery, the glove on the dominant hand of the operating surgeon became heavily contaminated with bacteria from the lower uterine segment following delivery of the infant. If this hand was placed behind the placenta by the surgeon during manual removal, those bacteria could be introduced into the underlying soft tissue and vascular system.

This report was followed up by another study by Lasley and colleagues [23] who evaluated 333 high-risk patients who also received intravenous antibiotic prophylaxis after cord clamping. The rate of postoperative endometritis was 15% in the group that had spontaneous delivery of the placenta compared with 27% in women who had manual extraction (RR 0.6; 95% CI, 0.3–0.9;

$p = 0.02$). This observation was confirmed by a recent Cochrane review [24] that included 15 reports (4694 women). The relative risk of endometritis in the group in which the placenta was removed manually was 1.64 (95% CI, 1.42–1.90). Manual removal of the placenta also resulted in greater blood loss, greater fall in the hematocrit post-delivery, and longer duration of hospital stay.

42.3 Wound Infection (Surgical Site Infection)

Wound infections are the second most common infection following cesarean delivery. In populations that have a disproportionate number of obese and morbidly obese patients, the number of wound infections may actually exceed the number of cases of endometritis.

Wound infections are potentially much more serious than endometritis. They are more likely to significantly prolong the patient's hospital stay, thus increasing expense. They also may lead to extremely serious sequela such as fascial dehiscence, evisceration, and necrotizing fasciitis.

The principal risk factors for postoperative wound infections are listed in Table 42.2. The major microorganisms are the pelvic flora (See Fig. 42.1), combined with the dominant skin organisms—streptococci and staphylococci. Wound infections typically take one of two forms: an incisional abscess or cellulitis. In the former, purulent material is present in the subcutaneous tissue above the fascia. In the latter, no pus is present in the wound, but the margins of the incisions are intensely erythematous, warm, and tender.

There are five key steps that are of proven value in reducing the frequency of wound infections: proper preparation of the surgical site, preoperative prophylactic antibiotics, proper closure of the deep subcutaneous layer, optimal skin closure, and application of a negative-pressure wound dressing in select patients.

Table 42.2 Principal risk factors for wound infection

- Obesity
- Inadequate or improper skin preparation
- Multiple prior surgical incisions
- Insulin-dependent diabetes
- Systemic corticosteroid use
- Immunosuppressive disorder

42.3.1 Preparation of the Surgical Site

In a landmark research published by Cruse and Foord [25] many years ago, the authors showed that shaving the hair just prior to the surgical procedure, rather than the night before surgery, significantly reduced the rate of wound infection. They also demonstrated that hair removal by use of clippers or depilatory creams, rather than by shaving, further decreased the rate of postoperative wound infection.

The standard antiseptic solution used for cleansing the surgical site was povidone-iodine for many years, until research suggested the use of chlorhexidine—alcohol. Darouiche et al. [26] reported the results of a well-designed, prospective, randomized multi-center trial comparing chlorhexidine-alcohol with povidone-iodine for skin preparation before surgery. The authors included 849 patients who underwent many different types of surgical procedures. They found that both superficial and deep wound infections were significantly less in patients who had a skin preparation with chlorhexidine-alcohol. The incidence was 4.2% compared with 8.6%, $p = 0.008$ for superficial wound infections and 1% compared with 3%, $p = 0.0005$ for deep wound infections.

Recently, a prospective randomized trial comparing chlorhexidine-alcohol (2% chlorhexidine gluconate with 70% isopropyl alcohol) to povidone-iodine (8.3% povidone-iodine with 72.5% isopropyl alcohol) in patients having cesarean delivery was published by Tuuli et al. [27]. The study included 1082 women who were followed for 30 days after surgery. The primary outcome measure was the frequency of surgical incisional infection. Endometritis, hospital readmission for infection, length of hospital stay, use of other healthcare services, other wound complications such as seroma, hematoma, and cellulitis were the secondary outcome measures. The rate

of incisional infection was significantly lower in the chlorhexidine-alcohol group (4.3%) compared with the povidone-iodine group (7.7%, $p = 0.02$). The beneficial effect of the chlorhexidine-alcohol preparation was not affected by whether the cesarean was scheduled or unscheduled, the presence or absence of obesity, the type of skin closure, the presence of chronic disease, or the presence or absence of diabetes. No significant difference was observed in the two groups in regard to the secondary outcome measures. Of note, patients in the chlorhexidine-alcohol group were significantly less likely to have physician office visits for assessment of possible wound complications. The large sample size and randomized design were the major strengths of this study. Also, the inclusion of emergency cesarean deliveries in the analysis was another strong point. Emergency procedures represent a substantial portion of cesarean deliveries, and they place the patient at increased risk for incisional infection because of the limited time available to prepare the skin before surgery.

In contrast to the results of the study by Tuuli et al. [27], a recent study by Ngai et al. [28] found no difference in the incidence of incisional infection when comparing the two antiseptic solutions, either separately or sequentially, except in morbidly obese patients. In these women, sequential application of both solutions reduced the infection rate. The study by Ngai et al. cannot be generalized as it specifically excluded emergency cesarean deliveries.

42.3.2 Preoperative Prophylactic Antibiotics

Research has proven that prophylactic antibiotics are more effective when given preoperative rather than after the umbilical cord is clamped. Also, single doses of antibiotics are comparable in effectiveness to multidose regimens. Moreover, the combination of cefazolin plus azithromycin is more effective than cefazolin alone in reducing the frequency of both endometritis and wound infection [15–17].

42.3.3 Closure of the Subcutaneous Layer of the Abdomen

Del Valle and colleagues [29] were among the first researchers to direct attention of the clinicians' to the optimal technique for closure of the subcutaneous layer of the abdomen. Four hundred and thirty-eight women who were undergoing cesarean delivery were randomly assigned to two groups—closure of Camper's fascia with absorbable suture (usually 3–0 plain catgut placed as either continuous or interrupted sutures) versus no closure. The skin was reapproximated with staples. A significantly higher incidence of wound dehiscence as a result of seroma, hematoma, or infection was observed in the group that did not have closure (16/216, 7.4% versus 6/222, 2.7%, $p = 0.03$).

Similar findings were reported by Naumann et al. [30] in a study of obese women having cesarean delivery. Two hundred and forty-five women with a subcutaneous layer of at least 2 cm in thickness were randomized to closure of the deep subcutaneous layer with a continuous suture of 3-0 polyglycolic acid versus no closure. The incidence of wound disruptions from all causes was 14.5% in the closure group versus 26.6% in the no closure group (RR 0.5, 95% CI, 0.3–0.9). Overall, 28 women (11.4%) developed wound seromas; the relative risk in the subcutaneous closure group was 0.3 (95% CI, 0.1–0.7); 17 (7%) developed wound infections. There was no difference in the frequency of wound infection.

An excellent meta-analysis followed these studies. Chelmow and colleagues [31] documented that, when the subcutaneous layer was more than 2 cm in thickness, closure of the bottom portion of this layer significantly reduced the incidence of wound disruption, primarily as a result of a decrease in the frequency of seroma (RR = 0.66, 95% CI, 0.41, 0.91).

Subsequently, Ramsey et al. [32] questioned the benefit of addition of a closed suction drain to reduce the frequency of wound disruptions beyond that achieved with subcutaneous closure alone in obese women. In a prospective randomized trial, they assigned women whose subcutane-

ous layer was >4 cm in thickness to subcutaneous closure alone (n = 149) versus closure plus a closed-system drain (131) with the primary end point being "composite wound morbidity." They found that the frequency of the composite outcome was actually higher in the closure plus drain group (22.7%) compared to suture closure alone (17.4%, RR = 1.3, 95% CI, 0.8–2.1).

There is no firm consensus on the choice of suture, gauge of suture, or technique for placement of the subcutaneous suture. At the author's medical center, a continuous suture of 3-0 polyglactin 910 is used for subcutaneous closure.

42.3.4 Closure of the Skin

The standard of care for skin closure has been surgical staples for many years. Recently, two comprehensive meta-analyses have shown that subcutaneous skin closure with suture provided an improved outcome when compared with surgical staples.

A systemic review and meta-analysis of five randomized controlled trials and one prospective cohort study were conducted by Tuuli et al. [33]. The review compared staples versus sutures for skin closure in women who had a transverse abdominal incision for cesarean delivery. The suture closure group included 684 patients while there were 803 women in the staple closure group. The review found that the two types of closures were equivalent with regard to pain, cosmesis, and patient satisfaction. It also reported that, although staple closure was less time consuming, it was associated with a twofold higher risk of wound infection or separation (pooled OR 2.06, 95% CI, 1.43–2.98, number needed to harm = 16).

A similar meta-analysis of five randomized controlled trials was conducted by Clay and colleagues [34]. A comparison of 492 women in the suture group with 385 women who received closure with staples was done. They analyzed incidence of wound separation and a "composite of wound complications," including dehiscence, infection, seroma, and hematoma. The odds ratio for the overall frequency of wound complications was 2.11 in the staples group ($p = 0.003$) while the odds ratio for wound separation was 4.01 in the staples group ($p < 0.001$). The operating time was 5 min shorter in the staples group.

A randomized controlled trial of 398 patients was conducted by Figueroa et al. [35], who compared staples and sutures for wound closure with wound disruption or infection at discharge, and subsequently at 4–6 weeks as primary end points. The risk of wound disruption or infection was 7.1% in the staples group versus 0.5% in the suture group at hospital discharge (RR = 14.1, 95% CI 1.9–106, $p < 0.001$). At 4–6 weeks, the cumulative risk of the primary outcome was 14.5% in the staples group and 5.9% in the suture group (RR = 2.5, 95% CI, 1.2–5.0, $p = 0.008$).

A recently published study by Buresch et al. [36] compared poliglecaprone 25 (Monocryl®) to polyglactin 910 (Vicryl®) for skin closure in 550 term patients undergoing nonemergency cesarean deliveries. The primary outcome was a composite of surgical site infection and wound separation, hematoma, or seroma within 30 days of surgery. The primary outcome was observed in 8.8% of women in the poliglecaprone 25 group versus 14.4% in the polyglactin 910 group (RR 0.61, 95% CI, 0.37–0.99, $p = 0.04$).

One relatively new twist related to wound closure is the role of battery-powered negative-pressure vacuum dressings. These devices presumably exert their beneficial effects by reducing wound edema, decreasing interstitial pressure, enhancing microvascular blood flow, redirecting stress forces, improving lymphatic drainage, and stimulating growth factors to produce granulation tissue. The two most commonly used dressings in the United States are the PICO® (Smith & Nephew, St. Petersburg, FL) and Prevena® (KCI, USA, San Antonio, TX) devices. With the PICO device, evaporation of tissue fluid occurs through a semipermeable covering. With the Prevena® the fluid is collected into an attached canister. The cost of these devices ranges between $300 and $500.

In 2018, Yu et al. [37] published a systematic review and meta-analysis of nine studies to determine if prophylactic use of negative-pressure devices was effective in reducing the frequency

of wound infection after cesarean delivery when compared to standard wound dressings. Six of the studies were randomized controlled trials, two were retrospective cohort studies, and one was a prospective cohort study. Prevena® and PICO® systems were the two most commonly used negative-pressure devices. In all the studies, majority of patients were at high risk for wound complications due to obesity. The absolute risk of wound infection in the intervention group was 5% (95% CI, 2.0–7.08) compared to 11% (95% CI, 7.0–16.0%) in the standard dressing group. The absolute risk reduction was 6% (95% CI, −10.0% to −3.0%), and the number needed to treat was 17.

In a subsequent publication, Hussamy and colleagues [38] enrolled 441 women with Class III obesity (BMI ≥ 40) in a randomized trial comparing a standard wound dressing to a negative-pressure dressing. The primary outcome was the composite rate of wound morbidity, and there was no significant difference between the two groups (17% in the negative-pressure group and 19% in the standard dressing group).

Echebiri and associates [39] recently reported a decision-analytic model based on a third-party payer's perspective to evaluate the cost-effectiveness of prophylactic application of negative-pressure wound therapy compared with a standard postoperative dressing in all women having cesarean delivery. They concluded that in patients at low-to-moderate risk for wound infection (≤14%), the negative-pressure therapy was not cost-effective. In very high-risk patients (risk of infection >14%), the device was cost-effective if priced below $192 per patient.

For the present time, it would be reasonable to reserve the use of these devices to morbidly obese patients having cesarean delivery, particularly after an extended period of labor and ruptured membranes.

42.4 Urinary Tract Infection

The most common organisms that cause urinary tract infections (UTIs) during pregnancy are the aerobic Gram-negative bacilli: *E. coli*, *Klebsiella pneumoniae*, *Proteus species*; and a group of three aerobic Gram-positive cocci—*group B streptococci*, enterococci, and *Staphylococcal saprophyticus* (Fig. 42.2). Post-cesarean UTIs result from two major factors: failure to eradicate previously-existing asymptomatic bacteriuria prior to surgery and introduction of bacteria into the bladder during insertion or maintenance of the urinary catheter [1].

All pregnant women should be screened for asymptomatic bacteriuria at their first antenatal visit. The best initial screening test is a urine culture; the sample should be a midstream clean catch specimen. If the urine culture is positive, the patient should be treated promptly, and a repeat culture should be obtained after treatment to confirm eradication of the microorganism. Subsequently, at each prenatal appointment, the patient's urine should be tested by dipstick for nitrites and leukocyte esterase. If either is positive, a urine culture should be obtained, and, if positive, the patient should be retreated. Patients who have multiple lower UTIs or a single episode of pyelonephritis during pregnancy should be on prophylactic antibiotics until after delivery [1].

During cesarean delivery, the bladder catheter should be inserted using a strict sterile technique. The catheter should then be removed as soon as possible after surgery, ideally within 12 h. The principal justifications for keeping the catheter in

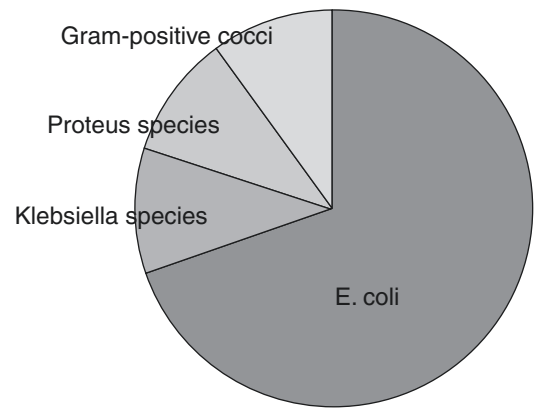

Fig. 42.2 Most common causes of UTIs in pregnant women

place for a longer period of time are an inability on the part of the patient to void spontaneously or a need to decompress the bladder because of a cystotomy repair.

42.5 Conclusions

There are many variations in the technique for cesarean delivery. However, the steps outlined above and summarized in Table 42.3 should be part of all procedures. If these steps are followed, the practitioner can expect the combined rate of endometritis and wound infection to be in the range of 5–8% and the rate of UTI to be ≤3%.

Table 42.3 Summary of measures to reduce the frequency of post-cesarean infection

Prophylaxis indicated	Prophylaxis not indicated
Endometritis	• Cleanse the vagina preoperatively with povidone-iodine • Administer cefazolin plus azithromycin preoperatively • Remove the placenta by gentle traction on the umbilical cord rather than by manual extraction
Wound (incisional) infection	• Clip (not shave) the hair in the surgical site just prior to the incision • Cleanse the abdominal skin with chlorhexidine • Administer cefazolin plus azithromycin preoperatively • Close the deep subcutaneous layer if it is >2 cm in thickness • Close the skin with suture rather than staples; Poliglecaprone25® is the preferred suture • In patients at increased risk for wound infection, apply a negative-pressure vacuum dressing
Urinary tract infection	• Treat pre-existing asymptomatic bacteriuria before surgery • Prepare the urethra in a sterile manner • Use strict sterile technique in inserting the catheter • Minimize the time the catheter is in place, ideally <12 h

Key Points

1. Infection is the most common complication following cesarean delivery.
2. The two principal infections are endometritis (organ space infection) and wound infection (surgical site infection).
3. The major pathogens that cause endometritis are anaerobic microorganisms, aerobic Gram-negative bacilli, and aerobic Gram-positive cocci (GBS, enterococci, staphylococci).
4. The major risk factors for endometritis are prolonged labor, long duration of ruptured membranes, and multiple internal examinations.
5. The three key interventions that reduce the risk of endometritis are preoperative systemic antibiotics, preoperative irrigation of the vagina with an iodophor solution, and removal of the placenta by cord traction.
6. The major organisms that cause wound infection are the same organisms that cause endometritis, combined with skin flora (aerobic streptococci and staphylococci).
7. Obesity is an important risk factor for development of wound infection.
8. Several interventions are helpful in reducing the frequency of wound infection. These include clipping rather than shaving the hair at the incision site, cleansing the skin preoperatively with chlorhexidine, administering systemic antibiotics preoperatively, closing the deep subcutaneous layer of the incision if it is >2 cm in depth, and closing the skin with a subcutaneous monofilament suture.
9. In obese patients, use of a negative-pressure vacuum dressing provides additional benefit in preventing a wound infection.

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43 Overuse of Antibiotics in Pregnancy: Beyond Antimicrobial Resistance

Anita Kotwani

43.1 Introduction

The discovery of antimicrobial agents is one of the most significant achievements of modern medicine practice. The use of antibiotics has revolutionized the management of infectious diseases during the second half of the last century. Antibiotics made it possible to treat infectious diseases such as septicemia, pneumonia, tuberculosis, and syphilis. However, this historic development had its drawbacks. The effectiveness of antibiotics misled the medical community to believe that infectious diseases had been conquered! Many doctors started prescribing antibiotics indiscriminately for prophylaxis and treatment of infections. Overlooking the Darwinian selection—the adaptation by life forms to challenging environments and survival of the fittest was a critical miss by the medical fraternity. Ever since antibiotics were developed in the 1940s, scientists have warned against their indiscriminate use and resulting bacterial or microbe resistance called antimicrobial resistance (AMR). In 1945 Nobel Laureate, Sir Alexander Fleming had predicted and cautioned against the overuse of antibiotics, especially due to undue public pressure to prescribe more antibiotics. Increased use of antibiotics during the past 60 years has exerted selective pressure on susceptible bacteria and favored the survival of resistant strains. Today's threat of widespread AMR and simultaneous, decline in the development of new antibiotics raises the probability of an environment without effective antimicrobials, where a patient can die from previously treatable infections. There is a great concern that modern medical treatments—from a simple cesarean section to complex treatment and procedure such as care of premature babies, transplants, surgeries, intensive care and cancer treatment—will become either impossible or be associated with major risks.

43.2 AMR: A Big Challenge

No doubt, antibiotics are wonder drugs and help to save lives, but unfortunately, they are being abused and misused. World Health Organization (WHO) defines rational use of medications as: "*Patients receive the appropriate medicines, in doses that meet their own individual requirements, for an adequate period of time and at the lowest cost, both to them and to the community*." This definition is true for the appropriate use of antibiotics as well. The irrational or inappropriate use of all medications, including antibiotics, is a considerable problem worldwide. As per the WHO estimates >50% of all medicines are being prescribed, dispensed, or sold incorrectly [1].

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The two most important issues allied to misuse may be prescriptions with too many medications per patient (polypharmacy) and the inappropriate use of antimicrobials. The repercussion of this practice promotes antimicrobial resistance, thus predisposing to life-threatening infections. AMR is defined as the resistance of a microorganism (bacteria, parasites, viruses, or fungi) to an antimicrobial drug that was originally effective for the treatment of infections caused by it [1]. Resistant strains of bacteria or any microbes survive, grow, and cause infections that are difficult to treat by available antibiotics. Antibiotics are not only used for humans but huge amounts are used for livestock, poultry, and agriculture, including aquaculture.

AMR is a multidimensional challenge affecting social, economic, and environmental, that encompass food production systems as well as human and animal health. The interdependence of human health, agriculture, animal health and the environment is recognized by the "One Health" concept. Resistant bacteria can be traced in animals, and food products meant for human consumption. Because microbes, including resistant microbes, travel freely, so the steps required for containment of AMR should be coordinated internationally, and each country is required to take the much-needed preventive steps [2].

A report by a renowned health economist, Jim O'Neil [3] postulated that if timely appropriate actions are not taken now to slow down the alarming rise of AMR, then by 2050, drug-resistant infections may risk ten million lives a year and incur a cumulative expenditure of 100 trillion USD. World Bank measured the impact of AMRs on the global economy from 2017 through 2050. The reports predict that the world would suffer a loss of 3.8 percent of its annual gross domestic product (GDP) by 2050 if a high AMR-impact situation prevails. Even in the situation of a relatively mild AMR, the impact on the annual global GDP would be 1.1 percent by 2050. The annual deficit in global GDP as a result of AMR would be comparable to the losses sustained by the global financial crisis of 2008. However, the long-term analysis concluded that the cost impacts of AMR on GDP would actually be worse than those of the 2008 financial crisis in two respects [4]. Firstly, the impact would be felt throughout the period up to 2050 and not just for a couple of very bad years. Secondly, with AMR, low-income countries would experience larger drops in economic growth than high-income countries, so the global burden of poverty and economic inequality would rise. So, directly or indirectly the impact of AMR will be borne by the low and middle-income countries.

In 2015, the WHO Global Action Plan (GAP) on antimicrobial resistance was adopted by the member states at the World Health Assembly. The GAP was framed after regular consultation with WHO in collaboration with two other UN agencies, Food and Agriculture Organization (FAO) and World organization for animal health, Office International des Epizooties (OIE). GAP on AMR has five strategic objectives [2]. They are:

1. To improve awareness and understanding of AMR via effective communication, education, and training.
2. To strengthen knowledge through surveillance and research.
3. To reduce the incidence of infection by effective sanitation, hygiene, and infection prevention measures.
4. To optimize the use of antimicrobial medicines in both human and animal health.
5. To develop sustainable investment that takes into account measures for global increase in investment in new medicines, diagnostic tools, vaccines, and other interventions.

In 2018, United Nations Environment Program (UNEP) also supported to fight against health threats related to interactions between humans, animals, and the environment, thus making it a UN tripartite plus (WHO/FAO/OIE/UNEP) agreement and urging countries to scale up a multisectoral response against AMR.

This action plan lays stress on the need for an effective "one health" approach with coordination of numerous stakeholders, such as human and veterinary medicines, environment, agriculture, food scientists, well-informed consumers, finance, and international sectors. As a result, most countries have prepared their National

Action Plan (NAP) on AMR, which is very well aligned with the GAP developed by WHO. For decreasing the selection pressure on microbes, we need to optimize the use of antibiotics (specific objective 4). In this specific objective, there are four main activities; regulated access to high-quality antimicrobials, surveillance of antimicrobial use, antimicrobial stewardship in hospital and community across human and animal sectors. Antimicrobial stewardship (AMS) programs are framed to optimize the use of antimicrobials, improve patient outcomes, and reduce AMR and its related healthcare costs. The Report of Organization for Economic Co-operation and Development (OECD) estimates that implementing AMS programs along with other policies to reduce antibiotic overuse and promote hospital hygiene, can help to save up to 1.6 million lives by 2050 and US$ 4.8 billion per year in the 33 OECD countries [5]. The aim of an AMS program is:

- Optimal use of antibiotics.
- To promote a change in behavior and practice related to prescribing and dispensing antibiotics.
- To improve the quality of care and patient outcomes.
- To cut down unnecessary healthcare costs.
- To reduce further emergence, selection, and spread of AMR.
- To prolong the lifespan of existing antibiotics.
- To reduce the adverse outcome of AMR on economy.
- To build the best practices regarding the rational use of antibiotics by healthcare professionals.

43.3 Antibiotics and Pregnancy

In this chapter, we will concentrate on issues surrounding antibiotic use and irrational use during pregnancy or in perinatal medicine and the associated problems in the newborn or child. Antibiotic misuse in pregnancy is a far graver problem than AMR in the population at large (AMR is briefly mentioned in the previous section). Although AMR is a global public health threat to everyone, its consequence in pregnancy can be concerning due to the risk of resistant bacteria crossing over to the neonate during delivery which is a vulnerable stage of life with regards to contracting infections. In addition to this, the use of antibiotics during pregnancy also carries the risk of potentially teratogenic effects, including spontaneous abortion [6], which is not being discussed here. Although most obstetric studies have examined the benefits of antibiotics from the perspective of short-term maternal and neonatal complications, very few publications have addressed the risks and long-term consequences. Information regarding safety and efficacy is generally not available from randomized controlled trials, as these studies are usually not feasible in pregnant women and are potentially unethical. Thus, pregnant state is often a standard criterion for exclusion from clinical trials. Data evaluation suggests that safety profile regarding infantile risk in pregnancy is available for only 10% of medications marketed since 1980 have [7].

Therefore, keeping in mind the risk of adverse effects from the use of antibiotics and the presence of AMR, it is important that maternal antibiotic use is appropriate without compromising the health of women if they experience a urinary tract infection (UTI) or other infections. Optimizing antibiotics use in perinatal medicine is a challenge but the rewards are extraordinary.

43.4 Antibiotic Overuse During Pregnancy

During pregnancy, most women receive at least one medication, with antibiotics being among the more frequently prescribed. There are many studies indicating that a high number of pregnant mothers consume antibiotics during pregnancy. One of the studies indicated that antibiotics are responsible for more than 80% of the medications prescribed during pregnancy, and more than 40% of pregnant women receive an antibiotic immediately before delivery [8]. In a recent prospective, longitudinal study, nulliparous pregnant women from a geographically and ethnically diverse cohort in the USA were followed-up from

first trimester till term (n = 9546) [9]. This study inferred that 97.1% of women had taken at least one medication during pregnancy, with 95.7% giving history of taking a medication in the first trimester. Polypharmacy (at least five medication or more medications) was reported from 30.5% women. Even after excluding vitamins, supplements, and vaccines, 73.4% of women took a medication during pregnancy, with 55.1% taking at least one in the first trimester. Medications taken in pregnancy and in the first trimester included: gastrointestinal or antiemetic agents (34.3%,19.5%), antibiotics (25.5%, 12.6%), and analgesics (23.7%, 15.6%).

Antibiotic use in pregnancy is generally aimed at preventing neonatal group B Streptococcus (GBS) sepsis, chorioamnionitis, preterm labor with intact or ruptured membranes, screening, and treatment of asymptomatic bacteriuria or bacterial vaginosis, and documented infections such as endometritis and UTI and also for cesarean prophylaxis. Therefore, a vast majority of infants are being exposed to antibiotics before delivery. Although indications for maternal antibiotics are sometimes justified, there are potential risks linked to their overuse and misuse that exceed the benefits. In the USA, the proportion of women receiving unindicted antibiotics has been shown to be approximately 40% to 45% [10]. There is evidence from the UK and other countries which suggests that antibiotics to treat UTIs are overprescribed in women who are pregnant [11, 12].

43.5 Main Conditions for Which Antibiotics Are Misused

43.5.1 Prophylaxis in Cesarean Sections and Operative Vaginal Deliveries

Cesarean section rates are on the rise both in developed countries and in developing countries. There is a 5- to 30-fold greater risk of postpartum infection-related complications, including endometritis, surgical site infection, sepsis and UTI in women delivering by cesarean section (1.1%–2.5%) as compared with those delivering vaginally (0.25–5%) [13]. However, there are very few data about the adverse effects of this practice on the neonate, which makes it difficult to determine the risk-benefit ratio. The simplest and shortest antibiotic regimen should be used (single dose regimens). This has been shown to be as effective as multiple-dose regimens, which unfortunately are sometimes extended to the postoperative period [14]. A recent large-scale study showed that the effectiveness of antibiotics for cesarean section births is similar when administered after or before the umbilical cord is clamped. This practice can be beneficial for newborns-developing microbiomes. The study also showed that the risk of infection at the site of C-section incisions is not increased if antibiotics are administered after the cord is clamped [15].

The medical literature does not support the use of routine antibiotic prophylaxis after normal vaginal birth. Instrumental vaginal delivery such as forceps or vacuum assisted are associated with an increased risk of a postpartum infection. In case of instrumental vaginal birth, there is benefit of a single dose of prophylactic antibiotic after delivery (co-amoxiclav, 1 g of amoxicillin with 200 mg of clavulanic acid) but there are no data to support more than one dose or the administration of antibiotics before delivery [16]. However, it is a common practice to give antibiotics for vaginal and cesarean sections. A study from India on a tertiary care hospital [17], revealed that 87% of the women who had a vaginal delivery and 98% of the women who underwent a cesarean section were prescribed antibiotics for 3.1 (±1.7) and 6.0 (±2.5) days, respectively. Moreover, 28% of both the women with vaginal deliveries and with cesarean sections were prescribed antibiotics at the time of discharge. The most commonly prescribed antibiotic group was third-generation cephalosporins in both the cases.

43.5.2 Prevention of Neonatal Group B Streptococcus (GBS) Sepsis

Antibiotic prophylaxis given intrapartum to decrease the risk of neonatal early-onset GBS infection has been associated with a significant decrease in its incidence. However, universal

GBS screening has some limitations, and recent evidence suggests a link between intrapartum antibiotic prophylaxis and short- and long-term adverse neonatal outcomes. One review inferred that intrapartum antibiotic prophylaxis was effective, but high-quality evidence to document the effectiveness of such a practice was limited [18]. In addition, the studies included did not consider the potential risks of antibiotics [18]. An Australian retrospective cohort study found that 7 of 10 term neonates with early-onset GBS infection were born to women who had negative results on screening [19]. Also, the authors did not find any variation in rates of infection between screened and unscreened pregnancies [19]. In another meta-analysis, it was opined that GBS colonization occurs in approximately 18% of pregnant women globally, with an inter-regional variation of about 11–35%. Without intrapartum antibiotic prophylaxis, about 50% of neonates born to GBS-positive mothers become colonized with GBS, and of those, GBS infections develop in 1–2% [20]. The current clinical practices are aimed at on identifying women who are at greatest risk of colonization and/or intrapartum transmission to target antibiotic prophylaxis for GBS.

Policies for the prevention of GBS neonatal sepsis are formulated by experts and national societies based on the number of women and fetuses they are willing to treat in order to prevent one case of GBS early-onset disease. Going by this approach of providing systematic antenatal screening and intrapartum prophylaxis to colonized women, about 700 and 1000 women and their fetuses need to be treated to prevent one case of GBS early-onset disease. Thus, it is of utmost importance to choose a strategy that exposes only the colonized women delivering preterm to antibiotic prophylaxis as they have the highest risk of transmitting infection to neonate [13].

43.5.3 Prevention of Preterm Birth

Inflammation and infection are clearly linked to preterm birth, but it is not known whether antibiotic therapy can avoid early delivery. A systematic review found that antibiotics administered during the second and third trimester to prevent preterm labor in the presence of intact membranes is not effective in reducing adverse pregnancy outcomes, preterm birth, or neonatal morbidity [21]. Moreover, antibiotic treatment for the prevention of preterm birth may be harmful.

43.5.4 Chorioamnionitis

A diagnosis of intrapartum chorioamnionitis requires prompt treatment with antibiotics to prevent maternal complications. However, using the development of fever during labor and delivery as a proxy for chorioamnionitis is not ideal, as maternal fever usually results from prolonged labor, not chorioamnionitis. A diagnosis of intrapartum clinical chorioamnionitis is made in the presence of fever, maternal or fetal tachycardia, uterine tenderness, foul-smelling or purulent amniotic fluid, leukocytosis, or an increase in C-reactive protein (CRP). It affects about 4–10% of women in labor. Chorioamnionitis has been found to be correlated with an increased risk of necrotizing enterocolitis and infant cerebral palsy, as well as maternal complications. The conventional practice is to use broad-spectrum antibiotics. Unfortunately, the risk of infant cerebral palsy persists irrespective of the antibiotic treatment, therefore the benefit of treatment for its prevention remains controversial. Whereas there is no confusion regarding the use of antibiotics for chorioamnionitis, but a correct diagnosis should be made before initiating the treatment. Therefore, careful assessment of maternal and fetal clinical signs and symptoms, maternal white blood cell counts, and other laboratory tests should be performed before initiating intravenous intrapartum antibiotics. If a woman does receive antibiotics, the duration of the antibiotics should be as short as possible. Data suggest that for women treated with an initial dose of intrapartum antibiotics for chorioamnionitis, one additional dose of antibiotics post-delivery is just as beneficial as a prolonged course [22].

43.5.5 Urinary Tract Infection

Urinary Tract Infection (UTI) is a relatively frequent infection that occurs during pregnancy. Approximately 60% of women during pregnancy have leukocytes in their urine without any infectious complications, thus, the presence of leukocytes should not be used to diagnose an asymptomatic UTI in pregnant women. Unfortunately, some clinicians prescribe antibiotics to women if they suspect a possible UTI. However, there is no rational reason to expose the mother and fetus to the potential side effects of these antibiotics. A recent Cochrane review found that antibiotics for asymptomatic bacteriuria in pregnant women may decrease the risk of bacteriuria during delivery (average relative risk [RR], 0.30; 95% confidence interval [CI], 0.018–0.53; 4 studies; 596 women); however, the results for serious adverse neonatal outcomes were inconclusive (average RR, 0.64; 95% CI, 0.023–1.79; 3 studies; 549 neonates). In the studies included, maternal adverse effects were rarely described, and 14 out of the 15 studies were assessed as having high or unclear risk of bias. GRADE software analysis showed low-risk pregnant women benefit from antibiotic treatment for asymptomatic bacteriuria [23].

43.5.6 Genital Infections

Screening and treating of genital infections like *Trichomonas vaginalis* or bacterial vaginosis for the prevention of preterm birth also add risk without confirmed benefit. Metronidazole treatment was found to actually increase the chances of preterm delivery (19% vs. 10.7% in the placebo group) [24]. The probability of having a positive vaginal culture during the screening of asymptomatic women is very high (20–50% for various organisms), but it does not always suggest a pathogenic infection. Unfortunately, antibiotics are administered to a large population of pregnant women for their normal vaginal flora.

43.6 Short- and Long-Term Negative Effects of Antibiotics During Pregnancy

Antibiotic use during pregnancy may be lifesaving, but at other times, antibiotic use may be unnecessary and lead to negative consequences. There are a good number of studies that have inferred that antibiotics alter the composition of the maternal and neonatal intestinal microbiota, which can play an major role in maternal and child health outcomes, such as immune and metabolic functions later in life [25–27]. The effect of the perinatal microbiome on immunity early in life is thought to affect neurodevelopment, potentially altering the risk of development of childhood asthma, atopy, allergy, obesity, and neurologic disorders. Concerns have been raised that extensive antepartum and intrapartum antibiotic use can potentially disrupt the infant's intestinal microbiota and alter maturation to the adult microbiome. However, current research studies on this possible connection have not sufficiently addressed potential confounding variables. In addition, these studies have not consistently controlled for the frequency, dose, timing, type (narrow range vs. broad spectrum), and indication of antibiotic usage [27].

Intrapartum antibiotic prophylaxis for GBS-positive women is commonly practiced in obstetrics and is administered in up to 40% of the deliveries. Infants of such mothers who have been exposed to antibiotics present with a lower bacterial diversity; the lesser proportion of *Actinobacter*, especially *Bifidobacteriaceae* and a relative greater proportion of proteobacteria in their gut microbiota compared with non-exposed infants. Such alterations during the "critical window" in infants when both the intestinal microbiota and the immune systems develop simultaneously has an important role to play in the development of the immunity in the infant. The potential long-term negative impact of these alterations on the children's health needs to be researched further.

Antibiotics are administered to prevent preterm birth, but it might have harmful long-term effects. One study found an associated greater risk of cerebral palsy and function impairment at age 7 years in children of women who received antibiotics for spontaneous preterm labor with intact membranes.

The main negative effects for which associations of antibiotic exposure during pregnancy with risks for neurologic disorders, obesity, asthma, allergy, anaphylaxis, infections during childhood, and antibiotic resistance are described below.

43.6.1 Gut Microbiome, Obesity, and Immunity

For over a decade, obesity has been associated with changes in the microbiome. Exposure to antibiotics in the prenatal period, that is in the second or third trimester has been found to be associated with an alteration in the composition of the infants' intestinal microbiome, an increased body mass index z-scores, waist circumferences and percentage of body fat [28]. This is reflected as an increased risk of obesity during childhood in such children. In a study conducted by Isaevska E et al. in 2020, it was reported that the use of antibiotics for treatment of vaginal infections in the mother during the third trimester of pregnancy was positively associated with an increased relative risk ratios for overweight/obesity in preschool children who were delivered vaginally [29].

Early postnatal innate immune development is driven by maternal microbiota during pregnancy. Illnesses such as autoimmune and allergic disorders, including childhood asthma, may be imprinted during infancy, only to manifest later in life [28].

43.6.2 Asthma

The Copenhagen prospective cohort study on asthma in childhood found a strong association between receiving antibiotics in the third trimester in the mother and increased risk of developing asthma in the children borne to such mothers [30]. Similar results were reported by another study, where prenatal systemic antibiotic use was a significant predictor of asthma by 3 years of age after controlling for confounders [31].

43.6.3 Impact on Fetal Brain

An increased risk of epilepsy in childhood has been documented in children with prenatal exposure to antibiotics as compared to unexposed children. The association is not found to be altered by the timing of the exposure, type of antibiotic, or antibiotic dose [32].

43.6.4 Maternal Anaphylaxis

The extensive use of antibiotics has also been related to maternal anaphylaxis during both pregnancy and the peripartum period. Maternal anaphylaxis followed by maternal hypotension affects fetal oxygenation and increases the chances of hypoxic-ischemic encephalopathy and permanent central nervous system injury to the fetus. This risk was found to occur after a few minutes of maternal anaphylaxis.

43.6.5 Childhood Infections

Antibiotic exposure during pregnancy has been correlated with a greater risk of hospitalization due to infections in children in the first 6 years of age. Greater risks of infections-related hospitalization were found when intrapartum antibiotics were prescribed and in women who received a greater number of antibiotics during pregnancy [33].

43.6.6 Multi-Resistant Bacteria

Development of multi-resistant bacteria or antimicrobial resistance is a major complication of antibiotic overuse, which is discussed at the beginning of the chapter.

43.7 Conclusion

A germane focus in antibiotic use in perinatal medicine has been to protect the mother and child from infection. No doubt this improves outcomes but nevertheless, such protection should not happen at the risk of injury to the uninfected mother and/or child. Antibiotics should only be prescribed during pregnancy when indicated. If a maternal infection is proven, narrow-spectrum antibiotics should be used to decrease the effects of antibiotics on the microbiome of the infant. There is a need to have antibiotic stewardship program in place and all medical professionals are to be taught in their pre-service curriculum and during their specialization about antimicrobial resistance and excessive and inappropriate use of antibiotics and their impact. The main purpose of controlling the usage of antimicrobials is to improve patient care. It proposes to ensure using the appropriate medications(s), only when necessary, at the correct dosage, and for the correct duration. Sometimes, better patient care involves starting broad-spectrum antibiotics. This management is also a component of antimicrobial stewardship, but is sometimes a necessity because infection is an important cause of neonatal morbidity and maternal mortality, with sepsis related to pregnancy accounts for 11% of maternal deaths. A recent systematic review and meta-analysis published [34], describes the frequency of maternal infection: the incidence of chorioamnionitis as 3.9%, endometritis 1.6%, wound infection 1.2%, maternal peripartum infection 1.1%, and sepsis 0.05%. This data clearly shows that an excessive number of women are treated with antibiotics and underlines the need to improve the use of antibiotics in perinatal medicine globally, both in developed and low-and middle-income countries.

Key Points

- Antibiotics use in pregnancy is common practice despite the lack of evidence on their safe use in this vulnerable period.
- The main conditions for which antibiotics are misused in pregnancy include prophylaxis in cesarean section and operational vaginal delivery, prevention of neonatal streptococcal sepsis, prevention of preterm birth, chorioamnionitis, urinary tract and genital infections.
- Antibiotic use in pregnancy is known to alter mother's and neonate's microbiome affecting immune and metabolic functions later in life.
- AMR in pregnancy can result in the transmission of resistant bacteria to neonate, increasing risk of failure to respond to antibiotic therapy for life-threatening infections in early days of life.
- Use of antibiotics after cord clamping is as effective in preventing postpartum infections after cesarean section as before and should be practiced.
- Certainty of diagnosis and carefully targeted therapy for pregnant women most at risk of transmitting GBS to neonate can prevent unnecessary use of antibiotics in pregnancy.
- The timing, type, and dosage of antibiotic exposure in pregnancy do not alter the adverse effects related to fetal brain development.
- Antibiotic stewardship programs in undergraduate medical training, in health facilities and pharmacies along with mass awareness on the appropriate use of antibiotics can prevent drug overuse and misuse.

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44 Bacteriophage Therapy in Pregnancy: An Alternative to Antibiotics

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44.1 Introduction

44.1.1 Pharmacokinetic and Pharmacodynamic Changes in Pregnancy

Pregnant women are often prescribed medications to treat a variety of conditions both related and unrelated to their pregnancy [1]. A retrospective study showed that 64% of all pregnant women in the United States received at least one prescription medication during their pregnancy, with an average of two prescription medications taken other than vitamin or mineral supplements [2]. Prescribing patterns in Europe are more varied [3]. Physicians are often forced to weigh the risks and benefits of pharmacotherapy in pregnancy with limited information, as medications are historically poorly studied in pregnancy [1]. Such calculations are all the more relevant in the case of infections during pregnancy, since these carry a significant risk of inducing preterm labor or leading to maternal sepsis [4].

Pregnancy results in extensive physiologic changes that impact nearly every organ system in the body, and which often significantly alter the bioavailability, distribution, and clearance of many drugs [1]. Gastric emptying is unchanged prior to labor; however, alterations in liver enzyme activity may impact the absorption and metabolism of several drugs, increasing the bioavailability of certain drugs such as codeine, while decreasing the bioavailability of others, such as metoprolol [5]. Pregnancy alters drug distribution due to an increase in body size and intravascular volume, which may lead to lower peak and steady state drug concentrations for a given dose [6]. Serum albumin concentration begins to decrease in the second trimester of pregnancy, reducing protein binding capacity and increasing the free fraction of highly protein-bound drugs such as midazolam, digoxin, phenytoin, and valproic acid [7]. Increased cardiac output during pregnancy increases renal blood flow and glomerular filtration rate by 50% beginning in the second trimester and extending through three months postpartum, resulting in significantly increased clearance of renally excreted drugs such as heparin [1]. Because the half-life of a drug depends on both its clearance and its volume of distribution, both of which are

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increased during pregnancy, each drug's half-life is altered in an unpredictable and often idiosyncratic way during pregnancy [1].

44.1.2 Pharmacokinetics and Pharmacodynamics of Common Antibiotics in Pregnancy

Pharmacokinetic and pharmacodynamic changes must be carefully considered in pregnancy, since there is usually no short-term clinical response to guide dose titration [1]. Similar to all medications in pregnancy, antibiotics undergo pharmacokinetic changes that include an increased volume of distribution, increased renal clearance, and decreased protein binding [1]. This decreased protein binding is not, however, believed to offset the decrease in drug concentration that results from an increased volume of distribution, and as a result the free plasma concentration and antimicrobial efficacy of antibiotics may be diminished in pregnancy [1].

Cefazolin is the most commonly administered antibiotic in pregnancy and the best studied [1]. The increased volume of distribution in pregnancy as well as the increased clearance of cefazolin necessitates both larger initial doses and more frequent dosing in order to maintain effective plasma concentrations [8]. The pharmacokinetics of ceftriaxone are not significantly altered in pregnancy [9]. Gentamicin is more rapidly cleared in pregnant women, necessitating larger doses and more frequent administration [10, 11]. Sulfonamides compete with bilirubin for albumin binding in the newborn, and may lead to kernicterus of the newborn, although they are generally considered safer when administered more remote from delivery [12]. Fetuses and neonates have significantly decreased capacity to metabolize antibiotics, which leads to prolonged rates of exposure for a given dose [1].

44.1.3 Placental Drug Transmission

The placenta is a semipermeable barrier regulating drug passage to the fetus, and is similar in some properties to the blood–brain barrier [1]. More importantly, it represents a metabolically active organ capable of altering the metabolism, uptake, and distribution of drugs administered to the mother [1]. Passive transfer of drugs across the placenta is determined by lipid solubility, and generally drugs that cross the blood–brain barrier will also readily traverse the placenta [1]. Other factors influencing placental transfer include charge, molecular weight, and concentration [1]. As a result, alterations in fetal acid–base status can alter placental drug transfer and result in unexpectedly high concentrations of acidic or basic drugs [1]. For example, a weakly basic drug, such as lidocaine, may accumulate and lead to toxicity in an acidotic fetus [1]. The placenta is less metabolically active than the liver; however, it does express both phase 1 (oxidation, reduction, hydrolysis) and phase 2 enzymes (conjugation), and drugs such as corticosteroids may undergo significant placental metabolism as a result [1].

44.2 Antibiotic Use in Pregnancy

44.2.1 Bacterial Infections

Antibiotic use during pregnancy is very common, with approximately 20–25% of all women receiving an antibiotic at some point during their pregnancy course [13]. Antibiotic use in pregnancy typically focuses on the narrow spectrum treatment of urinary tract infections and sexually transmitted infections such as *Treponema pallidum*, *Neisseria gonorrhoeae*, and *Chlamydia trachomatis* [14]. Treatment of these pathogens is important in pregnant patients, as inadequate treatment is associated with poor obstetrical outcomes such as spontaneous abortion, prematurity, and low birth weight [13]. Narrow spectrum antibiotics are also commonly used to treat Group B *Streptococcus* (GBS), or *Streptococcus agalactiae*, in order to prevent transmission and development of neonatal sepsis [15]. Broad-spectrum antibiotics are also used for pregnancy-related complications such as premature rupture of membranes and in utero infections, where associated morbidity and mortality is high [4].

44.2.2 Antibiotic Safety in Pregnancy

Despite the widespread use of antibiotics in pregnancy, data on their safety in this context is sparse [13]. In 1979, the Food and Drug Administration (FDA) developed a system categorizing the teratogenic risk of medications using the categories A, B, C, D, and X. These range from Category A, applied to a medication considered to have no risk in pregnancy, to Category X, applied to a medication with demonstrated teratogenicity, and therefore contraindicated in pregnancy [13]. Notably, there are no antibiotics considered to be Category A [13]. Penicillins, cephalosporins, vancomycin, macrolides, and clindamycin are all relatively safe in pregnancy and are classified as Category B [13]. For other antibiotics minimal data are available on their efficacy and teratogenicity in pregnancy, and additional studies are needed in order to determine their safety [13, 16]. The alphabetical labeling system was discontinued in 2015 and has since been replaced with descriptions of use in pregnancy, lactation, and females and males of reproductive potential in order to promote risk–benefit discussions between providers and their patients [17].

Few studies have thoroughly evaluated pharmacokinetic and pharmacodynamic changes of medications during pregnancy, in large part due to perceptions of modest economic benefit from such studies as well as significant potential harm [1]. In fact, historically even non-pregnant women of childbearing potential were excluded from clinical trials prior to formation of the Obstetric Pharmacology Research Units Network in 2003, which demonstrated that clinical investigations could be safely performed in pregnant woman, and argued for the inclusion of pregnant women in such studies [1]. Largely as a result of their influence, current regulations require pharmacokinetic and pharmacodynamic studies to include women of childbearing potential [1].

44.2.3 Antibiotic Resistance

The emergence of multi-drug-resistant pathogens has become a pressing threat to global health. This increasing resistance, which includes the extended spectrum beta-lactamase (ESBL) production of *Escherichia coli* and the methicillin resistance of *Staphylococcus* species is particularly concerning as it imposes further limitations on the availability of antimicrobials among the small selection of those considered safe in pregnancy [18]. In a recent review, approximately half of *Escherichia coli* isolates in pregnant women with urinary tract infections were reported to be ESBL-producing, and one-third of *Staphylococcus aureus* and coagulase-negative *Staphylococcus* species were shown to be methicillin-resistant [18]. Of the antibiotics considered safe in pregnancy, nitrofurantoin and fosfomycin are considered to have the least resistance [18]. Effective approaches to preventing antibiotic resistance, particularly in pathogens primarily affecting pregnant women, are multifactorial and must address both providers and patients [19]. Providers must be knowledgeable on the proper use of antibiotics and work to prevent unnecessary use, while simultaneously educating patients on the risks of antibiotic therapy and advocating for good hygiene practices in order to prevent urinary tract infections [19].

44.2.4 Microbial Dysbiosis

The microbiome of the human body is a diverse population of microorganisms, most of which reside in the gut, that have been linked to maintaining a healthy body [20]. Shifts in the microbiome, also called dysbiosis, have been associated with obesity, diabetes, atherosclerosis, and other disease states [20]. Dysbiosis may also occur in pregnancy, and in theory this state represents a bidirectional relationship wherein pregnancy affects the microbiome, which in turn impacts maternal and neonatal outcomes [20]. Early in pregnancy the maternal gut and vaginal microbiome experience a decrease in the overall number and diversity of bacteria, with a return in composition to that of a non-pregnant woman as term approaches [21, 22]. Dysregulation of the placental and amniotic fluid microbiomes has been linked to multiple pregnancy complications including

preeclampsia, intrauterine growth restriction, and premature rupture of membranes [20, 23].

Antibiotic use in pregnant women has been shown to produce vaginal dysbiosis with long-term sequelae on the neonatal microbiome [24]. Broad-spectrum antibiotic use during pregnancy has also been associated with an increased risk of childhood obesity, epilepsy, and asthma, although it has not been determined whether the primary maternal infection or the treatment is ultimately responsible for this association [20]. The maternal microbiome as well as maternal antibodies play a vital role in the postnatal development of immunity and lay the foundation for future immune functioning [25]. Ultimately, further studies are needed to determine the degree to which antibiotic use during pregnancy may disrupt this immune priming [25].

44.3 Introduction to Bacteriophages

44.3.1 Definitions

Bacteriophages are viruses that exclusively infect bacteria and are believed to be the most abundant organisms on the planet [26]. Bacteriophages were first discovered in the 1910s by Félix d'Hérelle and Frederick Twort, and were subsequently proposed as a potential mode of therapy for bacterial infection [4]. Extensive research into the therapeutic use of bacteriophages in the Western world, however, has been limited by the emergence of conventional antibiotics [4, 27]. Phage therapy has since undergone further investigation in Eastern Europe, particularly in the former Soviet Union, and has been sporadically used in these countries to treat bacterial infections [27]. In light of worsening antibiotic resistance, bacteriophage therapy has generated increased interest in Western countries as a possible alternative to conventional antibiotic therapy [28].

44.3.2 Mechanism of Action

Bacteriophages are naturally occurring bacterial parasites that depend on their host for survival and replication [14]. As obligate pathogens they can only replicate inside a living host, and must identify a suitable organism [14]. The bacteriophage life cycle begins with adsorption, which entails an initial survey of a potential host surface via reversible electrostatic forces [14]. The phage then attaches to an identified target on the host surface, with completion of the process varying slightly depending on the phage [14]. Following adsorption, genetic material, which is located within the head or capsid of the phage, is injected into the host [14]. Replication then occurs, resulting in the production of numerous copies of phage genetic material, which is in turn translated into various phage components [14]. Larger bacteriophages encode machinery for their own DNA replication, whereas smaller phages utilize existing host machinery to accomplish this [14]. Finally, translated components are assembled to create new bacteriophages, with the entire process culminating in progeny release via cell lysis [14, 28, 29].

Bacteriophages can be categorized by the type of life cycle they utilize during replication and virion release [28]. The most common life cycles are lytic (virulent) and lysogenic (temperate) [28]. Obligate lytic phages exclusively reproduce using the lytic cycle, wherein host replication and translation is entirely halted and the host machinery is utilized to encode phage genetic material [14]. Temperate phages utilize the lysogenic cycle, in which phage genetic material is either incorporated into the host genome or becomes a plasmid [14]. Replication in the host continues normally, but produces prophages, host daughter cells with phage genomic material [29]. Temperate phages may coexist with the host bacterium as a prophage in a lysogenic life cycle until an environmental trigger prompts a switch to the lytic cycle [29]. The prophage at this point may excise phage genetic material from the host genome in order to convert to a lytic cycle [14]. The final step of the bacteriophage life cycle is cell lysis, which is mediated by phage enzymes, such as lysins, and by holins [30]. Lysins are enzyme which act on the peptidoglycan layer of the bacterial cell wall, whereas holins are molecules which insert into the cytoplasmic membrane at a specific point in the cycle to allow lysins to reach the peptidogly-

Table 44.1 Comparison of bacteriophages and antibiotics [14, 31]

	Bacteriophages	Antibiotics
Mechanism of action	• Bactericidal via induced cell lysis	• Bacteriostatic or bactericidal via disruption of either cell wall formation or ribosome functioning
Dosage	• Dependent on route of administration, less dependent on absorption, bioavailability, or metabolism • Initial concentration may increase and adjust to concentration of target organism via host-dependent replication	• Dependent on absorption, bioavailability, route of administration, and metabolism • Initial concentration decreases due to hepatic metabolism and renal clearance, necessitating recurrent dosing
Microbiome disruption	• Limited disruption of normal microbiome due to phage specificity to target organism	• Higher risk of microbiome disruption, especially with broader spectrum antibiotics
Resistance	• Phage specificity limits potential resistance to a specific pathogen or smaller range of pathogens • Phage life cycle allows for adaptation to bacterial mutations	• Increased incidence of multi-drug-resistant pathogens secondary to widespread use and broad spectrum of activity
Side effects	• Limited side effect profile and generally considered safe • Patients may theoretically experience a systemic immune reaction due to widespread cell lysis	• Broad range of side effects depending on antibiotic selected, dosage, and spectrum of antibiotic coverage • Some antibiotic classes may impact growing fetus and are thus contraindicated in pregnant patients

can layer [30]. Upon release of virions via lysis, host cell death occurs [30]. These phage life cycles, particularly the lytic cycle that results in cell death of the host, demonstrate the potential for therapeutic utilization of bacteriophages to treat bacterial infections [14].

44.3.3 Bacteriophages and Antibiotics

There are several advantages of bacteriophages compared to antibiotics (Table 44.1). Bacteriophages are highly specific, with one phage typically infecting a narrow range of bacterial species [29, 32]. This specificity offers targeted, pathogen-specific treatment in contrast to the general and widespread bactericidal and bacteriostatic effects of antibiotics, and allows other microbiomes within the body to remain relatively undisturbed [14, 29, 32]. Sarker et al. demonstrated this property by administering a phage cocktail specific to *Escherichia coli* to healthy patients and finding no evidence of alteration in their gut microbiome afterward [32, 33]. This phage specificity also suggests unique approaches to the treatment of multi-drug-resistant bacteria, and may slow the rate of bacterial resistance compared to traditional antibiotics [34]. Because the targets of most bacteriophages are virulence factors on the bacterial organism, resistance to bacteriophages could result in less virulent bacterial strains, suggesting a potential synergistic effect with antibiotics [32]. Given the replicative nature of bacteriophages, their use also carries a dosing advantage, since unlike antibiotics, which may be rapidly cleared from the body, bacteriophages continue to replicate and produce progeny so long as the target organism is present, necessitating a smaller initial dose and fewer follow-up doses [32].

44.4 Potential Targets of Bacteriophages in Pregnancy

44.4.1 Urinary Tract Pathogens

Urinary tract infections may occur at any point throughout pregnancy and are commonly treated with antibiotics [16]. Depending on the gesta-

tional age, certain antibiotics may interfere with fetal development [16]. They may also produce dysbiosis as a result of their broad spectrum of activity, resulting in vaginal candidiasis or allowing for overgrowth of opportunistic pathogens [4]. These may in turn ascend from the vagina and can result in more severe, intrauterine infections, which have been associated with multiple adverse outcomes, including preterm labor and maternal sepsis [4]. Additionally, widespread and frequent antibiotic therapy for urinary tract infections has resulted in worsening antibiotic resistance and the emergence of multi-drug-resistant organisms, all of which pose an increased risk of severe infection to the pregnant woman and her fetus [4]. Bacteriophage therapy represents a possible alternative for some common urinary tract pathogens, especially in the setting of bacterial adherence to the urothelium and biofilm growth [4]. Uropathogenic *Escherichia coli* strains are among the most common pathogens isolated in uncomplicated urinary tract infections among all adults, and are responsible for a majority of urinary tract infections in pregnancy [35]. Chibeu et al. isolated three different phages that reduced biofilm growth of a uropathogenic *Escherichia coli* strain, while Sillankorva et al. demonstrated phage activity against urothelium-adherent uropathogenic *Escherichia coli* [35, 36].

Several in vitro studies have demonstrated bacteriophage activity on other urinary tract pathogens. Sybesma et al. isolated 41 *Escherichia coli* and nine *Klebsiella* strains from the urine of 50 patients with active urinary tract infections, then utilized four commercial bacteriophages and found lytic activity against all strains of *Klebsiella* and all but one *Escherichia coli* strain [37]. Another in vitro study with continuous flow of artificial urine showed decreased *Pseudomonas aeruginosa* and *Proteus mirabilis* biofilm growth on urinary catheters pre-treated with bacteriophage cocktails [38]. Sporadic case reports describe the use of bacteriophages in urinary tract infections, including the case of a 67-year-old female with a persistent *Pseudomonas aeruginosa* urinary tract infection, who was subsequently treated with a combination of a phage cocktail and antibiotics, resulting in successful bacterial eradication [39]. The first randomized, double-blinded, placebo-controlled clinical trial using bacteriophages involved randomization of patients scheduled for transurethral prostatic resection to either an intravesicular bacteriophage cocktail, antibiotic therapy, or placebo via bladder irrigation for therapy, or placebo via bladder irrigation for seven days [40]. No significant difference was seen in the rate of treatment success between these interventions [40]. Systematic investigation into the use of bacteriophage therapy on urinary tract infections has been limited to in vitro studies, and high quality, prospective studies on pregnant patients are needed to further evaluate the potential of this intervention as either an alternative or an adjunct to antibiotic therapy.

44.4.2 Group B *Streptococcus*

Group B *Streptococcus* (GBS), or *Streptococcus agalactiae*, is a Gram-positive organism that is routinely tested for and treated intrapartum with prophylactic antibiotics due to the risk of early-onset neonatal disease [15]. Antibiotic therapy for GBS is broad spectrum and affects the normal microbiota of the entire body, increasing the risk for the development of antibiotic resistance among other pathogens [15]. These factors combined with the potential for dysbiosis make bacteriophage therapy an intriguing alternative to antibiotic therapy for the treatment of GBS.

Several in vitro studies have investigated bacteriophage therapy for GBS. Pritchard et al. cloned a GBS bacteriophage lysin, a lytic enzyme responsible for degrading the host cell envelope to allow virion release, and demonstrated glycosidase and endopeptidase activity on both *Streptococcus agalactiae* and on other groups of B-hemolytic *Streptococci* [41]. Eradication of GBS serotypes as well as a significant decrease in bacterial colonization of the vagina and oropharynx has also been seen in murine models following administration of a bacteriophage lysin [42]. Investigations of whole bacteriophage therapy for GBS have been limited by challenges in identifying suitable phages [35]. Several lysogenic bacteriophages targeting GBS strains have been

identified from genomes of GBS isolates, as have other bacteriophages belonging to the family *Siphoviridae*, but no obligate lytic phages have been isolated [35, 43]. Lysogenic phages are not considered good candidates for phage therapy given their temperate nature when compared to obligate lytic phages; however, with increasing research on phages targeting GBS, the potential remains to either develop antimicrobial therapies utilizing temperate phages or to discover obligate lytic phages in the future [43].

44.4.3 Respiratory Tract Pathogens

Pneumonia occurs at the same rate in pregnant as in non-pregnant women, but is associated with significantly greater maternal and neonatal morbidity during pregnancy [44, 45]. As in non-pregnant patients, the causative agent in community-acquired pneumonia during pregnancy is often not identified; however, the most commonly identified pathogen is *Streptococcus pneumoniae*, followed by *Haemophilus influenzae* [46]. More infrequent pathogens identified include *Mycoplasma pneumoniae*, *Staphylococcus aureus*, *Legionella pneumophila*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* [46]. Viral pneumonia accounts for 5% of cases in pregnancy, with fungal and protozoal agents identified primarily in immunocompromised populations [46]. Physiologic changes to the respiratory system in pregnancy greatly increase rates of respiratory complications in patient with pneumonia, with increases seen in hospitalization, need for mechanical ventilation, bacteremia, and empyema [45, 47]. Pneumonia in pregnancy is also associated with adverse fetal outcomes, including preterm delivery, low birth weight, and increased mortality [44, 45, 47].

Several studies have examined the efficacy of bacteriophage-only therapy against common respiratory pathogens in pregnancy [31]. These have demonstrated bacteriophage activity against *Burkholderia cepacia* complex and against both acute and chronic *Pseudomonas aeruginosa* infections in murine models [48]. Other studies have evaluated the efficacy of combining antibiotics and bacteriophages in common respiratory pathogens [31]. In one study, phage therapy and ciprofloxacin were equally effective in reducing the bacterial load of *Klebsiella pneumoniae* on biofilms, and the combination of the two significantly reduced the development of either phage- or antibiotic-resistant strains [49]. Several studies have demonstrated the effectiveness of similar combinations of phage and antibiotic therapy at reducing the rate of either phage or bacterial resistance in *Pseudomonas aeruginosa* biofilms, with synergistic efficacy seen for a wide range of antibiotics in combination with phage therapy [31]. Another experimental design used gentamicin to induce aggregation of *Staphylococcus aureus*, rendering these colonies more susceptible to bacteriophage attack [50]. Finally, in one study the combination of antibiotic and bacteriophage therapy significantly increased survival in mice infected with *Streptococcus pneumoniae* [51]. The synergistic effect of antibiotic and phage therapy is believed to occur when bacteria evolve mechanisms of resistance to one mode of therapy, e.g., the development of efflux pumps to increase antibacterial resistance, generating more extracellular markers for bacteriophages to recognize, and thus making them more susceptible to phage attack [31]. Further in vivo studies are needed to assess the combination of bacteriophage and antibiotic therapy, as are complex in vivo and ex vivo models of chronic polymicrobial lung infections, as may be seen in cystic fibrosis [31].

44.4.4 *Listeria Monocytogenes*

Listeria monocytogenes is a Gram-positive bacterium responsible for listeriosis. Although this severe infection is rare, certain populations including immunocompromised people, pregnant women, neonates, and the elderly are at increased risk [52]. *Listeria monocytogenes* contamination is most commonly associated with the consumption of prepared foods, especially deli meats and soft cheeses, and various forms of bacteriophage pretreatment have demonstrated success in combating transmission [52]. Application of phage

P100 to foods at risk for contamination produced a significant reduction or complete eradication of *Listeria monocytogenes* on these foods, resulting in approval by the FDA/United States Department of Agriculture (USDA) for use on all food in 2007 [53]. Further pretreatments with phages and phage cocktails, including application to cheeses, spraying on fruit, and application to fresh-cut produce and ready-to-eat poultry, have been shown to successfully reduce *Listeria monocytogenes* contamination [26, 52, 53]. Biocontrol methods with bacteriophage application to food products is a more feasible use of bacteriophages in the case of *Listeria monocytogenes*, as the intracellular nature of listeriosis infection significantly limits the effectiveness of in vivo bacteriophage administration [52]. Indeed, in vivo bacteriophage therapy has not been historically effective at reducing bacterial growth in the setting of an intracellular infection, as in the case of *Mycobacterium avium* [52].

44.5 Routes of Bacteriophage Administration

44.5.1 Oral

Oral administration of bacteriophage therapy has been successfully given for gastrointestinal and some systemic infections [54]. The largest obstacle for oral phage therapy is the low pH of the stomach, as the acidic environment disrupts phage stabilization [54]. Concomitant use of yogurt, proton pump inhibitor therapy, or microencapsulation techniques have been suggested as methods for overcoming the low pH of gastric contents [14]. Phage instability within a gastric environment could be further exacerbated in pregnancy due to a reduction in gastric emptying that would theoretically increase phage exposure to the acidic environment [14, 55].

44.5.2 Inhaled

The feasibility of bacteriophage therapy for respiratory infections is largely dependent on the ability to deliver phage therapy through inhaled formulations, which is itself dependent on aerosol performance and phage biochemical stability [31]. Proposed delivery formulations include aerosolization of liquid phage formulations, liposome-encapsulated formulations, and inhalation of dried powders [31]. Proposed delivery mechanisms include various forms of nebulizers and metered dose inhalers [31]. Notable challenges to these approaches include demonstrating long-term stability of the phages within the suspension medium, and the fact that many of the most commonly utilized phage stabilizers are not yet approved for human use [31]. These phage preparations may be particularly effective in pregnancy, as changes to respiratory physiology in pregnancy are likely to enhance the absorption of inhaled therapies [55]. Inhaled bacteriophage therapy is believed to be safe for use in humans with no reported adverse events, but clinical trials and more robust in vivo studies are needed to establish parameters for the safety and efficacy of this mode of administration [31].

44.5.3 Intravenous

Over 100 years of literature have described the sporadic use of intravenous bacteriophages for the treatment of bacterial infections with minimal reported adverse events [56]. Advantages of intravenous administration include allowing bacteriophages to reach multiple sites and treat systemic infection [56]. Drawbacks to this mode of delivery include the potential for more rapid clearance of the phages and the development of host resistance via phage-specific antibodies [56]. Others have speculated that intravenous administration may increase the risk of significant systemic inflammatory reactions; however, recent studies that have utilized advanced purification techniques in phage preparations have demonstrated successful eradication of targeted bacteria without any severe adverse events [14].

It is unknown in what way the physiologic changes of pregnancy may impact intravenous administration of bacteriophages, as the parame-

ters of intravenous phage administration in non-pregnant humans remain widely undefined [14]. Drug pharmacokinetics are significantly altered in pregnancy due to increased heart rate, cardiac output, and uterine and renal blood flow, as discussed above. It is unclear what impact these physiologic alterations may have on phages, which unlike classical drug preparations, have a dose-independent relationship with serum plasma levels predicated on a need for bacterial interaction in order to maintain an acceptable level of treatment efficacy [14].

44.5.4 Topical

Topical bacteriophage therapy has been considered as a treatment for localized, multi-drug-resistant infections, with favorable results seen in the case of wound infections, sinusitis, burns, and *Clostridium difficile* bowel infections [56]. Localized intra-vaginal application of phages specific to genitourinary pathogens such as GBS, or skin administration to neonates to prevent colonization are areas of interest for phage therapy in pregnancy [14]. These modes of administration are attractive because they allow for delivery directly to the source of infection with minimal systemic disruption to the host immune system [14].

44.5.5 Placental Transfer

Information regarding the placental transfer of phages must be obtained prior to implementing bacteriophage therapy during pregnancy [14]. Animal models have shown mixed results on placental transfer following phage therapy, with phages injected into maternal serum seen in fetal circulation in two studies [14]. This finding suggests the potential for bacteriophage therapy to treat both maternal and fetal infections; however, further research is needed to clarify the mechanism of placental transfer of bacteriophages and to quantify concentration differences between maternal and fetal circulation [14].

44.6 Challenges in the Implementation of Bacteriophage Therapy

Several challenges in implementing bacteriophage therapy beyond identification of the appropriate phage life cycle, bacterial target, dosing, and route of administration warrant further discussion. One of the most commonly cited concerns with bacteriophage therapy is the potential to trigger a systemic immune response that could result in either phage inactivation or poorly tolerated side effects [57]. Interestingly, antibodies to bacteriophages or phage proteins have not been found in human blood; however, they have been identified in mouse blood [57]. Some speculate that antibodies are not produced because phages are able to rapidly reach the target bacterial cells [57]. If antibodies are produced, they have not been shown to decrease the therapeutic effect from multiple phage administrations, nor have adverse side effects been observed from either the phages or the lysin protein [57]. If antibodies were to form, one proposed solution would be to add phages that do not serologically cross-react [56].

Beyond concerns for antibody formation, there is the potential for a triggered immune response resulting in cytokine production [58]. This is particularly relevant as it has been speculated that inflammation rather than infection is responsible for 40% of spontaneous preterm births [58]. Specifically, cytokine production resulting in prostaglandin synthesis stimulates myometrial contractility, cervical ripening, degradation of fetal membrane extracellular matrix, and ultimately preterm labor [58]. In order to reduce the likelihood of cytokine formation, adjunctive therapy with NF-Kb inhibitors, TLR4 antagonists, TNF alpha biologics, and cytokine suppressive anti-inflammatory drugs have been proposed, albeit with no conclusive recommendations [58].

Intense focus has centered around a method of phage preparation that may decrease the immune response and reduce cytokine production [59]. There is less likely to be a reaction when exclusively virulent phages are used and the media is purified of large protein derivatives, bacteria,

molds, and debris, specifically lipopolysaccharide [59]. Lastly, phages and their proteins lyse bacterial cell walls and have the potential to release large amounts of bacterial endotoxins, which could lead to systemic shock; however, this outcome is not different from that seen with antibiotic use and should not be considered an impediment to bacteriopage therapy [59].

The ethical considerations of conducting research on pregnant women have hindered research into both phage and antibiotic therapy, limiting studies to primarily murine and in vitro models. Ultimately, given the potential for long-term alterations in the fetal biome with traditional antibiotic use as well as the reality of worsening antibiotic resistance, research into the use of targeted phage therapy in pregnant patients is extremely important and should be prioritized [14].

44.7 Summary

Antibiotics are often prescribed in pregnancy, since common antepartum infections such as pneumonia, urinary tract infections, sexually transmitted infections, *Streptococcus agalactiae* infections, and *Listeria monocytogenes* infections have been consistently associated with increased maternal and fetal morbidity, including an increased risk of preterm labor, low birth weight, and even death. Antibiotic therapy for these infections is often broad spectrum, and may produce both maternal and fetal dysbiosis. Bacteriophages are viruses that target and lyse particular bacterial species. These have been used both alone and in combination with antibiotics, and have shown efficacy in reducing bacterial proliferation, decreasing the formation of biofilms, and limiting bacterial resistance. Proposed mechanisms of administration are often linked to the targeted pathogen (e.g., inhaled therapy for respiratory infections), and include oral, inhaled, intravenous, and topical administration. The dynamics of placental transfer of bacteriophages remain unknown, but is a topic warranting further study. Ultimately, high quality prospective studies in human and particularly in pregnant patients are needed in order to determine the safety and efficacy of bacteriophages for either sole or adjunctive use in treating common infections in pregnancy. Despite the challenges this portends, the advantages of bacteriophage administration in providing narrow, targeted therapy offer significant benefits for both the maternal and fetal microbiome, and render such investigations a promising and worthwhile endeavor.

Key Points

- Antibiotic use during pregnancy is common, and is primarily directed against urinary tract infections, sexually transmitted infections, respiratory infections, and prophylaxis of *Streptococcus agalactiae*, or in the case of premature rupture of membranes.
- The emergence of multi-drug-resistant pathogens in pregnancy is worsening, with approximately half of *Escherichia coli* isolates in this population shown to be ESBL-producing and one-third of *Staphylococcus aureus* species shown to be methicillin-resistant.
- Antibiotic use in pregnancy may produce vaginal dysbiosis and have long-term sequelae on the neonatal microbiome, with associated risks including childhood obesity, epilepsy, and asthma.
- Bacteriophages are naturally occurring bacterial parasites, whose ability to lyse bacterial cells makes their use an attractive alternative to traditional antibiotics.
- Bacteriophages are highly specific, allowing targeted treatment of an infection while leaving other microbiomes within the body relatively undisturbed.
- In vitro studies have shown bacteriophage activity against urinary tract pathogens, but minimal efficacy has been seen in limited clinical trials.
- Bacteriophage activity against Group B *Streptococcus* has been seen in preclinical studies, but an inability to iden-

tify obligate lytic phages targeting this pathogen has limited the development of clinical trials.

- Bacteriophages have been most effective against respiratory pathogens when combined with antibiotic therapy, where they have been shown to act synergistically and to reduce antibiotic resistance.
- Pretreatment of susceptible foods with topical bacteriophage sprays has been shown to successfully reduce *Listeria monocytogenes* contamination.

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45 Engineering Design and Administrative Control for Infection Prevention in Obstetrics

Avdesh Mehta

45.1 Introduction

Infectious disease spread can happen indoors through airborne and droplet transmission, direct contact with contaminated surfaces (fomites), and waterborne transmission [1, 2]. Crowded inadequately ventilated spaces are also possible reservoirs of harmful pollutants. A single sneeze can discharge thousands of droplets at speeds from 50 to 200 miles/h in a lobby or corridor [1]. Indirect transmission can happen when a vulnerable person comes in contact with some object contaminated with infectious agents such as the COVID-19 virus. COVID-19 virus can live on plastic and stainless-steel surfaces for up to 72 h, on cardboard surfaces for up to 24 h, and on copper for up to 4 h [3]. Thus, handrails, door handles, water taps, chair handles, or even stethoscopes can potentially transmit disease if a susceptible person touches his mouth, nose, or eyes before washing hands [4]. The built space can be designed with the goal of inhibition of infectious diseases with strategies providing adequate space for social distancing in waiting areas, corridors, and entrance lobbies. The occurrence of superspreading events has been associated with minimum distance between beds of <1 m, lack of washing or changing facilities for staff or poor ventilation designs [5]. Space design, ventilation for dilution, air filtering, and disinfection are some of the feasible methods that are available for infection control by engineering design [6–8]. The importance of infection control must be recognized by the project head at the time of planning and design of a hospital building and should result in the involvement of an infection control team right at the beginning [9–11].

The healthcare environment of care (EOC) includes all the spaces and surfaces which are part of the built environment. These include spaces for patient care, support services, spaces for technical equipment and systems that provide air and water. EOC contributes to approximately 20% of the microbial reservoir seen in health care facilities [12]. Also, multidrug-resistant microorganisms, Clostridium difficile and norovirus are found in significant numbers in the EOC [13]. Infection control programs thus aim at the prevention of transmission of infectious diseases not only to the vulnerable group of patients but also the health care workers and the visitors. To decrease EOC as the source of infection, risk assessment for infection control (ICRA) has been developed. It is a process to ensure that infection prevention elements are incorporated during the planning and design of the health care facility [14, 15]. The main objective of

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engineering infection control is to make sure that no patient gets infected while hospitalized. The American Institute of Architects (AIA) guidelines which were recommended in 2010 for design and construction of health care facilities and hospitals are still followed for best practices in hospital designing [16]. Renovation or construction done without planning for risk management has also been associated with disease outbreaks especially with multidrug-resistant organisms [13, 17]. This chapter discusses the possible steps that can be taken for better infection control in the context of Donabedian model of structure, process, and outcome as related to hospital and healthcare facility design, operations, and quality control as relevant to obstetrics [18] (Fig. 45.1).

The hierarchy of controls model by The National Institute for Occupational Safety and Health (NIOSH) tells about the different methods of controlling or reducing risk of hazards for workers. In the hospital setting, this can be correlated to infection hazards for healthcare workers, patients, and visitors. This model also ranks these control methods in terms of their effectiveness [19] (Fig. 45.2).

According to this model removal of the source is the most effective method, so we remove children and all unnecessary visitors from infectious areas of the hospital, or when we tell people to stay away from a COVID isolation facility. The next control method, substitution, may not be applicable in hospital settings. Engineering or infrastructure controls are shown to be more effective than administrative controls while the use of PPE is shown to be the least effective method. Administrative controls include education, training, implementation of policies and procedures that reduce risk of infections, and ensuring that these are being adhered to. This explains why when all over the world the stress is being put on PPE in the COVID 19 scenario, a large number of healthcare workers are getting infected.

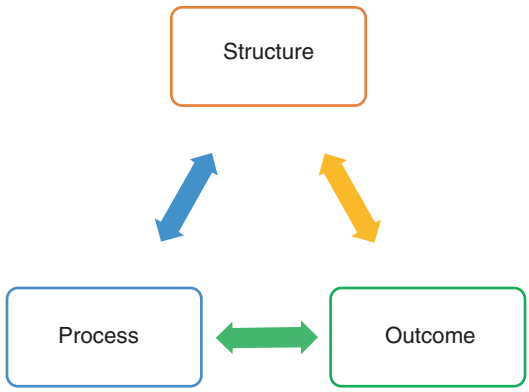

Fig. 45.1 Donabedin model of quality improvement

45.2 Infrastructure Design for Better Infection Control

Prevention through design initiative led by National Institute for Occupational Safety and Health (NIOSH) suggests that prevention or reduction of hazards can be achieved by weighing

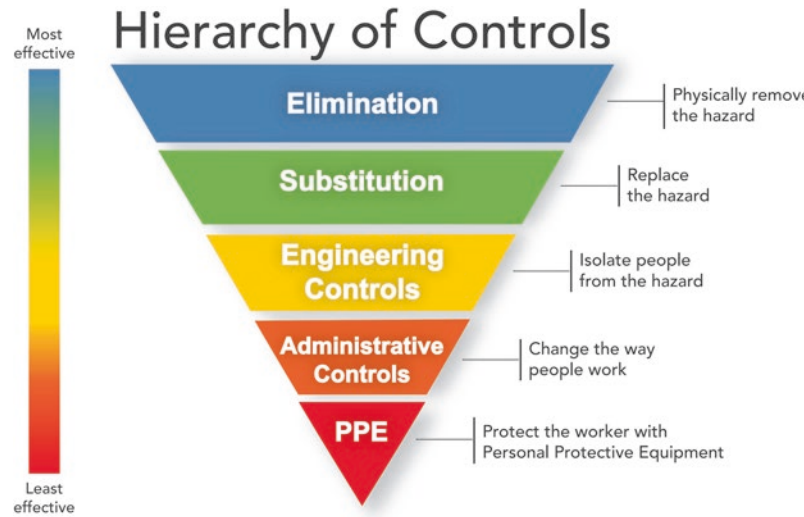

Fig. 45.2 Model of "hierarchy of controls" (National Institute for Occupational Safety and Health, Centres for Disease Control 2020) [19, 20]

design considerations that eliminate hazards and control risks to workers. This should include efforts to anticipate and eliminate by designing out hazards, through safer and better design, redesign or retrofit of new and existing workplaces, structures, facilities, equipment, tools, products, work processes, and the workflow in ways that reduce infection hazard and improve safety [21]. Following the COVID-19 pandemic, for better safety and reducing the chances of infection transmission it has been suggested [2] that:

- Corridors should be open ended and at least 2.6 m wide
- Copper/copper plated material should be used for frequently touched surfaces such as bed safety rails, staircase hand railing, and balcony railing
- Washbasins should be located for easier cleaning and their design should avoid spillage
- Taps with sensors can eliminate touch-based transmission in the washroom
- Walls should be plastered smooth with a non-porous easily cleanable finish, textured paint is to be avoided
- Entrance doors and air curtains should operate automatically to avoid touching
- Avoid or reduce the option of horizontal surfaces like ledges and ridges in the wall where dust can gather.

Infrastructure and engineering control includes proper architecture and planning of the hospital including operation theatre and labor room complex, zoning inside the OT complex, and control of the air and water quality as per the recommended international standards.

45.2.1 General Guidelines

45.2.1.1 Floor

Carpeting should be avoided because not only it is difficult to clean but it is also tough to move equipment like wheelchairs and trolleys over them. Hard surfaces like stone are easier to clean and maintain but have the disadvantage of creating more noise with traffic. Medical grade rubber sheet flooring having low volatile organic compounds (VOC) emission with welding of the seams is preferred because of lower noise and easy maintenance [22].

45.2.1.2 Fixtures and Fittings

Furniture: Non-upholstered surfaces with surface joints and seams should be avoided as they are not easily cleanable. Upholstery materials, if at all utilized in patient care areas must be non-porous, impermeable, and should not have untreated fabrics. Artificial leather or coated fabrics that are waterproof, non-porous, and can endure repeated cleansing with hospital-grade disinfectants should be preferred [17].

45.2.1.3 Decorative Waterfalls and Fountains

Decorative waterfalls and fountains should be avoided as they have been associated with outbreaks of Legionnaire's disease even by simply walking past them [17, 23].

45.2.1.4 Washbasins

Washbasins should be made of stainless steel or porcelain and of such design and size that minimizes splashing of water outside the basin. The gaps around the basin and the countertop should be sealed to avoid water seepage into the supporting cabinet, wall, or countertop. The water faucet outlet should be at least 10 in. above the bottom of the washbasin and the water stream should not drop directly into the drain, as that can agitate and splash contaminated water from inside the drain and spread infections. Water pressure in the faucet should be regulated to reduce the chances of splashing [17].

45.2.1.5 Lighting

Lighting of the work areas is a very essential component of the work system, but this we realize only if the power and the backup systems fail together and the working zone is plunged into darkness. Fortunately, this happens very rarely.

There are several means and methods of lighting that have their own characteristics and an understanding of this allows us to make optimum use of the available choices.

Natural Lighting

Natural lighting has the advantage that it is balanced white light which allows the maintenance of circadian rhythms, and has no recurring cost. Designing buildings with adequate sunlight entry into the rooms and the built space can inhibit microbial survival and reduce transmission of nosocomial infections [2, 21].

Electric Ceiling Light Fittings

Electric ceiling lights have the advantage that they can be controlled or switched at will and require minimal maintenance, but of course, they incur a recurring cost of the electricity consumed. They usually suffer from an incomplete light spectrum that leads to several problems in the workplace since medical examination and diagnosis often requires the examination of the patient parts such as eyes or tongue for subtle shades of coloration. To offset this limitation, full-spectrum white lights are also available now but their cost is significantly higher. It is best to choose fittings which after installation, are flush with the ceiling and are easy to clean and maintain. The joint between the light fitting and the ceiling should be sealed.

Concealed Light Fittings

Concealed light fittings are sometimes used for special effects and soft lighting, but methods such as cove lighting, or lights hidden behind structural elements lead to the creation of dead spaces in the hospital zone that are dirt collection spots and are often difficult to clean. This is totally undesirable in the clean/sterile zones like OTs and labor rooms.

Ultraviolet Light

Ultraviolet Germicidal Irradiation (UVGI) has been suggested for reducing surgical site infections but this has the disadvantage that it can only reach the visible surfaces.

Focused Lights

Operating lights and procedure lights are constructed such that their light is focused intensely into a spot so that the lumens at the working area reach a very high level so that the fine procedures can be properly carried out. These often combine several lamps with the arrangement that the light from all the lamps is focused on the same spot. The better models of these lights have adjustable brightness and sometimes color temperature adjustment. The older halogen and Xenon lamps are now superseded by LED lamps that have a lower thermal wastage, thereby operate cooler and have a long operating life. The illumination requirements for different work areas of a hospital are shown in Table 45.1.

Table 45.1 Illumination requirements [24]

Applications and tasks	Horizontal targets (lux)	Vertical targets (lux)
Patient room corridors: Inpatient (day)	100	50
Patient room corridors: Inpatient (night)	50	20
Special patient care (critical care), patient room: general	100	20
Special patient care (critical care), patient room: night observation	100	6
Patient room, night observation	30	6
Neonatal intensive care, general (day)	500	100
Neonatal intensive care, general (night)	100	20
Nursery, general	100	30
Nursery, observation	300	50
Dental suite: examination, hygiene, treatment	1000	300

Adapted from: Delgado A, Keene K. Integrating health and energy efficiency in healthcare facilities. United States. https://doi.org/10.2172/1773167

45.2.1.6 Air Quality and HVAC (Heating Ventilation and Air Conditioning)

The air in the premises has important implications in infection control. Stale air leads to accumulation of high concentrations of unhealthy gases and microorganisms [17]. This is detrimental to the patients, staff and the visitors and can have both short-term and long-term negative health effects on them; and a higher incidence of cross-infection among patients and staff is also

seen. Thus, a good air handling system makes sure of a certain minimum number of air exchanges per hour, which means that the air in the room is exchanged a certain number of times in each hour. Good natural ventilation designs can often deliver a higher ventilation rate then powered ventilation in an energy-efficient way [2, 25]. The airborne infection transmission risk is reduced significantly when the number of air changes per hour (ACH) is increased inside the built environment. With 12 ACH, it takes 20 min to bring down the concentration of droplets to 1.8% while this is achieved in 10 min with 24 ACH [26]. Infection reduction design measures include having adequate cross ventilation, preferring open-ended corridors over closed-ended ones, and integrating the courtyard design to create ventilation space [2]. The American Society of Heating, Refrigerating and Air-Conditioning Engineers, "ASHRAE Standard 170-2021, Ventilation of Health Care Facilities" gives detailed guidelines for air handling and ventilation in health care facilities [27] .(Table 45.2).

Air Entry and Exhaust

In these air exchanges, a certain proportion of fresh air is also introduced every time. The fresh air intake should be designed to be located away from generator exhaust, bio-medical waste storage areas, and other possible contaminating sources. The air exhaust duct outlet should be located as far away from the fresh air intake port as possible so that cross contamination is prevented.

Air Quality Control

The fresh air that is taken in needs to be conditioned. The first step is filtration of macro contaminants like flying insects such as mosquitos and flies, followed by temperature correction by heating or cooling as per requirement, humidification or dehumidification as needed, and finally, high-efficiency particulate absorbing (HEPA) filtration [28] in the sterile zones like operating room and labor room. Ideally, the clean air entry in these rooms should happen in a laminar fashion directly above the patient area. Air handling units of the HVAC should be located by design and planning, so as to avoid the need for the intrusion of maintenance personnel into patient care or surgical areas. Air distribution ducting should be designed for easy inspection and service access so that cleaning and maintenance is easily done.

Any construction, renovation, or maintenance activities can disrupt and release organisms and contaminants posing hazards to staff and patients [17]. In such situations, special precautions must be taken to contain the spread of all hazardous materials and protect the patients and staff. Pressure differential between isolation rooms and the surroundings is another way of reducing

Table 45.2 ASHRAE standard 170-2021 ventilation design parameters for inpatient spaces [24]

Function of space	Pressure relationship to adjacent areas	Minimum outdoor ACH	Minimum total ACH	Design relative humidity (%)
Cesarean delivery room	Positive	4	20	20–60
Critical care patient care station	No requirement	2	6	30–60
Operating room	Positive	4	20	20–60
Procedure room	Positive	3	15	20–60
Treatment room	No requirement	2	6	20–60
Endoscope cleaning	Negative	2	10	No requirement
Physical therapy	Negative	2	6	Max 65
Laboratory work area, pathology	Negative	2	6	No requirement

Adapted from: Delgado A, Keene K. Integrating health and energy efficiency in healthcare facilities. United States. https://doi.org/10.2172/1773167

infection transmission [29–33]. When the patient is infectious, the isolation room should be maintained at a negative pressure with respect to the environment.

Air Handling Considerations for Different Types of Rooms

Airborne infection isolation rooms (AIIRs) are of the following four types [34]:

- *Class S* which has a neutral or standard room air pressure, such as standard air conditioning.
- *Class P* which has a positive room air pressure to protect an immune-compromised patient from airborne transmittable infections.
- *Class N* which has a negative room air pressure, to protect others from a patient afflicted with an infectious disease having airborne transmission.
- *Class Q* which has a negative room air pressure with additional barriers including an Anteroom, for full quarantine isolation.

Airborne Infection Isolation (AII) rooms are the alternative to Class N mentioned above. These should have 12 ACH, a negative pressure of at least 2.5 Pa (0.01 in. water gauge) and the air from these rooms should be exhausted directly to the outside environment in a safe way so as not to put the neighborhood people at danger [35].

Single patient rooms are preferable to open wards as that reduces the risk of respiratory viral and bacterial infections with multidrug-resistant organisms [5, 36]. Protecting environment room (PE) for immunocompromised/immunosuppressed, e.g., transplant patients at risk of acquiring infections, are maintained at a positive air pressure with respect to the environment; so that whenever a door/window is opened, clean air from inside the room flows out; thus airborne microorganisms cannot move in. These rooms are designed such that they are supplied with airflow filtered with HEPA filter and have a well-sealed smooth ceiling without any open joints and crevices [28].

45.2.2 Layout Design of Labor Room

45.2.2.1 Patient, Staff and Material Flow Pathways

Right at the designing stage, detailed consideration must be given to the pathways followed for movement of materials and equipment, staff, patients, visitors, food and supplies, besides biomedical waste and disposal items. These paths must be unidirectional without interfering with each other and must be isolated from each other either physically or by controlling the timings [37].

Entry of Staff, Patient and Materials

Staff, patients, and material should have a separate entry. The patient entry should lead into a reception space where nursing takeover can be done with the labor room admission checklist. This space should lead to the prelabor observation beds.

The staff entry should lead into changing rooms with the attached restrooms and then the scrub area, from where they can enter the sterile section of the labor room.

Material entry should happen through a receiving/checking area. After checking and inventory control, the material supplies should be taken out in a clean way, discarding the outer packaging, and then kept in the storage area for use as required.

In a traditional labor room, the patient comes to the pre-delivery bed and is kept there under observation till she is about to deliver. Such pre-delivery rooms, typically, have multiple beds shared by multiple patients, who also share a common toilet. When the patient is about to deliver, she is moved to the delivery table in the delivery room and after delivery, the patient is moved to the recovery room. The recovery room is again usually has multiple beds shared by the patients. In this arrangement as each service is required, the patient moves to avail the service; this system is likely to spread any infection carried by one patient to the others because apart from the common airspace, multiple touchpoints are also shared like the toilet, beds, staff and

monitoring equipment including the doctor's stethoscope [4, 38].

To eliminate this infection possibility by design, the concept has evolved where one patient stays throughout at the same place, and all the services come to the patient as and when required. This concept is known as "Labour Delivery Recovery Post-natal (LDRP)" unit. Since the patient does not move and does not share anything with other patients, the chances of cross-infection are eliminated provided the staff follow standard operating procedure (SOP) for sanitation and infection control (Fig. 45.3).

45.2.2.2 Zoning

The labor room and surgical complex are organized into four different zones; outermost is the protective zone, leading into the clean zone, then the sterile zone, and finally the disposal zone.

Protective Zone

This contains the administrative elements like the office of nurse in-charge, counter for receiving store supplies, staff entrance, lockers and changing rooms, patient reception, and counseling/documentation room. It forms the protective barrier between the clean areas and the rest of the less clean area of the hospital.

Clean Zone

This zone is only accessible to staff after changing their clothes in the protective zone. Prepared patients are brought here after transfer to labor room/OT stretcher from the ward trolley. This space contains the clean surgical supply store, medical store (clean supplies are brought in this zone after discarding their protective outer packaging), surgical instrument store, anesthesia store, anesthesia induction room, anesthetist's

Fig. 45.3 Sample layout of LDRP (eight bed design)

room and flash sterilization room. Frozen section laboratory, if provided, should be located here.

Sterile Zone

This is the cleanest part of the whole complex where procedures that require full asepsis are done using sterile instruments. The highest degree of cleanliness and aseptic environment is maintained here. The delivery table/OT table is usually located in the center of the room. Large hospitals might have more than one delivery room/operation theatre in the sterile zone.

Disposal Zone

The disposal zone forms the corridor from where used instruments contaminated with blood and body fluids, used linen and biomedical waste are removed. This zone must have a separate exit path and it must operate in a unidirectional traffic mode, i.e., always from inside to outside which is maintained by a door or hatch kept locked from inside.

45.2.2.3 Clean Utility/Clean Store

It is the room for storage of clean supplies.

45.2.2.4 Soiled/Dirty Utility

This is the room for storage of used and soiled linen, biomedical waste, and other disposal items. It should have access from inside the labor room so that the waste and disposal items can be placed there in proper biomedical waste (BMW) segregation bins as per local regulatory requirements. There should be an independent separate access from the outside for removal and disposal of the waste.

45.2.2.5 Infant Resuscitation Area

Newborn resuscitation corner should be created within the delivery room and this may be connected to the nursery or NICU via a pass-through window or door. Floor area of at least 40 ft^2 should be provided for the infant. A total of three oxygen, three air, and three vacuum outlets along with 12 electrical points should be available in the OT. In the labor room, one oxygen, one air, and one vacuum outlet along with six electrical points should be available. Pass-through doors/windows should be located such that the privacy of the patient is maintained when these are opened, while allowing easy exchange of the infant between staff. In the case of a pass-through window in an OT, a positive pressure gradient must be maintained inside the OT so that air flows out of the OT when the window is opened [22].

45.2.3 Infrastructure Recommendations

45.2.3.1 Flooring

Ceramic tiles are sometimes chosen because of easy installation, low cost, and decent finish, but they tend to crack easily with a load of heavy equipment and the numerous joints harbor organisms, making infection control difficult. Hardstone or epoxy flooring should be preferred; this should be jointless and the edges with the walls should be rounded. Medical grade rubber having an antistatic and fire-resistant rating should be applied in a monolithic sheet form with all seams and edges welded watertight. There should not be any steps or incline as that can interfere with the movement of equipment and trolleys.

45.2.3.2 Walls

Walls should be easily cleanable and resistant to housekeeping chemicals. Walls with ledges, ridges, and textured surfaces should be avoided because these tend to collect dust which is difficult to clean and can create difficulties for infection control. The vertical surfaces should be given a smooth finish, with all gaps, joints, cracks, and crevices filled up; wall joints with door frames and windows should be sealed with silicone gel. Smooth, non-glossy washable antibacterial paint should be preferred to reduce glare, easy maintenance, and better infection control.

45.2.3.3 Corners

Corners of the rooms and the edges between the walls, and the floor with the walls, should be rounded so that dirt and microorganisms do not accumulate in the recesses.

45.2.3.4 Ceiling

The FGI (Facility Guidelines Institute) recommends that areas with special requirements such as operation room, isolation room, and labor room where air quality is important should have ceilings that are effectively sealed without any gaps, cracks, or crevices so that air pressure can be maintained and contamination does not occur [17]. This should have a non-porous surface finish that is easily cleanable. Thus, sound-absorbing ceiling material should not be used. The ceiling is important because above it is the plenum area where the air conditioning, HEPA filtered laminar airflow outlet, operating lights pendants, gas and electrical outlet pendants, and also room lighting fixtures are fitted. As these fittings need to leave a clear height above the medical teams' heads, the labor room and OT roof must be designed with an extra height of at least 15 ft from the floor.

45.2.3.5 Work Surfaces

Work surfaces should be non-porous stone or preferably stainless steel for easy cleaning and sanitation.

45.2.3.6 Ventilation and Air Conditioning

Proper ventilation, humidity (<68%), and temperature control are important not only for comfort but also for microbiological control. Positive pressure of 2.5 Pa or 0.01 inches water gauge with 12 to 15 ACH, with at least 20% fresh air should be introduced from the ceiling above the patient in a laminar way and exhausted near the floor [35] (Fig. 45.4).

This laminar airflow prevents the microparticle shed by the operating team, from falling into the surgical field as shown in Fig. 45.5 [39].

45.2.4 Operation Theatre Complex

Several things in the layout and infrastructure design of the operation theatre complex are similar to the labor room in terms of zoning, clean and dirty store, infant corner, flooring, walls and ceiling, air quality, and HVAC.

The differences which exist, are because of the differences in the workflow. First of all, the antenatal beds are replaced by induction rooms, where the patient is prepared for anesthesia. The operating room has more equipment and pendants from the roof because of the requirement of good operating lights, besides gas, suction, and electrical outlets for the anesthesia machine. The anesthesia machine and the monitoring equipment also need more space. An operating room size of at least 20 × 20 ft or 6 × 6 m is rec-

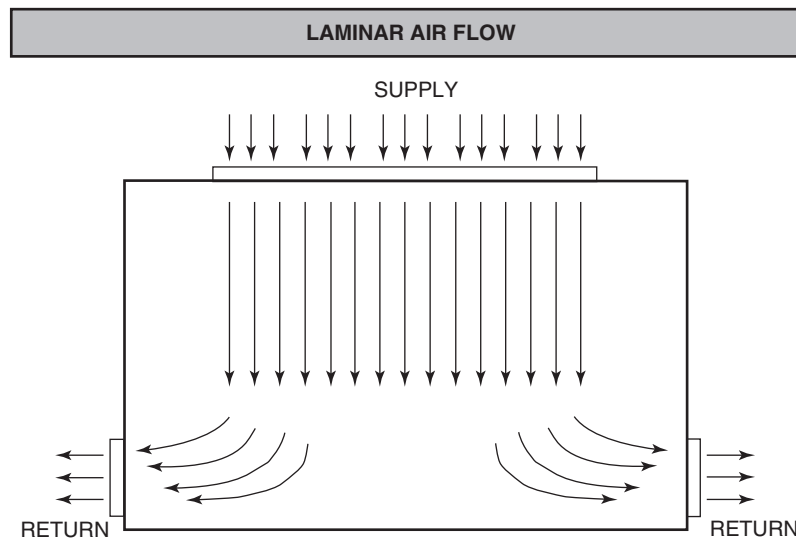

Fig. 45.4 Laminar airflow

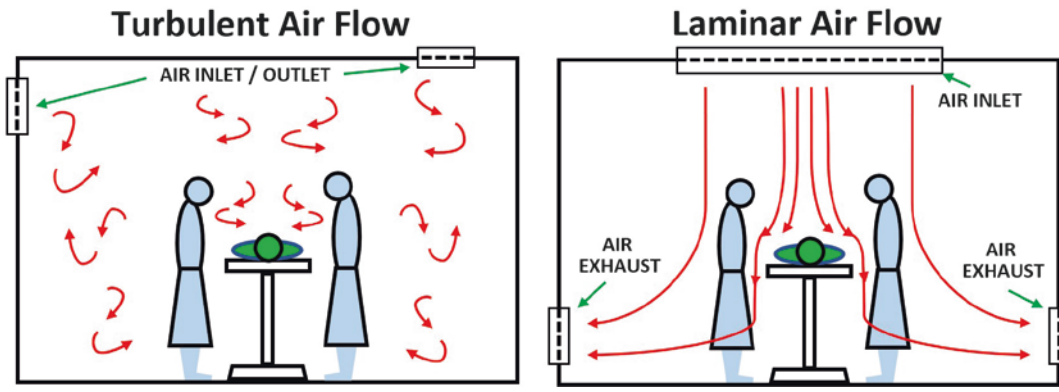

Fig. 45.5 Turbulent and laminar airflow in the OT

Fig. 45.6 Layout of operation theatre complex with four operation theatres

ommended. The postoperative recovery room is also equipped with oxygen and suction for each bed, often along with monitoring equipment. These differences lead to some modifications of the layout as given in the example below (Figs. 45.6 and 45.7).

45.3 Layout Stacking of the Hospital Building

One of the important methods of reducing infections is to create zoning in the hospital; open public access zone (e.g., OPD), restricted public

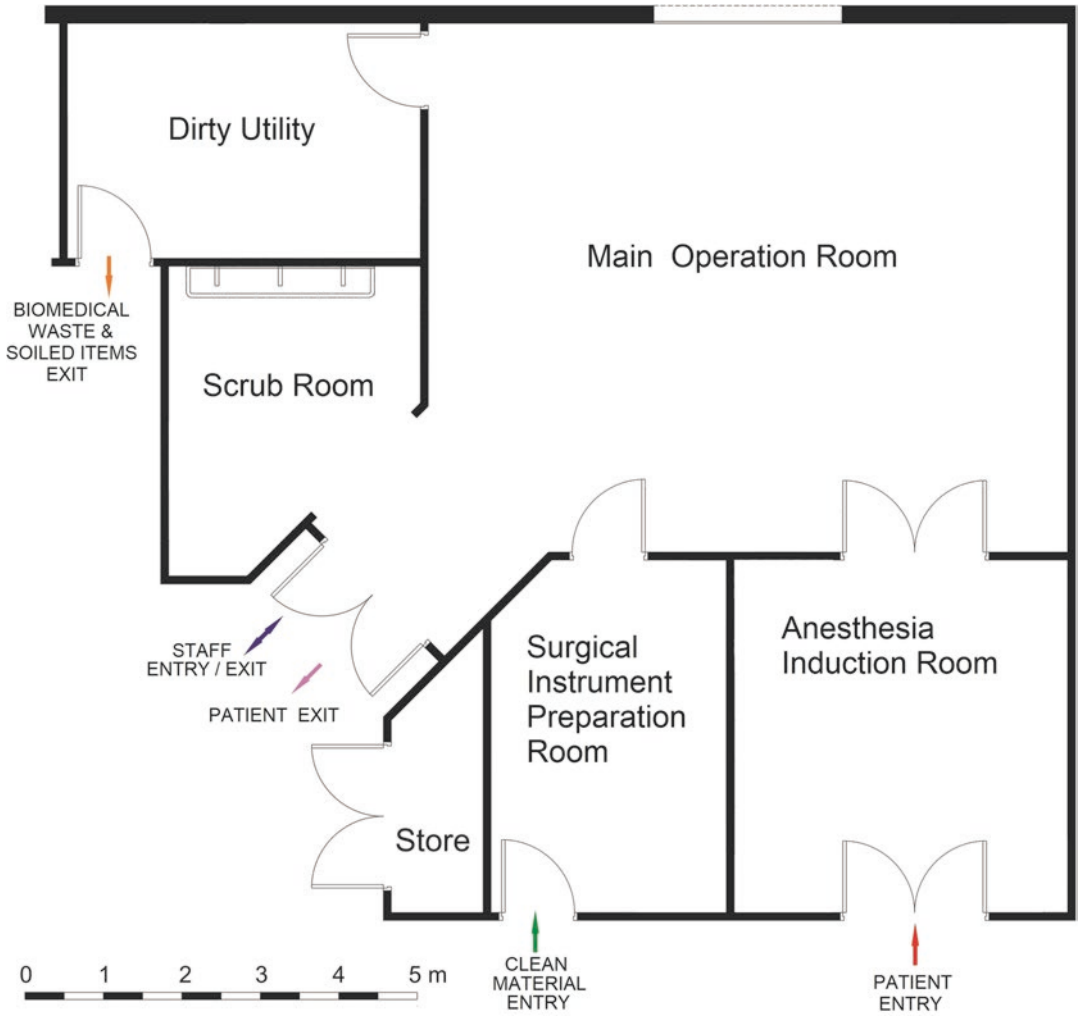

Fig. 45.7 Single operating theatre layout

access zone (e.g., IPD/wards), and clean zone (e.g., OT, labor room, ICU, laundry and CSSD). For this and to facilitate patient access, the OPD and emergency is usually located on the ground floor, OT, labor room, and ICU are located on the first floor, while, laundry and CSSD are located in the basement. To avoid the movement of clean/sterile/soiled materials across the patient area in ground floor, dedicated sterile, clean, and dirty dumb waiters are used (Fig. 45.8). Dumb waiters are small automated lifts used only for moving materials between two floors.

45.4 Processes Essential for Infection Control

The design elements that lead to better infection control are only under control at the design/construction or renovation stage of the hospital. Besides, this is controlled by the owners/ management board. For the practicing clinician, the chance to influence this is miniscule. Rather, the major improvement that they can implement in real life involves administrative tools.

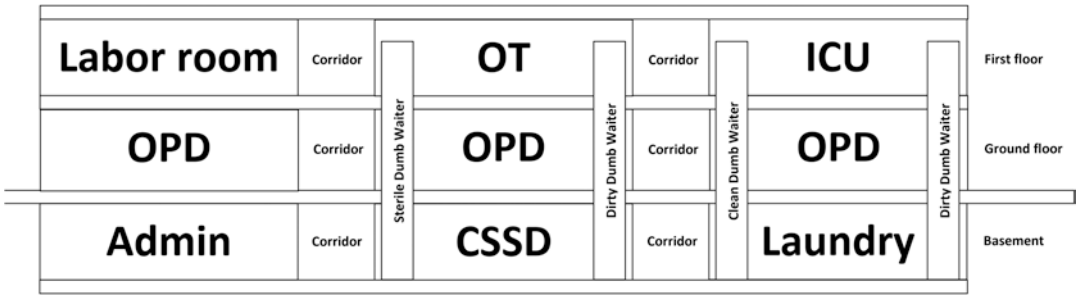

Fig. 45.8 Layout stacking of hospital building

The administrative tools for preventing maternal infections include important processes such as sterilization and disinfection of the sterile zones, strict implementation of the zoning restrictions, hand hygiene and right use of PPE by the staff, along with the support services like CSSD, laundry, housekeeping, and biomedical waste management. Creation of, and then adherence to standard operating procedures (SOPs) for all of these activities plays a crucial role in achieving infection control [40].

Development of an effective Infection Control Risk Assessment (ICRA) process can prevent hospital-acquired infections (HAIs). Awareness of the airflow patterns and their control by use of pressure differential helps minimize or eliminate inadvertent dispersal and spread of dust and infection [41]. Air sampling should be done periodically to determine indoor air quality. Particle counters and anemometers may be used to determine particle concentration and sample volume Microbiological sampling of air is controversial because there are no established consensus standards, yet it gives us some indication of the effectiveness of the sterilization practices being followed. Special precautions must be taken whenever there is demolition or renovation work going on inside the hospital or outside in the neighborhood to prevent the spread of dust and infections.

45.4.1 Hand Hygiene

Hand hygiene has been proven beyond doubt to be the most important factor in the prevention of nosocomial infections. Soap and water are the essential ingredients that must be made available to the staff and patients at the point of clinical care. Education and motivation of the staff and patients are the drivers that make this happen, while training can ensure that it is done in an effective manner. The several moments of hand hygiene (moments that are in fact opportunities to defeat infections) and the six steps of hand wash should be known to all staff. Handwashing gets neglected when the washbasin is located too far from the point of care. It is essential that there should be a washbasin inside the nursing stations in every ward with taps that are elbow operated or sensor operated type and installed in the wall at least 10 in. above the washbasin. Ideally, there should be a washbasin inside each patient care room and every OPD clinic room.

According to the Australasian Health Facility Guidelines, hand wash basins should have edges that curve up so as to curtail splashes, big enough to allow good hand hygiene without the risk of touching the sides in the process, either sealed to the wall or installed sufficiently distant from the wall to allow proper cleaning, have a watertight splashback, without plugs. Running water should be delivered mixed to a suitable temperature for handwashing. Washbasins should be made of a durable, scratch-resistant material (such as porcelain or stainless steel) and should be easily cleanable. Polycarbonate or other molded synthetic plastic-like materials are not suitable [42].

45.4.1.1 Washbasin Design Types

Type A-Clinical Basin: Large

The Type A clinical scrub washbasin is required in selected areas where clinical hand wash is required prior to any procedures that may be done in non-operating room settings. It is similar

to a kitchen sink, The tap is elbow type, wall-mounted, and at sufficient height to allow comfortable hand wash without stooping and at the same time keeping the arms raised.

Type B-Clinical Basin: Medium

The basin is medium-sized and wall-mounted or on the basin with elbow or wrist hands-free operation. It is used in areas where hand hygiene is required by visitors and staff for patient care and aseptic procedures.

Type C-Non-clinical Basin: Small/Medium

This is a small wall-mounted basin.

Scrub Sink/Trough

This is a long deep sink that should be big enough to accommodate one or more staff simultaneously scrubbing for a surgical procedure. The scrub stations should be sufficiently high and deep to allow washing hands up to the elbow without splashing water outside and without the hand touching the wall or any part of the scrub station. The tap should be of sufficient height so that the hands and arms can be washed while keeping the hands raised (Table 45.3).

45.4.2 Personal Protective Equipment

Adequate personal protective equipment (PPE) must be made available to all staff at risk of exposure to patients and their potential infections. This includes doctors, nurses, technicians, housekeeping, laundry, dietary, and even maintenance staff. Administrative staff who are not required to interact with or visit patients are not at risk. The staff at risk must be provided the training on the importance of protective gear, when and how to use it properly. PPE donning and doffing areas must be created with adequate space, airflow, shower, BMW handling, and containment.

45.4.3 Support Services

Infection control in the department cannot be successful without the involvement and commitment of the support services. These include the central sterile supply department (CSSD), laundry, housekeeping, Biomedical Waste Management, and an infection control program that is hospital wide.

Table 45.3 Washbasin selection guideline

Space/room	Washbasin type	Installation details
Inpatient rooms (single and multi-beded)	B	A washbasin should be installed in each single, double, or four bed patient room. Every bed should have alcohol-based hand rub nearby
Delivery/birthing rooms	A	Washbasin must be installed in each room in addition to alcohol-based hand rub
Critical care—adult, paediatric and neonatal	A	A washbasin should be available in every single room or shared between a pair of patients in shared rooms. In NICU, one hand washbasin per four beds is required
Day-care ward (e.g. MTP)	B	Washbasin required for every four patient beds
Treatment/procedure room (e.g., Coloposcopy)	A	Washbasin required in each room
OPD consultation room	B	Washbasin required in each OPD consultation room
Clean utility rooms	B	Washbasin required in every such room
Dirty utility rooms	B	Washbasin required in every such room
Isolation anteroom/airlock/ inpatient unit corridors	B	Maybe required in case washbasin is not installed inside the patient room
Staff/visitor toilets	C	
Baby change room	C	
Operating room/labor room	Scrub trough	Every operating room/delivery room should have one. In case of multiple OTs/delivery rooms located together, these may be shared between two rooms

45.4.3.1 Sterilisation and Central Sterile Supplies Department (CSSD)

The Central sterile supply department has the crucial function of ensuring that all medical equipment and surgical consumables are supplied to the entire hospital and specially to the labor room and operation theatre with an assurance of complete sterility. It must have separate spaces for receiving the soiled instruments, disinfection, washing and cleaning, drying, inspection and testing, packing, sterilizing, sterile storage area and dispatch area (Fig. 45.9). All these processes must happen sequentially and the material must move in a unidirectional way and sufficient space must be available for various processes and equipment.

The infrastructure requirements like floor, walls, ceiling, air handling, and lighting are similar to the operation theatre but in reverse. Soiled instruments receiving area and the disinfection area are in the dirty zone. Clean zone is where washing, drying, examination, and packing happens. There should be separate entry point for the dirty material and exit point for the sterile material.

Examination step is very important because it detects and prevents damaged instruments from reaching the operation table, creating difficulty during surgery. Micro-instruments must be examined under magnification, cutting instruments must be tested by cutting thin sheets of rubber (such as a glove), and holding instruments must also be tested for their grip and pull. The operation of all locks and levers must be tested for smooth motion. Any manufacturer-recommended lubrication of instruments that may be required, is done at this stage.

The sterilization autoclave should ideally be double door type, i.e., opening on both sides, with one side opening into the clean zone and the other side opening into the sterile zone, with a wall around the washing machine that is sealed all around to maintain complete isolation between the two zones. Automatic locking system is there so that both sides cannot open simultaneously. First, the equipment batch to be sterilized is loaded into the machine from the clean side, the door shut and the machine started. After the sterilization cycle is completed, this door on the clean side remains locked, while now only the door on the sterile side can be opened, whereupon the sterilized batch is taken out.

The clean zone must have HEPA filtered air supply, because, the maximum sterility that can be maintained here, is what will reach the OT.

The CSSD must ensure strict quality control parameters and verification of the processes to

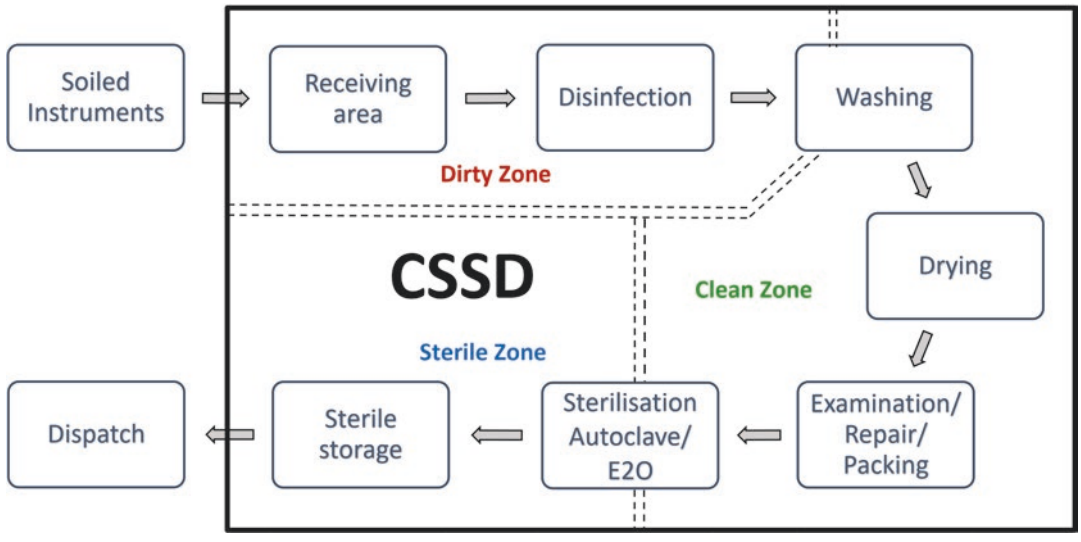

Fig. 45.9 Unidirectional flow of materials in CSSD

ensure that sterilization is achieved and documented records for the same must be maintained.

45.4.3.2 Housekeeping

Keeping a hospital hygienic means not only removing dirt but also maintaining an environment that is optimal for patient safety. Patients with acute symptoms that may cause contamination of the surrounding area with body fluids, for example, vomiting or diarrhea, are more likely to cause cross-infection. Thus, the touch surfaces e.g., bathrooms, commodes, utility rooms, tables, chairs, kitchen preparation surfaces, computer keyboards, and mouse should be disinfected more often. Surfaces that are soiled cannot be disinfected effectively unless they are cleaned first. Fixed or portable non-critical patient care equipment including intravenous stands, blood pressure measurement cuffs, and stethoscopes are [4, 43] high-touch items which are used by healthcare workers such that they touch the patients (such as stethoscopes) or recurrently touched by healthcare staff and patients (such as IV stands) or often shared among patients (e.g. B.P. cuffs) should also cleaned and disinfected often.

The acronym WASTE may be used to recall the variables important in cleaning, whether removing soil or disinfecting and cleaning on a microbiological level [44].

W	Workforce
A	Area
S	Substance
T	Technique
E	Equipment

Workforce refers to the staff that will do the cleaning. Area means the place to be cleaned, the contamination level, and the nature of the surface. Substance implies the cleaning or disinfection chemical, soap, or detergent. Technique is process of using the chemicals and tools for cleaning. Equipment are the tools and machinery used for cleaning.

Environmental cleaning standard operating procedure (SOPs) should be developed to include the consumables and tools required, the preliminary steps such as hand wash and PPE, step-by-step instructions on the actual cleaning procedure, and finally the collection of soiled cleaning supplies and their safe disposal [45]. Cleaning checklists can assist to confirm that all the steps of the SOP are accomplished and some step is not missed. Cleaning logs help confirm the workflow for the staff and finally serve as records for periodic or scheduled cleaning tasks that have been performed.

Sterile zones like labor room and operation theatre should follow a cleaning schedule that includes monthly cleaning of ceilings, weekly cleaning of all walls, floor cleaning at least daily, and also in between every patient. This cleaning should be done by mopping and cleaning with soap and water solution and followed by mopping with a sanitizing solution. This is essential because sanitizing solutions do not work in the presence of dirt. Brooms should not be allowed in the premises because brooms raise dust and nosocomial infection rates increase with their use (Table 45.4).

45.4.3.3 Laundry

Soiled linen must be carefully handled using standard PPE while avoiding agitation to minimize dispersal of dust, bacteria, virus, and bagged before moving out to the laundry to avoid shaking off dust/ infectious particles and spreading them during transport [46]. The laundry process must include effective disinfection followed by washing with detergents and effective cleaning to maintain hygiene. Hot wash cycle is preferred for better sanitation. The laundry must have a unidirectional flow of materials so that cross-contamination does not occur (Fig. 45.10).

Clean linen should be packed before sending out so that unintentional contamination does not occur during transportation and handling. Operational packing of laundry can be achieved by [41]:

1. Putting clean linen in a basket or trolley lined with a fresh new liner, and then covering up or closing the pack
2. Putting clean linen in a cleaned trolley and covering it with a disposable sheet or a laun-

Table 45.4 Recommended cleaning and disinfection frequency and process (for labor room/O.T.) [45]

Frequency	Process
Before and after every procedure & once daily at the least	*Remove waste bins for disposal and soiled linen for reprocessing* Clean and disinfect: • High-contact surfaces & floors with emphasis on the patient zone • Surfaces that appear soiled with blood or body fluids
After the last delivery (terminal cleaning)	*All the above and additionally* • Clean and disinfect other high-contact objects (e.g., door knobs and electrical switches) • Clean and disinfect hand washbasins • Clean and disinfect the complete floor
Scheduled basis	*Floor* • To be cleaned daily in the morning, between every patient, and at end of day, with disinfection and sanitation each time as per hospital policy *Walls/shelves/counters tops* • To be cleaned and disinfected whenever visibly soiled • To be cleaned and disinfected once a week for the full height up to the ceiling *Cupboards* • To be cleaned and disinfected externally including the top, once a week • To be emptied and all shelves cleaned and disinfected and then restocked, once a month *Ceiling* • To be cleaned once a month

Source: CDC and ICAN. Best practices for environmental cleaning in healthcare facilities in resource-limited settings. Atlanta, GA: US Department of Health and Human Services, CDC; Cape Town, South Africa: Infection Control Africa Network; 2019

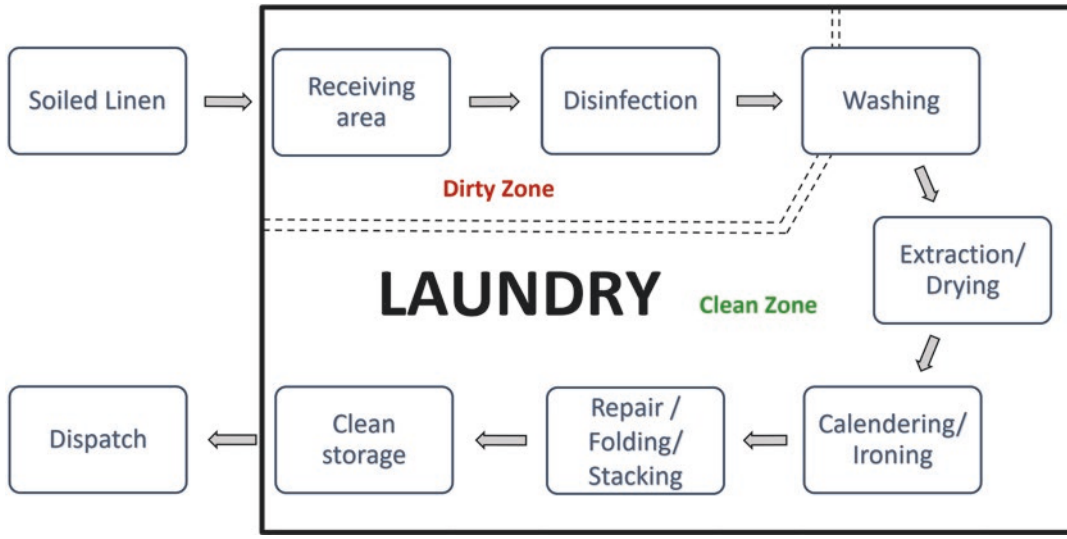

Fig. 45.10 Schematic layout of a laundry

dered textile sheet that is fixed over the trolley.

3. Enclosing each stack of clean laundered items in plastic or any other suitable packaging material that is then sealed or closed with tape.

45.4.3.4 Biomedical Waste Management

Proper segregation at source is essential for safe disposal of biomedical waste. Color-coded bins with biohazard symbols and foot-operated covers should be located in suitable areas not far away

from the nursing station. Non-chlorinated plastic bags of the appropriate color should be lined inside of the bins and biomedical waste segregation posters as per the mandatory requirement should be displayed over the location of the bins. The staff should undergo repeated training on biomedical waste segregation to ensure compliance and safety. The biomedical waste must be emptied at least once every 24 h and more often if the bags get filled up. For removal of the biomedical waste, the waste bags must be tied close and then transported in a covered trolley with Biohazard symbol and text printed on it, to the central biomedical holding storage area, till handing over to the waste disposal agency. The central biomedical waste storage area must be secured from birds, animals, scavengers and kept under lock and key to prevent unauthorized entry/pilferage. This store must also display the Biohazard symbol along with text.

45.5 Quality Control and Outcome Analysis

45.5.1 Quality Control Data

Data that is indicative of infection control measures and their effectiveness should be collected on a regular basis. Some examples of these indicators are:

1. Hand hygiene compliance rate—It indicates the percentage of people washing hands properly, or using sanitizer properly, whenever they should be doing so.
2. Incidence of surgical site infection after surgery—The incidence rate of postoperative infection tells us whether the asepsis is up to the mark and it gives us an early indication in case of something going wrong.
3. Incidence of puerperal sepsis—The data in comparison to past trends and the national and international trends, gives us a reality check.
4. Catheter-associated urinary tract infection rate—This is a measure of the skill and diligence of the doctors and staff concerned with the catheterisation of the patients. Further localization of the data, may allow us to pinpoint the doctor/staff concerned and then we can take specific steps for corrective and preventive action.
5. Air quality monitoring data—Air quality data includes temperature, humidity, PM 2.5 count, and air exposure plate culture colony count. These are important indicators of engineering quality control.

45.5.2 Housekeeping Monitoring Data

Housekeeping effectiveness must be monitored for the practices and their effectiveness to ensure good infection control and safety for the patient, staff, and visitors. Methods of assessing the effectiveness of cleaning practices include [45]:

45.5.2.1 Direct Performance Observations

Observers make standardized structured observations with the help of checklists that are specific to the type of patient care area. It is suitable for big spaces and is easy to employ with the possibility of establishing standards. It allows immediate and direct feedback to the individual staff and identifies gaps for staff training. The main disadvantage is that it is labor-intensive and does not really measure or correlate with a biological infectious load.

45.5.2.2 Visual Assessment

In the visual assessment, the observers visually inspect the cleanliness of articles after the area has been cleaned, which can be done for example using a gloved hand to wipe surfaces and inspect for dust caught on the glove. This method is easy to implement, inexpensive, and allows immediate and direct feedback to concerned staff. Its disadvantage lies in it being subjective and it also does not correlate to bioburden.

45.5.2.3 Fluorescent Markers

This procedure uses a tracing agent (e.g. a chemical tracer which may be a fluorescent) which is applied to mark predetermined objects and surfaces prior to cleaning. After cleaning, a trained

observer uses a detecting agent (e.g., ultraviolet light) to determine if any tracer chemical is remaining. The count of the number of the items that still show the tracer is used to give a score depending on how many items were cleaned fully, partly, or left out. The method is quick, objective, inexpensive, allows benchmarking and it provides immediate feedback on performance. But the method does not assess bioburden, is labor and time intensive and some difficulties may be encountered in proper cleaning of tracer chemicals from rough or porous surfaces.

Methods for assessing the level of cleanliness include:

- ATP bioluminescence—This consists of measuring the residual biological burden by detecting ATP. Presence of ATP implies that organic material (biologic or microbial) is existing on an article or surface. Testing is done before and after cleaning to assess the efficacy of cleaning. a numeric score is generated according to the percentage of marked surfaces that were found acceptable.
- Environmental cultures—Taking a culture of the surface itself with a swab or contact agar plate method to check for bacterial contamination.

- The advantages and disadvantages of both methods are compared in Table 45.5.

45.6 Data Analysis, Interpretation, and Corrective Action

The data that is collected should be analyzed and summarised in a meaningful format which will help to easily understand the current status of the quality. The quality control data is then compared with the past trends and also compared with similar data from other hospitals. This comparison tells us whether we are doing well and identifies the areas that could be prioritized for improvement. If some data shows a sudden deterioration in comparison to past trends, it tells us that something has gone wrong in that aspect and an investigation in the form of root cause analysis might be needed to find out the corrective action that could be useful in controlling and improving the particular aspect. Once the corrective action is taken, we could go a step further and make changes to the system which prevent the repetition of the problem. Such preventive action is the quality tool that reduces problems and mistakes, thereby leading to a continual improvement of quality.

45.7 Conclusion

Infection prevention is an important issue in healthcare as it directly affects patient morbidity, outcome, and cost. While caution and fol-

Table 45.5 Advantages and disadvantages of monitoring methods for assessing cleanliness [45]

Method	Advantages	Disadvantages
ATP bioluminescence	• Fast • Gives quick feedback • Minimum training needed • Factual	• Costly • Specificity and sensitivity and is low • Threshold for defining the level of cleanliness is not standardized • Technology constantly changing • Interference of cleaning products which can enhance or decrease ATP levels
Environmental cultures	• Highly sensitive and specific • Provide direct evidence of existence of specific pathogens • Objective	• Costly • Long time required for results (>48 h) • Availability of lab resources and trained personnel required for interpreting results • Threshold for determining the level of cleanliness is not defined (e.g., number of colony-forming units/unit surface area)

Source: CDC and ICAN. Best practices for environmental cleaning in healthcare facilities in resource-limited settings. Atlanta, GA: US Department of Health and Human Services, CDC; Cape Town, South Africa: Infection Control Africa Network; 2019

lowing proper procedure in performing patient care is important, many times it is not enough. This is amply proven as a harsh truth when we find that in some hospitals despite following the prescribed procedure and use of full PPE, a large number of healthcare workers are getting infected with COVID 19, while in some other hospitals, the staff are hardly affected, if at all. This indicates that the hospital with better planning and design in terms of layout, choice of materials and finishes, air handling, and waste management, is safer for the staff and patients. Healthcare project promotors and doctors need to be aware that it is possible to have long-term benefits with minor changes at the design stage. An experienced and knowledgeable hospital planner must be involved in the early stages of the project.

Key Points

- Structural design should facilitate functional efficiency and at the same time improve patient outcomes in terms of better infection control and enhanced patient safety.
- The processes followed in the labor room and the operation theatre should be focused on making patient safety a priority and that should automatically include infection prevention and control.
- The labor room and surgical complex are organized into four different zones for better infection control; outermost is the protective zone, leading into the clean zone, then the sterile zone, and finally the disposal zone.
- Layout stacking of the hospital building helps to reduce infections; OPD and emergency is usually located on the ground floor, OT, labor room, and ICU are located on the first floor, while, laundry and CSSD are located in the basement.
- The administrative tools for preventing maternal infections include important processes such as strict implementation of the zoning restrictions, hand hygiene, and right use of PPE by the staff, along with the support services like CSSD, laundry, housekeeping, and biomedical waste management.
- Quality control data must be collected and analyzed to ensure that the structural integrity and the process parameters are being maintained within acceptable limits.

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