Practical Guide to Oral Exams in Obstetrics and Gynecology

Questions & Answers

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Görker Sel
Faculty of Medicine
Department of Obstetrics and Gynecology
Zonguldak Bülent Ecevit University
Zonguldak
Turkey

ISBN 978-3-030-29668-1 ISBN 978-3-030-29669-8 (eBook)
https://doi.org/10.1007/978-3-030-29669-8

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

Preface

This book is designed with questions and detailed answers, especially for medical students, who are facing difficulties in clinical visits and oral exams. For instance; "What is the definition of threatened abortion?", "what are the risk factors for spontaneous abortion?", 'how would you manage a woman admitting to emergency service complaining with first-trimester vaginal bleeding?", and so on. After every question, there are answers in a listed format that you need to know which can be used in oral exams. I believe this book is not just for medical students; it would be also beneficial to obstetrics and gynecology residents to get ready for clinical visits and to foresee possible clinical problems that they would be facing and learn how to solve them.

Generally, textbooks follow a classical order. They first name the illness, then tell every detail of it, and finally explain the treatment. But in real life, no one tells you the patients' diagnosis, and I believe the most challenging is to learn how to decide the correct diagnosis after ruling out the differential diagnosis that you think after taking the anamnesis (main complaint and history of the patient) and physical examination of the patient.

In medical school, I see that students generally do not know how to take anamnesis and how to ask questions to the patient for the differential diagnosis. I hope this book would be helpful for learners to categorize the main answers of the clinical problems and diseases.

Also, I believe that question-and-answer design, as in oral exams, is an appropriate method for medical school students who are getting ready for the exams, and this format is also easy to read and review the topic.

In this book, all chapters aim to give the main essence of the problems, describe the main features of the disease or situation, and try not to drown medical students in details that they have not learned at first step.

In that essence, I hope this book would be a practical book for medical students to get ready for the frequently asked questions in clinical visits and exams.

Before I let the readers to surf in the chapters of this book, I would like to thank my professors; Mehmet and Müge Harma, Ülkü Özmen, and Aykut Barut, who taught me the art of learning and teaching surgery at medical school.

Also, I am grateful to my dear family, my mother, Belgin; my father, Halit; and my brothers, Artun and Bilgehan, for their support in all means of my life.

Last but not least, I would like to thank all the contributors for their contributions and support to this book.

It would be my honor to see this book on medical students' and residents' hands.

Zonguldak, Turkey Görker Sel

The original version of the book was revised. The correction to the book is available at https://doi.org/10.1007/978-3-030-29669-8_52

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Contributors

Adile Yeşim Akdemir Faculty of Medicine, Department of Obstetrics and Gynecology, Zonguldak Bülent Ecevit University, Zonguldak, Turkey

Tuba Zengin Aksel Gynecological Oncology Department, Kayseri Education and Research Hospital, Kayseri, Turkey

İ. İlker Arıkan Faculty of Medicine, Department of Obstetrics and Gynecology, Beykent University, İstanbul, Turkey

Büşra Aynalı Faculty of Medicine, Department of Obstetrics and Gynecology, Zonguldak Bülent Ecevit University, Zonguldak, Turkey

Aykut Barut Faculty of Medicine, Department of Obstetrics and Gynecology, Zonguldak Bülent Ecevit University, Zonguldak, Turkey

Mehmet Bülbül Faculty of Medicine, Department of Obstetrics and Gynecology, Adıyaman University, Adıyaman, Turkey

Anıl Turhan Çakır Gynecological Oncology Department, Zonguldak State Hospital, Zonguldak, Turkey

Güldeniz Karadeniz Çakmak Faculty of Medicine, General Surgery Department, Zonguldak Bülent Ecevit University, Zonguldak, Turkey

Eray Çalışkan Faculty of Medicine, Department of Obstetrics and Gynecology, İstanbul Okan University, İstanbul, Turkey

Fadime Dinçer Faculty of Medicine, Department of Obstetrics and Gynecology, Zonguldak Bülent Ecevit University, Zonguldak, Turkey

Yusuf Günay Faculty of Medicine, General Surgery Department, Zonguldak Bülent Ecevit University, Zonguldak, Turkey

Mehmet İ. Harma Faculty of Medicine, Department of Obstetrics and Gynecology, Gynecological Oncology Zonguldak Bülent Ecevit University, Zonguldak, Turkey

Müge Harma Faculty of Medicine, Department of Obstetrics and Gynecology, Gynecological Oncology Zonguldak Bülent Ecevit University, Zonguldak, Turkey

Su Harma Faculty of Medicine, Demiroğlu Bilim University, İstanbul, Turkey

Talip Karaçor Faculty of Medicine, Department of Obstetrics and Gynecology, Adıyaman University, Adıyaman, Turkey

Mehmet Can Nacar Faculty of Medicine, Department of Obstetrics and Gynecology, Adıyaman University, Adıyaman, Turkey

Onur Numan Faculty of Medicine, Department of Obstetrics and Gynecology, Yeni Yüzyıl University, İstanbul, Turkey

Ülkü Özmen Faculty of Medicine, Department of Obstetrics and Gynecology, Zonguldak Bülent Ecevit University, Zonguldak, Turkey

Görker Sel Faculty of Medicine, Department of Obstetrics and Gynecology, Zonguldak Bülent Ecevit University, Zonguldak, Turkey

Avni Ozan Tekin Faculty of Medicine, Department of Obstetrics and Gynecology, Zonguldak Bülent Ecevit University, Zonguldak, Turkey

Hasan Yüksel Faculty of Medicine, Department of Obstetrics and Gynecology, Adnan Menderes University, Aydın, Turkey

Chapter 1
Obstetrics: History Taking and Physical Examination

A patient admitted to you as first trimester pregnant woman. How would you take her anamnesis (History taking)?

- Patient's name, age, occupation, residential info.
- Blood type (if the patient is rhesus (Rh) negative, ask the partner's blood type, also this should be confirmed by official documentation).
- Gravidity, parity, miscarriage, stillbirth, ectopic pregnancy.
- Also TPAL annotation is another method to define the total number of pregnancies. TPAL: Term delivery, Preterm delivery, Abortions including ectopic pregnancies, Living children; for example, it is written as 1001, meaning she gave birth to one term fetus and that infant is living now, she has no history of abortions and preterm births.
- Past obstetric history, namely Previous pregnancies: modes of delivery (e.g., spontaneous vaginal delivery, caesarian section), gestation at delivery (e.g. preterm, post term), birth weight (e.g., macrosomia, low birth weight), antenatal complications (e.g., hypertension, diabetes), how long her labour lasted-long labour or not, intrapartum complications (e.g., dystocia), postnatal complications (e.g., postpartum hemorrhage).
- First day of last menstrual period (LMP); if it is not known, corrected first day of LMP could be dated by using ultrasound scans from 8th to 13th weeks of gestation.
- Gestational age is reported as weeks + days by using the first day of LMP (e.g., 30 + 4 means 30 weeks and 4 days).
- Current pregnancy history: first and/or second trimester screening tests, fetal anomaly screening, oral glucose tolerance test (OGTT), vaccination records.
- History of any gynecological diseases and/or examinations, contraception (family planning), cervical screening results.

Acknowledgments The author would like to thank Dr. Fadime Dinçer who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_1

- History of any systemic diseases. Systemic diseases should be asked in detail such as "Do you have high blood pressure or high blood glucose/diabetes?" since most of the patients do not answer direct questions clearly otherwise.
- Past surgical history: Should be asked in detail such as "Did you have any caesarian section? Or any abdominal surgery like appendectomy?" for more accurate answers, since some patients show reluctance to answer those questions as they do not think as answers to those questions are important.
- Drug history (regular medications, allergies, illicit drugs as well), alcohol, smoking.
- Family history: consanguinity, inherited genetic diseases (e.g., thalassemia, thrombophilia, cystic fibrosis), history of previous fetal anomaly.

A patient who delivered a twin pregnancy at term. How would you note her chart, para 1 or para 2?

- This patient who has delivered twins after 20 weeks would be noted to be a Gravid 1 Para 1, G1P1A0L2.
- TPAL annotation: 1002.

How would you perform an obstetrical examination, after taking obstetrical anamnesis?

- Inspection/observation:
  - Abdominal distention.
  - Any asymmetry? (myoma uteri, etc.).
  - Skin lesions: linea nigra, striae gravidarum, stria albicans, scars or deformities from previous operations.
- Abdominal examination (palpation):
  - Measurement of symphysis pubis and fundal height. It can be measured in centimeters with tape after 20 weeks. For example, 30 weeks pregnant women have a symphysis fundal length of 30 ± 2 cm.
  - At 36 weeks gestation, fundal height is at xiphoid process/metasternum.
  - Fetal habitus: longitudinal, transvers, or oblique.
  - The presentation of the fetus: for example, head, breech
  - Amniotic fluid volume: While we use ultrasound to detect these data nowadays, manual examination (palpation) is also important in case we do not have any access to ultrasound. In terms of amniotic fluid, for example, polyhydramnios may be thought in case of distended uterus without feeling any fetal parts while palpating the abdomen.
- Auscultation of fetal heart beats:
  - After 12 weeks of gestation, you can use hand Doppler. After 24th gestational weeks, you can use fetal stethoscope. The number of fetal heart beats per minute should be noted (120–160/min).
- General physical examination:
  - Weight and height of the patient; body mass index (BMI).
  - Blood pressure, pulse rate, SPO_2.

- Auscultation of the heart and lungs of the pregnant woman at rest.
- Thyroid gland, palpation of the neck.
- Breast examination (any mass, lumps)
- Varicose veins
- Skeletal anomaly: scoliosis, kyphosis.

How would you calculate the estimated date of delivery (EDD), what is the name of this rule?

- The estimated date of delivery (EDD) can be calculated from the first day of the last menstrual period (LMP) by adding 9 months and 7 days to this date; also EDD can be calculated by subtracting 3 months from the first day of the LMP and adding on 7 days. This is called Naegele's rule.

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Chapter 2
Approach to Acute Abdominal Pain in Pregnancy and Postpartum Period

What are the mostly encountered reasons of abdominal pain in the first trimester of pregnancy?

- Ectopic pregnancy.
- Pain due to round ligament tension is usually observed in the right lower quadrant.
- Abortion.

What are the life-threatening reasons of abdominal pain in the second half of pregnancy?

- Ablatio placenta
- Pregnancy-related liver diseases (severe preeclampsia, HELLP, acute fatty liver of pregnancy, pain due to stretching of Glisson's capsule)
- Uterine rupture

What causes abdominal pain in the second half of pregnancy?

- Labour pain (preterm labour)
- Intra-amniotic infection
- Pain in the upper quadrant of the abdomen due to fetal head, secondary to breech presentation

What are the rare reasons of abdominal pain in the second half of pregnancy?

- Uterine incarceration (second trimester)

What are the causes of abdominal pain that may occur frequently in every trimester of pregnancy?

- Degeneration of a leiomyoma, torsion of a pedunculated fibroid
- Ovarian cyst rupture, bleeding
- Constipation

Acknowledgments The author would like to thank Dr. Yusuf Günay who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_2

What are the rare causes of abdominal pain that may occur in every trimester of pregnancy?

- Ovarian torsion, torsion of adnexal structures: It is more common in pregnancy than in non-pregnant women.
- Uterine torsion.
- Pelvic inflammatory disease.

What are the life-threatening causes of upper abdominal pain during pregnancy?

- Intestinal obstruction (adhesion, volvulus, intussusception, hernia): crampy abdominal pain, vomiting, obstipation
- Perforated ulcer
- Visceral artery aneurysm
- Hepatic rupture

What are the common causes of upper abdominal pain during pregnancy?

- Gastroesophageal reflux
- Diseases related to gall bladder: stone, acute cholecystitis
- Pneumonia

What are the rare causes of upper abdominal pain during pregnancy?

- Acute hepatitis
- Pancreatic diseases
- Rectus sheath hematoma
- Adrenal hemorrhage
- Hiatal hernia
- Spleen-related disorders

What are the causes of right upper quadrant pain during pregnancy?

- Cholelithiasis, which is present in 12% of pregnant women; also other causes are HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, fatty liver of pregnancy, and Budd–Chiari syndrome, acute hepatitis, pancreatitis, primary sclerosing cholangitis, and appendicitis (since the cecum is progressively displaced cranially by the gravid uterus).

What are the frequent causes of abdominal pain in the lower quadrant during pregnancy?

- Acute appendicitis: Appendicitis affects about 1 in 1500 pregnant women. It is the most common cause of abdominal pain due to non-obstetric reasons and also the most common surgery performed during pregnancy. Particular attention should be paid to the second trimester. In addition, microscopic hematuria and pyuria in one third of appendicitis patients may also be related to ureteral irritation.
- Nephrolithiasis.

What are the rare causes of abdominal pain in the lower quadrant during pregnancy?

- Inflammatory bowel disease (IBD)
- Diverticulitis (Meckel's diverticulum, rarely seen)

What are the life-threatening causes of abdominal pain in more than one quadrant during pregnancy?
- Trauma
- Spontaneous hemoperitoneum
- Aneurysm (arterial; splenic, renal, uterine, ovarian, aorta)
- Mesenteric venous thrombus

What are the common causes of widespread abdominal pain (in more than one quadrant)?
- Gastroenteritis
- Sickle cell crisis
- Hereditary angioedema
- Familial Mediterranean fever (FMF)

What are the other rare causes of widespread abdominal pain (in more than one quadrant)?
- Iliopsoas abscess
- Superficial nerve entrapment
- Abdominal wall hernias

What tests would you order from pregnant women with abdominal pain?
- Complete blood count (CBC)
- Urine analysis
- Liver, pancreatic, and renal function tests (aminotransferases, bilirubin, amylase, lipase, BUN, creatinine, electrolytes)

Which imaging methods do you prefer in a pregnant woman with abdominal pain?
- First, ultrasound (US) (abdomen, pelvis)
- MRI (if no clear diagnosis is made in US) (gadolinium is not used, due to fetal effects)
- Laparoscopy: A diagnostic procedure that can be performed if the diagnosis cannot be made and the pain does not relieve.

What are the causes of acute abdominal pain in the postpartum period?
- Necrotizing fascitis
- Abdominal compartment syndrome, bowel obstruction, adhesions secondary to previous surgery
- Group A streptococcal infection

What are the common causes of frequent acute abdominal pain in the postpartum period?
- Pain due to uterine involution, physiological
- Urinary retention
- Endometritis: fever, uterine tenderness, smelly vaginal discharge
- Incisional complications: seroma, hematoma, infection, dehiscence

What are the causes (rare causes) of other acute abdominal pain in the postpartum period?
- Ovarian and thrombophlebitis: usually occur 1 week after delivery; fever, general fatigue, and pain. Usually the right ovarian vein. Heparin is applied.

- Clostridioides difficile-induced diarrhea and colitis.
- Hemorrhage; intra-abdominal or retroperitoneal.
- Ogilvie's syndrome (acute colonic pseudo-obstruction): postop ileus, massif dilatation of the column without mechanical obstruction.
- Liver diseases secondary to pregnancy.
- Separation of the symphysis pubis: pain encountered after the delivery of the baby. When pressure is applied to the bilateral trochanter, the pain increases and the patient describes the location of the pain as pelvic bone.
- Foreign body, gauze.
- Pain secondary to organ injuries not recognized in operation, intestinal.
- Intraabdominal, pelvic abscess.

What are the factors that make acute abdomen more challenging during pregnancy?
- Nonspecific leukocytosis
- Displacement of abdominal and pelvic structures from their normal locations by the gravid uterus
- Difficult abdominal examination
- Nonspecific nausea and vomiting

In which trimester the non-perforated acute appendicitis incidence is highest?
- Second trimester of the pregnancy

In which trimester the perforated acute appendicitis incidence is highest?
- Third trimester of the pregnancy

What is the fetal loss rate in non-perforated acute appendicitis?
- 3–5%

What is the fetal loss rate in perforated acute appendicitis?
- 20–25%

What is the estimated negative acute appendicitis rate during pregnancy?
- About 35%

When is a concomitant cesarean section indicated at the time of appendectomy?
- The gestation is above 37 weeks and already a cesarean is anticipated.

What are the factors that increase gallstone formation during pregnancy?
- Elevated serum cholesterol and lipid levels.
- Decreased gallbladder motility and delayed emptying.
- Estrogen increases cholesterol secretion, progesterone reduces soluble bile acid secretion.

What is the treatment for acute cholecystitis during pregnancy?
- Traditionally, definitive surgery is usually deferred in uncomplicated cases.
- Preferred antibiotics include cephalosporin and clindamycin.
- However, some researchers are of the opinion that a conservative approach is associated with higher relapse rates in the range of 40–70%.

- In pregnant women with biliary tract disease, laparoscopic cholecystectomy was superior to nonoperative management during the first and second trimesters.

What is the treatment for complicated acute cholecystitis during pregnancy?
- In pregnant women with cholangitis or pancreatitis, endoscopic retrograde cholangiopancreatography (ERCP) can be safely performed with minimal risk of ionizing radiation exposure.
- Elective cholecystectomy can then be performed postpartum.

When should cholecystectomy be performed during pregnancy?
- Whereas once it was thought that the second trimester was the optimal time for cholecystectomy due to decreased spontaneous abortions and preterm labor, there is a growing evidence that suggests laparoscopy can be performed in all trimesters with equal safety.

What are the etiologies of acute pancreatitis in pregnant?
- Cholelithiasis.
- Congenital or acquired hypertriglyceridemia.
- Even though hypertriglyceridemia can occur in any trimester, pancreatitis commonly occurs in the third trimester.
- Pancreatitis can be associated with preeclampsia–eclampsia or hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome.

What is the management of acute pancreatitis during pregnancy?
- Conservative with adequate bowel rest, nasogastric aspiration, proper hydration, electrolyte correction, and analgesics.
- Meperidine is the analgesic of choice, and short-term administration is relatively safe in pregnancy.
- The role of antibiotics, radiological aspiration, parenteral nutrition, and surgical intervention should be considered in case of complications such as abscess, hemorrhage, necrosis, or sepsis.

What periods are associated with increased small bowel obstruction during pregnancy?
- 16th–20th week
- 36th week
- Immediate puerperium

What are the causes of small bowel obstruction during pregnancy?
- Adhesive obstruction occurs more commonly in advanced pregnancy. Reported rates are 6%, 28%, 45%, and 21% during the first, second, third trimesters, and puerperium, respectively.
- Volvulus (25%).
- Intussusceptions (5%).
- Hernia (3%).
- Carcinoma (1%).
- Idiopathic “ileus” (8%).

In which condition the risk of fetal irradiation is largely ignored?
- Small bowel obstruction. Abdominal X-ray can be done.

What is the treatment for small bowel obstruction during pregnancy?
- Bowel rest, intravenous hydration, and nasogastric aspiration with close monitoring.
- Urgent surgical intervention is mandatory in case of failure of conservative therapy as denoted by signs of impending bowel strangulation or symptoms of fetal distress.

Which incision is preferred for small bowel obstruction during pregnancy?
- Midline incision

What are the most common causes of intra-abdominal hemorrhage during pregnancy?
- Rupture of splenic artery aneurysm
- Rupture of the dilated high-pressure veins of the ovary and broad ligaments at the time of labor

What are the mortality rates of pregnant and fetus in artery rupture?
- 75% in pregnant women and is associated with a fetal mortality of 95%

What is the most common cause of non-obstetrical maternal death during pregnancy?
- Trauma

Which test should be done in fetal–maternal trauma?
- Kleihauer–Betke test should be performed to detect the presence of fetal red blood cells in the maternal circulation due to fetal–maternal hemorrhage

When does fetus become more vulnerable to trauma?
- Pregnancy ≥24 weeks, in whom a viable fetus is very vulnerable to injury because of its size and extra pelvic position.

What are the treatments of urolithiasis that are contraindicated during pregnancy?
- Extracorporeal lithotripsy and percutaneous nephrolithotomy

What consequences are determined in pregnancy after a pre-pregnancy of abdominal hernia repair?
- If the hernia is repaired by suture alone, it increases the risk of recurrence of symptoms during pregnancy.
- A hernia repair with mesh may restrict the flexibility of the abdominal wall, potentially causing pain during a subsequent pregnancy.

Which option is preferred for rectal cancer treatment during pregnancy?
- Generally, in the first 20 weeks (first half) of pregnancy, treatment delay can lead to disease progression and compromise the mother's life; therefore, pregnancy would be terminated and early cancer treatment should be started.
- In the second 20 weeks (second half) of pregnancy, surgery can be delayed for saving the fetus.

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Chapter 3
Abortions and Recurrent Pregnancy Losses

What are the causes and percentages of the first trimester vaginal bleedings?
- 30% abortus, 10–15% ectopic pregnancy, 0.2% mole

What is the most important reason for maternal mortality in the first trimester of pregnancy?
- Ectopic pregnancy. The 5% mortality rate in the first trimester of pregnancy is due to ectopic pregnancy (rupture, bleeding, hemorrhagic shock, disseminated intravascular coagulation, etc.).

What are the main features of spontaneous abortions or miscarriages?
- Pregnancy losses occurring prior to 20th or 24th week of gestation or fetus weighing below 500 g are defined as abortion.
- It is the most frequent complication of early pregnancy.
- Abortion is less detected in patients with previous healthy pregnancies.
- After 15th gestational week, abortion rates decrease.

What is the classical clinical presentation and symptoms of a patient with spontaneous abortion?
- Vaginal bleeding (scant or heavy), unfortunately volume of the bleeding does not give a clue about abortion.
- Pelvic pain in crampy or in dull character, could be constant or intermittent, as well.

What are the risk factors for spontaneous abortion?
- Advanced maternal age
- Having history of previous spontaneous abortion
- Smoking, alcohol, cocaine, nonsteroidal anti-inflammatory drug (NSAID) (not acetaminophen) consumption. Also it is important to note that even smoking just

Acknowledgments The author would like to thank Dr. Fadime Dinçer who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_3

one cigarette daily throughout pregnancy doubled the risk for sudden unexpected infant death (SUID). Moreover, women who reduced or quit smoking during pregnancy cut the SUID risk by 12 and 20 percent, respectively according to recent research in USA.
- Having body mass index (BMI) beyond the normal limits, at the beginning of pregnancy (extremes of maternal weight)
- Fever
- Trauma
- Congenital anomalies
- Uterine structural abnormalities (such as uterine septus)
- Infection (*Listeria monocytogenes*, *Toxoplasma gondii*, parvovirus B19, rubella, herpes simplex, cytomegalovirus, Zika)
- Maternal systemic diseases (HT, DM, thyroid diseases, celiac, systemic lupus erythematosus (SLE), antiphospholipid syndrome)
- Caffeine consuming ≥4 servings/day (pre-pregnancy coffee intake as well)
- Women with lower socioeconomic status, women with agricultural and related work, lower income, and lower educational attainment

What is the most common known cause of spontaneous abortion in the first trimester?
- Fetal chromosomal anomalies

What are the most common chromosomal abnormalities among spontaneous abortions?
- Most common chromosomal abnormality among spontaneous abortions is autosomal trisomies, the most common of those is trisomy 16.
- Additionally, trisomy 1 is never observed in abortions.

What is the most common cause of spontaneous abortion in the second trimester?
- Cervical insufficiency

What are the differential diagnoses of spontaneous abortions?
- Physiological (secondary to implantation)
- Ectopic pregnancy
- Gestational trophoblastic diseases (GTD)
- Cervical, vaginal or uterine pathology, neoplasms, trauma
- Sub-chorionic hematoma
- Rectal bleeding, hemorrhoids
- Hematuria

What are the classifications of abortions?
- Threatened abortion (abortus imminence)
- Missed abortion
- Empty sac (anembryonic pregnancy, blighted ovum-obsolete terms)
- Inevitable abortion (abortus incipiens)
- Incomplete abortion

- Complete abortion
- Septic abortion

What is the description of threatened abortion?
- Vaginal bleeding occurs but cervical os is closed, and fetal cardiac activity is still present.

What are the possible adverse outcomes encountered in later trimesters in pregnancy related to threatened abortion in the first trimester?
- Miscarriage, preterm birth, premature rupture of membranes (PPROM), intrauterine growth restriction (IUGR), antepartum bleeding.

What is the description of the missed abortion?
- Vaginal bleeding occurs, and cervical os is closed, but with nonviable intrauterine pregnancy. Fetal cardiac activity is absent.

What is the description or diagnosis of empty sac?
- It is diagnosed sonographically as the presence of a gestational sac larger than 25 mm without evidence of embryonic tissues like yolk sac or embryo, due to development arrest of the embryo at the very beginning of gestation.

What is the definition of abortus incipiens?
- Vaginal bleeding occurs, cervical os is dilated, and fetal cardiac activity is still present. Pelvic pain is evident. Products of the conceptus could be observed through the dilated cervical os, but not felt out of the uterus (as in incomplete abortion).

What is the description of incomplete abortion?
- Vaginal bleeding occurs, and cervical os is dilated. Pelvic pain is in crampy nature. Not all of the products of the conceptus are out of the uterus; for instance, placental tissue may be retained in utero.

What is the description of complete abortion?
- Patient is relieved now, and pain is resolved or mild, not like in incomplete abortion. The main reason of the pain is the dilatation of the cervix, but now as all products of the conceptus is expelled out of the uterus totally, cervical os is closed as well.
- Uterus becomes smaller and contracted.

What is the description of septic abortion and management of it?
- Endomyometritis is the most common clinical picture.
- There is fever, foul-smelling discharge, severe sensitivity, and tenderness in the abdomen and uterus during cervical examination.
- DIC can develop in neglected cases.
- In case of septic abortion, the cavity is cleaned by curettage, and broad spectrum antibiotics are given to the patient.
- If there are signs of sepsis and the reproduction request is completed, hysterectomy can be performed.

What is the definition of induced abortions and methods for the treatment?

- Abortions induced in which maternal conditions with cardiac decompensated heart diseases, severe hypertensive vascular diseases, severe diabetes, or in cases of severe anomalies of the fetus.

  Medical methods
  Three most commonly used agents are:

  - An antiprogesteron, mifepristone (RU486).
  - Misoprostol, a prostaglandin E1 (the most commonly used, 4 × 2 buccal, 4 × 2 vaginal, 12 × 1 vaginal dosings are available, but should not be used in cases of history of cesarean section, should be remembered that it may lead to uterine rupture).
  - Methotrexate, which is an antimetabolite (it is usually applied in uterine pregnancies in hard-to-reach places such as corn, cesarean scar pregnancy, with intramuscular dose of 50 mg/m^2).

  Surgical methods

  - Dilatation and curettage (D/C)
    - Vacuum curettage
    - Surgical curettage (sharp curettage)
  - Dilatation and evacuation (D/E)
  - Hysterotomy or hysterectomy

What are the complications that may occur during the treatment of spontaneous abortus?

- Hemorrhage (secondary to coagulopathies or cervical–uterine laceration)
- Uterine perforation (especially after sharp curettage)
- Retained products of the conceptus, placenta (generally prevented during ultrasound check during or after the procedure)
- Endometritis (septic abortion may occur if antibiotics are required)

Describe the diagnostic steps of spontaneous abortion.

- *Anamnesis*: Advanced maternal age? The correct gestational age should be calculated. The drugs given to the pregnant women should be questioned (e.g., acetylsalicylic acid-aspirin, enoxaparin). Are there bleeding disorders (gingival-nosebleeds, easily bruising on the skin, as well as Von Willebrand disease (vWD) may have been previously diagnosed)? Trauma? Consanguineous marriage (chromosomal anomaly)? The amount of bleeding and the relationship between bleeding and coitus should be questioned (secondary bleeding due to cervical ectropion or cervical polyp). Foul smelling vaginal discharge? (Septic abortion?).
- *Physical examination*: Evidence of bleeding from the uterus should be proven by speculum (perhaps the patient may have misinterpreted hemorrhoids as vaginal bleeding or may have misinterpreted hematuria as vaginal bleeding). The amount of bleeding should be questioned and observed, and presence of cervical

dilatation and protrusion of the conceptual material should be determined. In addition, the presence of infected vaginal discharge and tenderness of the uterus are also indicatives of the septic abortion.

- Although bimanual examination and uterine size determination are methods used in the past, after the extended usage of ultrasound, it is no longer applied in the first plan, but should not be forgotten though.
- Pelvic ultrasound is the most useful test. Detection of fetal cardiac activity is one of the most important findings. Gestational sac size, shape, and presence of the yolk sac are important parameters in the evaluation. If fetal heart rate cannot be evaluated on suprapubic ultrasound, it is recommended to evaluate with transvaginal ultrasound.
- *Human chorionic gonadotropin (hCG) assessment*: Generally, a single value of hCG does not give a clue (e.g., crown lump length, CRL: <5–6 mm) if the fetal heart rate is not advanced in the week to be observed. The change in hCG values is seen every 2 days, doubling (more than 66% increase is meant) gives positive information about healthy pregnancy, but the reduction of hCG with 35% or more is a strong indicator of miscarriage. If hCG level plateaus, it suggests ectopic pregnancy (see ectopic pregnancy).
- Assessment of Rh antigen. (Rh_o(D) immune globulin, namely Rhogam is applied if indirect coombs negative to prevent RhD isoimmunization).
- Progesterone: <5 ng/mL is compatible with abortions, but not routinely used.
- Complete blood count (CBC) to reveal anemia, low platelet levels in patients with excessive bleeding; it is important to evaluate the white blood cell (especially in patients with septic abortion) as well.
- In the treatment of abortus imminens, we apply the only promising treatment namely progestins; intramuscular, oral and vaginal. However in situations like vaginal bleeding, vaginal route is not preferred, also it is important to remember that intramuscular application may be painful for the patients. However a recent research find that vaginal progesterone from bleeding onset until 16 weeks of gestation resulted in similar miscarriage and live birth rates (at least 34 weeks gestation) as placebo.
- Efficacy of daily physical activity restriction, bed rest, and hydration (except in the case of dehydration) has not been demonstrated, and care should be taken to ensure that sustained rest can lead to thromboembolic morbidities.

What is the definition of recurrent pregnancy loss, habitual abortion?

- Two or more consecutive pregnancy losses that occurred clinically before the 20th week of pregnancy. Incidence is 1% of couples.
- Genetic-related abortions are usually in the early stages of pregnancy (5–8 weeks); abortions related to autoimmune and uterine anomalies usually occur in later periods of pregnancy (12–20 weeks).

What are the epidemiological factors for recurrent pregnancy loss?

- Increased maternal age (abortion rate is minimal between 20 and 24 years, maximum at 40 years of age).
- Reproductive history: Healthy or miscarriage history of previous pregnancy.

- Genetic factors: 50% of first trimester abortions form chromosomal abnormalities of embryo.
- Parental chromosomal abnormalities: The most common type of reciprocal (Robertson-balanced) translocation (two acrocentric chromosomes combine in the centromeric region with short arm loss) is a phenotype of the normal but high–low rate and the risk of congenital anomaly due to unbalanced chromosome arrangement.
- Embryonic aneuploidy and polyploidy: Chromosome deletion or extra chromosome formation (mono-trisomy) during meiosis. Triploidy occurs when there is an extra set of chromosomes, namely 69 chromosomes. Most of the trisomies are due to advanced maternal age.
- Single gene mutations, skewed X chromosome inactivation.

What are the main causes and percentiles of recurrent pregnancy loss?

1. Immunological causes and thrombophilia: 15–20%
2. Anatomical causes: 15%
3. Endocrine causes: 8–12%
4. Other causes: 10%
5. Genetic causes: 2–4%
6. Infectious causes: 0.5–1%

Describe immunologic causes and thrombophilia for recurrent pregnancy loss.

- Antiphospholipid antibody syndrome (APS):
- It is characterized by the development of antibodies against phospholipids.
- The main risk factor for poor pregnancy outcomes are anticardiolipin antibodies, lupus anticoagulant, and anti β2-glycoprotein-1 antibodies.
- The main pathology of APS to cause pregnancy loss is placental thrombosis. Disruption of uteroplacental circulation.

What are the diagnostic criteria of APS?

- *Clinical diagnostic criteria*:

  1. One or more types of vascular thrombosis (arterial, venous)
  2. Pregnancy complications

     (a) Three or more spontaneous abortions developing before the tenth gestational week
     (b) Unexplained one or more fetal death after 10 weeks of gestation with a morphologically normal fetus
     (c) Preterm birth before 34 weeks accompanied by severe preeclampsia and placental insufficiency

- *Laboratory diagnostic criteria*:

  1. High levels of IgG and/or IgM anti-cardiolipin antibodies
  2. Lupus anticoagulant positivity
  3. Anti-β2-glycoprotein-1 antibodies have a titer of >99th percentile

What are the treatment options for antiphospholipid antibody syndrome (APS) and thrombophilia before and after conception?

- In all cases leading to thrombosis in placental vessels, preconception low-dose acetylsalicylic acid (ASA, aspirin) 50–150 mg/day is started.
- In addition to aspirin intake after conception, 5000 U SC Low molecular weight heparin (LMWH) is continued until delivery.
- With this treatment, 70–80% live birth is achieved.
- As for Thrombophilia:
- Loss of pregnancy in genetic thrombophilia occurs with placental thrombosis and infarct.
- The most common are activated protein C resistance (factor V Leiden (FVL) mutation) and prothrombin gene mutation. Methylene tetrahydrofolate reductase (MTHFR) mutation is third frequently seen.
- Others are antithrombin III gene mutations (antithrombin III is the most important inhibitor of coagulation proteinases), protein-C, protein-S, and factor XIII deficiencies.
- Treatment is applied with ASA (80 or 100 mg) and heparin or LMWH, as in APS.

What is the role of ASA in APS?

- ASA has antiplatelet effects. Also acts as a potent stimulator of IL-3 through its ability to raise leukotriene production, which induces the production of IL-3 both in vitro and in vivo, which stimulates normal trophoblast growth and hormone expression.

What are the anatomical reasons for recurrent pregnancy loss (RPL)?

- Congenital uterine anomalies: Mullerian canal development, fusion, canal formation, septal resorption abnormalities.
- Uterus septus (septate uterus) is the uterine anomaly with the highest abortion rate (especially at the second trimestery) and uterine anomaly with gaining most benefit from the operation (resection of the septus, hysteroscopy).
- Cervical insufficiency: Second trimester abortions.
- Fibroids: Mechanical distortion of the uterine cavity, abnormal vascularization, endometrial inflammation, abnormal endocrine environment. Subserous fibroids have no negative effects; however, submucosal fibroids are having particularly importance.
- Adhesions in the uterine cavity: As in Asherman syndrome (acquired condition that leads intrauterine adhesions, generally after harsh currettage or infections).

What are the endocrine disorders for RPL?

- Luteal phase defect (LPD) and progesterone insufficiency: defective corpus luteum, insufficient progesterone.
- Polycystic ovary syndrome (PCOS), hyperandrogenism: insulin resistance, decreased endometrial receptivity, reduced implantation rates, associated with increased abortion rates.
- Diabetes mellitus (DM): There is a direct correlation among the glycosylated hemoglobin (HbA1C) values and the incidence of pregnancy loss and congenital malformations in poorly controlled diabetic patients. But patients with

insulin-dependent diabetes mellitus (DM) with normal or near-normal glycemic control are not at higher risk for RPL. It is recommended to have a pre-pregnancy level of HbA1c ≤6.6–7.5%.
- Hypothyroidism: Thyroid hormones have an impact on the oocytes at the level of the granulosa and luteal cells that interferes with normal ovulation.

What are the coagulation immunological factors for RPL?
- Thrombophilia: antiphospholipid syndrome (APS).
- Antiphospholipid antibodies: lupus anticoagulant, anti-cardiolipin antibodies.
- Hereditary thrombophilia defects: active protein C resistance (APCR), protein C-S and antithrombin III insufficiency, hyperhomocysteinemia, thrombin gene mutation. Especially FVL gene mutation is important.
- Maternofetal alloimmune disorder: HLA mismatch.

What are the less prevalent factors for RPL?
- Infections: less role. They do more sporadic miscarriages, not recurrent. Toxo, rubella, CMV, listeria, herpes.
- Environmental: more associated with sporadic miscarriages. Smoking, alcohol, high caffeine (more than three cups per day), anesthetic gases?
- Psychological factors: depression in 33% of those with recurrent miscarriage. Stress-induced abortion in animal studies.

What is the most common cause of RPL?
- In more than half of the cases (50–60%), the cause is unknown (idiopathic).

What should be investigated in couples presenting with RPL (habitual abortion)?
- Chromosome analysis of both spouses.
- Ultrasound: PCOS, uterine anomalies.
- Early follicular phase (days 2–4): FSH, LH, and testosterone levels.
- APS: lupus anticoagulant, anticardiolipin IgG-IgM values should be at least 2 times positive at least 6 weeks apart (if one time positive and the other time negative results are obtained, the test is performed third time).
- Activated protein C resistance: factor V genotype evaluation by PCR.
- When systemic diseases are suspected, endocrinologic evaluations such as TSH and fasting blood glucose are also performed.

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Chapter 4
Antenatal Follow-Up

In which gestational week does the transition from embryo to fetus happen?
- Eighth gestational week

What is the definition (difference) of parity and abortion?
- Fetuses who are born after 20 weeks and who weigh more than 500 g are considered as parity (birth), and if they do not provide at least one of the >20 weeks and >500 g condition, they are considered as abortion.

Specify the time intervals for the first, second, and third trimesters.
- 0–14 weeks—first trimester
- 14–28 weeks—second trimester
- 28–42 weeks—third trimester

How is pregnancy diagnosed at the first trimester of pregnancy?
- It could be diagnosed with β-hCG positivity in urine (most pregnancy tests detect pregnancy when β-hCG level is >20 mIU/mL) or in blood for the patients who come with the complaint of menstrual delay, or else it could be diagnosed with β-hCG positivity (>5 mIU/mL) for the patients who come with another complaint, while trying to exclude pregnancy. Also, in case of nausea, vomiting, fatigue, abdominal pain, and breast tenderness, pregnancy might be one of the preliminary diagnosis.

What do we question in the first anamnesis of pregnancy in antenatal follow-up?
- Age
- Place of birth
- Education
- Profession

Acknowledgments The author would like to thank Dr. Su Harma who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_4

- Medical history: disease, accident, surgery, medication, allergy, smoking, alcohol
- Family history: any systemic or genetically inherited disease
- Consanguineous marriage
- Vaccination records (immunization records): tetanus, hepatitis, rubella
- Gravida, parity, abortion, living child, type of delivery, cesarean section (indication, time, place), multiple pregnancy, presentation disorder, preterm, postterm, etc.

What do we look for in the initial examination of antenatal follow-up?

- Weight and BMI (obese, cachectic)
- Height (short—150 cm)
- Blood pressure (>140/90 mmHg)
- Thyroid (diffuse-nodular goiter)
- Heart-lungs, for systemic illnesses
- Breast, any mass?
- Abdomen (previous incisions, scar): This is actually important since patients sometimes forget to tell about their previous operations
- Extremities (trauma, varicose veins)
- Pelvic examination (if necessary rectovaginal) pelvic capacity

  Promontorium (>11.5 cm)
  Ischial spine (≥9 cm)
  Subpubic angle (≥90°)
  Coccyx

What are the intervals between antenatal follow-up, according to gestational weeks?

- 4 weeks apart until 28/32 weeks
- 2 weeks apart until 36 weeks
- Weekly follow-up until 40 weeks
- Every 2 days in the last week of gestation

How is the gestational age calculation done?

- Anamnesis: Naegele's rule (add 7 days and subtract 3 months to the first day of last menstruation)
- Fetal heart beat (ultrasound, Doppler)
- Daily fetal movement assessment, fetal kicks (16–20 weeks)
- Height of fundus (at the level of umbilicus at the 20th week)
- Ultrasound (US) measurements (week calculation according to the crown–rump length (CRL) is the most consistent, the second trimester biparietal diameter (BPD) measurement can be used in patients without older measurements, but there is a margin of error up to 2 weeks)

What are the parameters used to evaluate fetal well-being?

- Electronic fetal monitoring, electrocardiogram starting from the 30th to 32nd gestational week (fetal central nervous system maturation ↑, fetal viability ↑)

– Non-stress test (NST): recording fetal heart rate and uterine contraction
– Contraction stress test (CST): recording fetal heart rate by creating uterine contractions
– Biophysical profile (BPP): NST (fetal heart rate patterns) with US (fetal tonus, fetal movement, fetal respiration, amniotic fluid)
– Modified BPP: NST and amniotic fluid index (AFI)
– Amniotic fluid volume–index (AFV–AFI): 5 cm ↓ (oligohydramnios), 24 cm ↑ (polyhydramnios)
– Fetal movements: ten fetal movements/2 h
– Doppler measurements of fetal and uteroplacental circulations: umbilical artery and vein, uterine artery, fetal cerebral arteries middle cerebral artery (MCA), fetal veins ductus venosus (DV)

Explain the parameters of BPP scoring.
– NST/electronic fetal monitoring
– Fetal respiration—30 s in 30 min
– Fetal movement—three or more gross body/extremity movements within 30 min
– Fetal muscle tone—at least one flexion and extension movement of fetal extremities
– Amniotic fluid—a single pocket >3 cm or more than one pocket >2 cm; 2 points for each parameters.

Which laboratory tests should we perform at the first evaluation of pregnancy?
• Complete blood count (CBC), biochemistry, blood type (ABO, Rh), VDRL, Toxo IgM, rubella IgM, CMV IgM (only for those working in neonatal intensive care, not routine), HBsAg, HCV, HIV, PAP smear (≥21 years old), urinalysis, in case of Rh incompatibility indirect Coombs if possible.

Which screening test do we perform in the first trimester of pregnancy?
• Double test. It is also called as Down syndrome screening test. Nuchal translucency (NT) is measured by ultrasound. β-hCG and pregnancy-associated plasma protein A (PAPPa) are measured in maternal blood. NT is expected to be less than 3 mm. If it is greater than that, chorionic villus sampling (CVS) is recommended before 15 weeks, fetal echocardiography is also recommended (18th week), since greater than 3.0–3.5 mm NT measurement in the first-trimester ultrasound is an indication to suspect a fetal heart defect.

Which screening test can we perform in the second trimester?
• Triple screen test is performed: free β-hCG, alpha fetoprotein (AFP), unconjugated estriol (uE3) (15–20 weeks).
• Quad screen test: free β-hCG, AFP, uE3, dimeric inhibin A (DIA) (15–20 weeks).
• Penta test: AFP, uE3, dimeric inhibin A, hCG, hyperglycosylated hCG (15–20 weeks).
• Abnormality scanning with ultrasound is performed (18–22 weeks).

Which screening test do we perform in the third trimester?

- Blood glucose at first hour after oral loading of 50 g glucose at 24–28 weeks
  - >140 mg/dL, gestational diabetes suspicion; >200 mg/dL = GDM
  - Diagnostic test is applied if >135–140 mg/dL is measured at 50 g oral glucose challenge test (OGCT)
- 100 g oral Glucose tolerance test (OGTT)–100 g oral glucose loading
  NDDG criteria (O'Sullivan and Mahan)
  - Fasting blood glucose: 105 mg/dL
  - At 1 h: 190 mg/dL
  - At 2 h: 165 mg/dL
  - At 3 h: 145 mg/dL

  ADA criteria (Carpenter and Coustan)
  - Fasting blood glucose: 95 mg/dL
  - At 1 h: 180 mg/dL
  - At 2 h: 155 mg/dL
  - At 3 h: 140 mg/dL

Which suggestions could be proposed for the diet of pregnant women during antenatal follow-up?

- In the first trimester, an additional 150 kcal is added to the daily calorie requirement and then 350 kcal is added.
- 1–1.5 kg/month weight gain should be expected, 10–12 kg totally.
- Iron: Gastrointestinal system (GIS) absorption 10–20%, 30 mg/day—iron supplementation, anemia → 60–120 mg/day.
- Folic acid: 0.4 mg/day.
- Calcium: 1.5 g/day.
- Protein: 85 mg/day.
- Vitamin D: 9 drops/day; 1200 IU.
- In case of balanced nutrition, routine multivitamin and mineral supplementation is unnecessary, excluding iron, according to some recent researches omega3 supplementation is also prudent to advise (An increased intake of omega 3 long chain polyunsaturated fatty acids (LCPUFA) during pregnancy can reduce the risk of premature births, according to a Cochrane review-2018).

What would be your suggestions regarding traveling during pregnancy?

- Long road trip is not recommended—15 min resting between 2 h; not to cause deep venous thrombosis (DVT).
- Seat belt should be worn.
- Airline—unrestricted until 28th week. The problem is to stay itnactive for a long time, not in-cab pressure.
- Aircraft companies are asked for a doctor's report at 28–36 weeks.
- In case of abortus imminens, preterm uterine contractions, antepartum bleeding, traveling would be risky.

What are the complaints that can be encountered frequently during pregnancy?

- Nausea, vomiting
- Heartburn, indigestion
- Constipation
- Muscle cramps
- Hemorrhoids, lower extremity varicose veins
- Edema in hands, face, abdominal skin, legs
- Back/low back pain
- Pollakiuria
- Vaginal discharge—leucorrhea

What are the important complaints during pregnancy?

- Vaginal bleeding
- Severe edema
- Water breaks
- Weight loss/gain abnormally
- Reduction/discontinuation of fetal movements
- Severe headache
- Severe Epigastric or right upper quadrant pain
- Visual defects
- Fever

Which vaccines are safe in pregnancy?

- Two vaccines are routinely recommended during pregnancy.
- Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap): Recommended regularly to those who are not vaccinated or who did not get a booster shot for 10 years.
- Influenza: It is recommended to be done after 14 weeks of pregnancy, during flu season. It can be done in any week if the medical condition requires.
- Hepatitis B: May be recommended to high-risk and nonimmunized women

Which vaccines are not suitable for pregnancy?

- Measles, mumps, rubella [Measles, Mumps, Rubella (MMR)]: pregnancy is forbidden at least 1 month after vaccination.
- Chickenpox (varicella): prohibited pregnancy for at least 1 month.
- Hepatitis A: unreliable, if necessary.
- Pneumococcus: unreliable, it can be applied in pregnant women with high-risk pregnancy/chronic disease.
- Oral/inactivated polio: can be done if necessary.
- Rabies: can be done if necessary.
- Meningococcal: can be done to those at severe risk.

What are the dental care recommendations for pregnant women?

- Gingival hypertrophy (epulis) is common—bleeding, pain
- Soft toothbrush is recommended

- Tooth filling and extraction can be done if can not be postponed to the postpartum

What are the recommendations for exercise in pregnant women?

- Daily non-strenuous brisk walking/exercise for an hour—sympathetic activity, muscular venous pump also prevents DVT
- Daily house works
- Swimming
- Yoga

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Chapter 5
Physiological Changes During Pregnancy

What are the physiological changes of the uterus during pregnancy?

- During pregnancy the weight of uterus increases up to 800–1200 g from 50–70 g.
- Hyperplasia dominates the first 6 weeks, and hypertrophy and elongation in muscle fibers are present mostly after the first trimester.
- Myometrium increases the protein synthesis due to the estradiol (E2) stimulation. (This mechanism is the main pathway of uterine hypertrophy.)
- By the end of the 12th week, uterus is too large to stay in the pelvis.
- Term uterus contains approximately 5 L volume, which could be more up to 20 L.
- A term gravid uterus has 500–1000 times more capacity than a non-gravid uterus.
- Uterine growth is asymmetrical; the myometrium in the fundal and placental area widens more than the rest.
- Uterus makes a rotation to the right, secondary to rectum-sigmoid colon.

What is the meaning of Braxton Hicks contraction?

- Uterus has painless, nonrhythmic contractions starting in the first trimester (5–25 mmHg). These contractions appear suddenly in an unexpected time (Braxton Hicks contractions). The frequency of the contractions increases in the last 3 months but does not change the cervical examination and is not a premature birth threat.

What are the physiological uteroplacental blood flow changes during pregnancy?

- Placental perfusion is related to the blood coming from uterine and ovarian vessels.
- Uteroplacental blood flow increases progressively during pregnancy, and by the end of the pregnancy, it reaches up to 450–650 mL/min (10 times greater than before pregnancy values)

Acknowledgments The author would like to thank Dr. Su Harma who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_5

- Eighty-five percent of the uterine blood flow heads for the placenta.
- The speed of the blood flow depends on the arterial and venous pressure difference, and autoregulation does not affect the placental blood flow. The decrease in arterial pressure does not change the placental vascular resistance.

Which factors are responsible for vascular pressure decrease in uteroplacental flow?

- The changes in estradiol, progesterone, catecholamine metabolism, and vasodilator prostaglandins are responsible for vascular pressure decrease.

Where is the primarily responsible region of the placental resistance?

- The primarily responsible region of the placental resistance is the distal uterine arteriolar bed.

What are the physiological changes of the cervix during pregnancy?

- In contrast to the uterus, the cervix has a very little amount of muscle. It is composed of 85% of connective tissue.
- Throughout pregnancy, it softens and gets a purple color. There are changes within the connective tissue; collagen concentration decreases, and proteoglycan concentrations change.
- After the conception, a thick mucus plug closes off the cervix.
- Ectropion (proliferation of the cervical mucus glands—increase in the number of glands in the external os region).
- Immediately after the labor starts, this mucus plug comes out in the form of bloody show.

What are the physiological changes of the ovaries during pregnancy?

- Corpus luteum (CL) is the main factor responsible for progesterone production during the first 6–8 weeks of pregnancy. After 8–10 weeks, it has a relatively decreased effect, placenta takes over this function from CL.
- Ovulation does not take place during pregnancy.
- Muscles of the fallopian tube get slightly hypertrophied, and mucosal epithelium partially becomes more flat.

What are the physiological changes for the vagina and the perineum during pregnancy?

- The muscles and skin of the perineum and vulva face an increase in vascularity and hyperemia.
- The characteristic violet color of vagina *(Chadwick sign)* during pregnancy is due to the hyperemia.
- Mucosal thickening. Papillae widen, and rugae become more significant.
- Muscular hypertrophy. Softening of the connective tissue. Thus, the vagina can widen during the labor easily.
- The glycogen content of the mucosal cells increases, and an acidic physiologic white secretion forms.

What are the physiological changes of the skin during pregnancy?

- Increased skin pigmentation: The effect of melanocyte-stimulating hormone (MSH) increases estradiol and progesterone on melanocytes, and excess production of melanin occurs.
- Stria; red, slightly depressed lines, usually occurs on the abdomen, sometimes may occur on the breasts and thigh, as well. There is no correlation between the skin's tension and severity of the lesions.
- Linea nigra; the midline of the abdominal skin becomes significantly pigmented and takes a brown-black color.
- Chloasma or melasma gravidarum (pregnancy mask); brown spots on the face and neck, using sunscreen before going out is useful.
- New nevus can appear, and the already existing ones can expand their size.
- Diastasis recti; rectus abdominis muscles in abdomen separate during pregnancy.
- Sweating and sebaceous gland secretions increase during pregnancy.
- Hair; on the last term of pregnancy, the hair follicles on the telogen phase lessen, and after birth the ratio significantly increases and hair loss happens, it is physiologic.
- The increasing levels of estradiol cause vascular dilation and proliferation, and spider angioma is seen mostly on face-chest and arms.

Describe the physiology of metabolic changes, average weight gain during pregnancy.

- The average weight gain during pregnancy is 12.5 kg.
- The majority of the weight belongs to the fetus, maternal fat stores, uterus and its contents, breasts, increased blood volume, extravascular, and extracellular fluid.
- The increase in progesterone escalates the lipid accumulation.
- Leptin is effective on the gestational weight gain.

Describe the water and electrolyte metabolism during pregnancy.

- On the term phase of pregnancy, the fetus, placenta, and amniotic fluid are about 3.5 kg.
- Pitting edema on the ankles and legs occurs in most of the women, especially at the end of the day.
- Interstitial hydrostatic osmotic pressure is decreased, and plasma colloid osmotic pressure is also decreased. The main reason for the physiological edema is the increase of vascular permeability and mucopolysaccharide content of the interstitial matter, rather than the decrease of the plasma oncotic pressure.
- Serum aldosterone levels are increased. With atrial natriuretic peptide (ANP) increase, the plasma volume decreases, which enables the fluid passage to the interstitial compartment.
- Na retention is seen from the first week of the pregnancy. (Renal tubular reabsorption of Na increases due to the activation of renin-angiotensin system.)

Describe the carbohydrate metabolism in pregnancy.

- Normal pregnancy is characterized with moderate interprandial hypoglycemia.
- After the meal, there are both prolonged hyperglycemia and hyperinsulinemia with increased glucagon suppression.
- The aim of such mechanism is to provide nutrition to the fetus with postprandial prolonged glucose transportation.
- First source of the pregnant women is glycogen, then lipids.

Describe acid–base balance during the pregnancy.

- There are minor increases in ventilation during pregnancy, and this leads to a mild respiratory alkalosis by decreasing PCO_2 of blood.
- A slight decrease in plasma bicarbonate from 26 to 22 mmol/L partially compensates this.
- As a result, there is a minimal increase in blood pH, the oxygen dissociation curve shifts to the left, and the affinity of maternal hemoglobin to oxygen increases.
- The transition from maternal blood to the fetus has decreased, but the transition from the fetus to the mother increases.

Explain hematological changes in pregnancy.

- Blood volume: In normal pregnancies, blood volume about term or at term is approximately 50% higher than pre-pregnancy blood volumes.
- Hemoglobin and hematocrit levels decrease slightly during pregnancy, although erythropoiesis increases.
- Leukocyte count is highly variable in normal pregnancy, usually varies between 5000 and 12,000/μL

Describe the changes in clotting factors during pregnancy.

- Fibrinogen concentration increases by 50% during normal pregnancy.
- The risk of thromboembolism during pregnancy is increased by 3–5.5, and important to note that in the purperium this risk is increased by three- to four in comparision to pregnancy period.
- Fibrinogen increases so sedimentation increases, as well.
- Factor VII, VIII, IX, and X activities increased significantly, factor II slightly increased.
- Factor XII and XIII decreased.
- The level of ATIII has not changed.
- Plasminogen increases, plasmin activity decreases.

Describe the cardiovascular system-heart-related changes in pregnancy.

- The most important changes in pregnancy are seen in cardiovascular system (CVS).
- The most important changes in cardiac functions occur during the first 8 weeks of pregnancy.
- Physiological dilatation occurs in the heart. Cardiac compliance and myocardial contractility increase.

- Ejection fraction (EF) does not decrease! With the increase in blood volume, the diameter of the right atrium increases progressively, at the 30th week, it becomes maximum.
- Pregnant women may have some degree of benign pericardial effusion.
- Heart rate at rest increases by approximately 10 pulses/min.
- A loud, widely split first heart sound due to early closure of the mitral valve and both components are exacerbated.
- The third sound (S3) is strong and easy to hear. S4 is always pathological to hear.
- At the same time, a systolic murmur that is lost immediately after birth is heard in 90% of women.
- Left axis deviation in electrocardiography (ECG).
- Arterial blood pressure and vascular resistance are reduced.
- In early pregnancy, the cardiac output is significantly increased during rest, continues to increase, and remains high during the rest of pregnancy.
- In late pregnancy, typically cardiac output is higher when the woman is lying on her side compared to lying on her back.
- In supine position, the enlarged uterus continuously presses the blood from the lower extremity into the venous system, which reduces cardiac filling and reduces the cardiac output.

Describe the changes in the respiratory system during pregnancy.

- Tidal volume, inspiratory capacity, oxygen intake per minute are increased as pregnancy progresses.
- Tidal volume increases by 45% during pregnancy, with approximately half of the change occurring during the first trimester.
- Minute ventilation increases by 45% during pregnancy, with increasing evident early in the first trimester, as a result of increase in tidal volume.
- Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), peak expiratory flow not changing or modestly increasing with unaltered FEV_1/FVC index.
- Lung compliance, respiration rate, vital capacity, inspiratory reserve volume: unchanged.
- Functional residual capacity (FRC), expiratory reserve volume (ERV), residual volume, total lung capacity: decreases.
- FRC is reduced to 80% of the non-pregnant volume by term gestation.
- A 25% reduction of ERV and a 15% reduction of residual volume account for the change. Inspiratory capacity increases by 15% during the third trimester because of increases of tidal volume and inspiratory reserve volume.

Describe blood gas changes related to acid–base balance during pregnancy.

- PO_2, arterial pH, base deficit: increases
- PCO_2, bicarbonate: decreases

Describe the changes in the urinary system during pregnancy.

- Renal dimension increases 1 cm.

- Dilatation of the pelvis, calyx, and ureters (especially in the right kidney with grade 1 hydro-nephrosis is usual, no intervention needed upto grade 3, followed-up weekly by renal ultrasound).
- Glomerular filtration rate (GFR) and renal plasma flow (RPF) increase by 50%.
- Renal bicarbonate threshold decreases.
- Serum osmolality decreases.
- Physiological glycosuria is observed within 50% of pregnant women.

Describe the breast-related changes in pregnancy.

- Tenderness, weight gain, growth of the breasts.
- Estradiol → ductal growth.
- Progesterone → alveolar growth.
- Breasts might start leaking a little colostrum starting from the second trimester, it is natural, no intervention is needed.
- Pimple-like pores on the surface the areola: Montgomery tubercles (sebaceous glands).

Describe the changes in the gastrointestinal tract during pregnancy.

- Gastric emptying and intestinal transit times are prolonged in pregnancy due to hormonal and mechanical factors.
- Pyrosis is common in pregnancy and occurs with the reflux of acidic secretions into the lower esophagus.
- Hemorrhoids are quite common.
- Oral saliva becomes acidic ≫ dental caries.
- Ptyalism; especially in hyperemesis gravidarum (HG).
- Gingival enlargement.
- Gastroesophageal reflux (GER) is frequently observed. The lower esophageal sphincter (LES) relaxes, due to a progressive rise in circulating estrogen (E2) and progesterone (P), the intraabdominal pressure increases, the distal esophagus motility decreases.
- Gastric acidity is increased due to placental pepsin, tonus, and motility decreased. Time for stomach emptying increased. Depends on progesterone.
- Anesthesia, caution to aspiration.
- Small bowel motility decreases. Ca and Fe absorption is increased.
- Increased absorption of water and sodium in the proximal colon, causing constipation.
- Decrease in motility depends on the increase of progesterone (P) and endogenous opioids.

Explain the changes in liver function tests during pregnancy.

- ALP increases significantly due to placental synthesis.
- ALT, AST, LDH, bilirubin: unchanged.
- Albumin decreases, globulin increases slightly, transferrin increases.
- Spider angioma, palmar erythema.
- Fibrinogen increases by 50%.

Explain the changes in the gallbladder during pregnancy.
- Cholesterol stones are common.
- Size increases, emptying time is extended.
- The bile salts may accumulate due to intrahepatic cholestasis in the skin and cause generalized itching.

Explain hormonal changes related to carbohydrate metabolism during pregnancy.
- Human placental lactogen (HPL): lipolysis and free fatty acids in circulation increase.
- Very high levels of E2 and P (antagonize the peripheral effects of insulin).
- The physiologic factors responsible for the decrease of insulin sensitivity; HPL, progesterone, prolactin, and cortisol.
- Increase of the BMI (increased need for insulin).
- Increase in free cortisol.
- After an initial decrease in the first 8 weeks of pregnancy, there is a steady increase in triacylglycerols, fatty acids, cholesterol, lipoproteins, and phospholipids. The higher concentrations of estrogen and insulin resistance are thought to be responsible for the hypertriglyceridemia of pregnancy.

Explain the changes in immunoglobulins during pregnancy.
- IgM and IgD increase, and IgG decreases.

Describe the changes in lipid metabolism during pregnancy.
- Triglyceride levels increase continuously, 2–3 times increase in term. However, returns to normal at the postpartum sixth week.
- Total cholesterol increased by 50% in term.
- Apolipoprotein B is an important structural protein of LDL and VLDL and increases during pregnancy.
- Lipoprotein A decreases in pregnant women.
- The HDL_2 remains doubled in the mid-trimester, then decreases and stabilizes with by 15% increase.
- Apolipoprotein A-1 is the leading lipoprotein of HDL, elevated in the third trimester.
- Primary aim of lipid and lipoprotein changes in pregnant women; provide the energy store to the mother with increased triglycerides and maintain the presence of glucose for the fetus.
- Increased LDL, required for steroid synthesis in the placenta.

Describe the pituitary gland changes during pregnancy.
- It grows 135% compared to non-pregnant women (the most growing endocrine gland in volume during pregnancy).
- However, the incidence of pituitary prolactinomas does not increase in pregnancy.
- Prolactin in the term is increased by 10 times compared to the period before pregnancy, prolactin is not tested in the blood in pregnant women, and it is monitored by visual examination.

Describe the changes of the thyroid gland.

- Pregnant women are euthyroid.
- Slight growth of thyroid gland is common.
- Circulating thyroxine binding protein is increased (depending on E2).
- TT4 (Total Tyroxine): rises.
- TT3 (Total Triiodothyronine): rises.
- Free T4-FT3: Increases slightly in the first trimester and approaches the lower limit of normal in the third trimester.
- There is an inverse relationship between Thyroid-stimulating hormone (TSH) and hCG, and TSH decreases in the first trimester as hCG increases (does not exceed normal limits).
- Thyroid-releasing hormone (TRH) does not increase, and it can pass through the placenta and stimulate the fetal pituitary.
- Basal metabolism in pregnancy increased by 25%.

Explain the changes in parathyroid glands in pregnancy.

- Parathyroid hormone (PTH) plasma concentrations decrease during the first trimester.
- Progressively increases in the rest of pregnancy.
- Increased levels are likely due to reduced calcium levels in normal pregnant women.
- The total calcium level decreases in pregnant women, but the ionized calcium level is only minimally reduced.
- The effect of PTH on bone resorption is blocked by E2.
- Pregnant women have physiological hyperparathyroidism
- Calcitonin increased.
- 1,25-Dihydroxyvitamin D levels are elevated.

Explain the changes in adrenal glands during pregnancy.

- The level of cortisol bound to transcortin is increased.
- The increase in total cortisol results from the slowing of metabolism rather than the increase in synthesis.
- ACTH increases (placental source).
- Renin activity increases.
- Increased E2 and Progesterone causes hyperplasia in beta cells in the pancreas, and insulin secretion increases.
- With increased insulin; peripheral use of glucose increases, and maternal hypoglycemia occurs.
- Lipid storage increases.
- With hPL released from syncytiotrophoblasts, insulin resistance develops in the periphery, lipolysis is accelerated, gluconeogenesis decreases, glycogenolysis increases, and peripheral glucose levels increase. (The mother uses fats as fuel and directs glucose and amino acids to the fetus.)
- The level of secretion of glucagon mildly increases in pregnancy.

What are the changes in the musculoskeletal system during pregnancy?

- Progressive lordosis is characteristic of normal pregnancy, causing low back pain (fluid accumulation in the connective tissue also increases pain) (low back pain due to disc herniation is rare in pregnant women) (acetaminophen could be administered).
- There is increased mobility in sacroiliac, sacrococcygeal, and pubic joints due to hormonal changes during pregnancy, related to relaxin.
- Relaxin: produced by CL, decidua, placenta.
- Relaxin: relaxation of the myometrium, separation of the symphysis pubis (separation), and softening of the cervix.
- Joint pain is more associated with E2 and Progesterone.

Describe the changes in the pelvic organs during pregnancy.

- Chadwick sign: vulva, cervix, and vagina appear dark red or purple
- Goodell sign: softening of the cervix after sixth week
- Hegar sign: softening of isthmus uteri
- Ladin sign: uterus softening in the middle anterior where uterus and cervix meet
- McDonald sign: uterus easily flexed at the point where it meets with the cervix
- Sign of Braun von Fernwald: softening of uterus at the implantation site by palpation at 4–5 weeks of gestation
- Piskacek symptom: asymmetric growth of uterus at the implantation site after 6 weeks of gestation

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Chapter 6
Perinatal Care

What is the goal of perinatal care?
- The care of women and fetus or newborn given; before, during, and after delivery; from the 28th week of gestation through the seventh day after delivery
- Fetal health
- Recognizing diseases and intrauterine treatment
- First trimester fetal life, detecting major anomalies
- Second trimester congenital anomalies, syndromes, toxic effects
- Third trimester fetal well-being

Which methods are being used for perinatal care?
- Non-stress test (NST)
- Contraction stress test (CST)
- Fetal biophysics profile (BPP)
- Amniotic fluid index (AFI)
- Doppler ultrasound
- Counting of fetal movements (kick counting)

Why is perinatal care important?
- Fetal death is seen in 1% of all third trimester low-risk pregnancies without routine perinatal care.
- Two thirds of deaths are intrauterine, and this rate increases especially in high-risk patients.

Which pregnancies are considered as high-risk pregnancies in the aspect of uteroplacental insufficiency?
- Prolonged pregnancy
- Diabetes mellitus (DM)
- Hypertension (HT)

Acknowledgments The author would like to thank Dr. Büşra Aynalı who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_6

- Isoimmunization
- Stillbirth in previous pregnancies
- Intrauterine growth restriction (IUGR)
- Advanced mother age
- Discordant multiple pregnancy, as in twin-to-twin transfusion syndrome (TTTS)
- Antiphospholipid syndrome (APS)

Describe the role of non-stress test (NST) in perinatal care

- A good test interpreted as reactive. There should be:
  - At least two fetal movements
  - At the same time two accelerations lasting 15 s and not less than 15 beats/min in 20 min of monitoring for reactivity
- Fetal heart rate: 120–160/min
- In some fetuses, 110–120/min fetal heart beats can also be considered as normal
- May be physiologically non-reactive NST before 30th gestational week

What is the role of the stress test (CST) in evaluating fetal well-being?

- It is the most precious test for the evaluation of fetal well-being.
- Blood flow to intervillous area decreases during uterine contractions.
- Blood supply decreases up to 30%.
- If there is no placental insufficiency, the baby responds to it as acceleration.
- Responds as deceleration if there is insufficiency.

How would you apply contraction stress test (CST)?

- Test is done by creating contractions, three contractions within 10 min.
- Oxytocin is given to form contraction, or nipple stimulation.
- Should be laid semi-Fowler and 30–45° lateral position to avoid supine hypotension.
- The CST is used for its high negative predictive value.

What is the meaning of positive CST?

- Late decelerations present with more than half of the uterine contractions. Generally it shows placental respiratory insufficiency is present.

What is the meaning of negative CST?

- No late deceleration presents with adequate uterine contractions present. Generally marker of fetal well-being.

What are the contraindications of contraction stress test (CST)?

- It should not be done to patients who are at risk of premature birth.
- Premature rupture of membranes (PROM).
- Multiple pregnancy.
- Pregnant with vaginal bleeding.
- Cervical cerclage.
- Preterm labor.

- Placenta previa or ablation placenta.
- Patients who previously had C/S with vertical (classical uterine) incision.
- Previous history of myomectomy.

What are the evaluation criteria of CST?

Comment	Criteria	Incidence (%)
Negative	3 contractions/10 min No deceleration	80
Positive	Deceleration with 50% contraction	3–5
Suspicious	Temporary deceleration	5
Hyperstimulation	More than 5 times deceleration with contraction in 10 min	5
Insufficient	Fewer than three contractions occur within 10 minutes, or quality of tracing is inadequate for accurate interpretation. Repeat test on the following day.	5

What are the parameters of fetal biophysical profile (BPP) evaluation?

Parameter	Normal (2 points)	Abnormal (0 point)
NST	Reactive	Non-reactive
Fetal respiration	Lasting for 30 s at 30 m	No movement or less than 30 s
Movement	At least three fetal movement	Reduced movements
Tonus	Extension, flexion Opening and closing of hands	Continuous extension and open fingers
Amnion fluid	At least 2 cm of pocket in two planes	Less fluid

- If the score is 10, probability of fetal death in 2 weeks is 0%.
- If the score is 0, probability of fetal death is around 60%.

What are the parameters in the modified fetal biophysical profile (BPP)?

- NST and Amniotic fluid index (AFI) measurements: also indicators for fetal well-being.

What are the features of the amniotic fluid volume?

- 200 mL at 16th week.
- 1000 mL at the beginning of the third trimester.
- Weekly decreases by 150 mL after 38 weeks.
- Renewed about 95% per day.
- It is directly related to uteroplacental blood flow.
- If uteroplacental blood flow decreases, fetal renal blood flow and fetal renal glomerular filtration rate (GFR) also decreases so oligohydramnios occurs.
- It is the sum of the deepest pockets on the four uterine quadrants.
- Perinatal mortality and morbidity increased in patients with Amniotic fluid index (AFI) below 5 cm.

How would you advise your patient to count fetal movements?
- Fetal movements/kicks indicate fetal well-being.
- Fetal movements may decrease due to the decrease of amnion fluid in the third trimester.
- Fetal movements should be at least 10 per day.

Which vessels are measured by Doppler velocimetry?
- Uterine artery
- Umbilical artery
- Fetal middle cerebral artery (MCA)
- Umbilical vein
- Ductus venosus (DV)

What are the characteristics of Doppler measurement?
- Ultrasound sound waves hit the blood, and moving elements like erythrocytes turn back those waves.
- Frequencies of the outgoing sound waves and returning sound waves are different.
- This is called the Doppler effect, and the frequency change is called the Doppler frequency.
- Blood flow in the ultrasound is measured by measuring the movement of blood flow.
- A sound wave is sent from the transducer to capture blood flow.
- The echoes obtained from the fixed tissues through which the sound wave passes are always the same.
- Echoes obtained from moving tissues such as blood vary according to the return of the signal to the recipient.

Which Doppler indexes are used during pregnancy?
- Systole/diastole (A/B).
- Pulsatility index (S-D/mean).
- It is difficult to calculate, but it is the most reliable measurement in very small vessels or vessels without diastole flow. It can be easily calculated.
- Resistance index (S-D/S).

Relationship between fetal circulation and Doppler ultrasound?
- Diastole flow of umbilical artery increases near term.
- High S/D ratio is a very important parameter in IUGR.
- Excessively affected fetuses do not have diastolic flow or have reverse flow.

Explain the importance of Doppler measurement for ductus arteriosus.
- Doppler measurement of Ductus arteriosus should be considered as primary in the use of indomethacin and other nonsteroidal anti-inflammatory drugs, due to the side effect of the prostaglandin inhibitors (PGI) that is early closure of ductus arteriosus. Indomethacin is used for tocolysis and in the treatment of polyhydramnios.
- Indomethacin causes constriction at ductus arteriosus, to increase in pulmonary flow and reactive pulmonary arteriolar hypertrophy; pulmonary hypertension.
- If the medication is discontinued before 32nd week, this condition is resolved.

In which case is Doppler measurement of the mid cerebral artery (MCA) used?

- Peak systolic velocity (PSV) increases (>1.5 MoM) in case of fetal anemia—due to increased cardiac output and decreased blood viscosity.
- MCA/placental blood flow rate may be used depending on the brain protective effect in the presence of fetal hypoxemia.

In which situations uterine artery Doppler measurement is used?

- In normal pregnancy, uterine blood flow increases from 50 mL/min to 500–700 mL/min.
- Uterine blood flow is characterized by high diastolic blood flow.
- Increased resistance and presence of diastolic notch indicate hypertension.
- Pregnancies that will develop HT or preeclampsia may be predicted in Doppler measurements performed at 16–20th gestational ages.

What is the most valuable test for evaluating fetal well-being?

- CST

What is the mechanism of late deceleration in NST or CST?

- In fetuses with reduced oxygen reserve, periodic decreases in oxygen during contractions reach the critical level, which trigger the carotid chemoreceptors. As a reflex, an alpha sympathetic response that constricts the low-resistance arterial bed is initiated. This results in a systemic arterial hypertension that causes the baroreceptors to produce a vagal response that slows down the fetal heart rate and is seen as a late deceleration.

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Chapter 7
Perinatal Infections

What does TORCH stand for?

- The term "TORCH" is used to designate microorganisms that are associated with known congenital disease and stands for:
- **T:** Toxoplasmosis gondii
- **O (Other):** *Listeria monocytogenes*, *Treponema pallidum*, varicella zoster virus (VZV), human immunodeficiency virus (HIV), enteroviruses, and parvovirus B19
- **R:** Rubella
- **C:** Cytomegalovirus (CMV)
- **H:** Herpes simplex virus-1 (HSV-1) and HSV-2

What are the common fetal symptoms and clinical characteristics of perinatal infections?

- Abortus or preterm labor
- Low birth weight
- Hepatomegaly
- Splenomegaly
- Jaundice
- Petechiae and purpura
- Microphthalmia
- Microcephaly
- Hydrocephaly
- Cataract
- Retinopathy
- Cerebral calcification
- Glaucoma

Acknowledgments The author would like to thank Dr. Adile Yeşim Akdemir and Dr. Büşra Aynalı who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_7

- Congenital heart diseases
- Osteochondritis
- Mucocutaneous lesions

What are the main features of toxoplasmosis?
- Microbiological agent: *Toxoplasma gondii.*
- 1/8000 pregnant women in the United States.
- Intracranial calcification, chorioretinitis, hydrocephaly are detected in 60% of all cases.
- The risk of maternal infection is higher during the third trimester.
- Toxoplasmosis is the intrauterine infection where the hydrocephaly is mostly seen.
- May be asymptomatic in the newborn.
- May cause chorioretinitis and learning disabilities in the following ages.
- Transmission with eating vegetables, fruits, raw meat, etc. which are contaminated with oocysts, especially shed from cats' feces.

What are the main symptoms of acute toxoplasmosis during pregnancy?
- Ninety percent: asymptomatic
- Ten percent: infectious mononucleosis (IM, mono) like clinic
- Lymphadenopathy (commonly cervical)
- Fever
- Weakness, malaise
- Headache
- Myalgia

Which perinatal complications of toxoplasmosis could be observed during the first trimester of pregnancy?
- Abortus
- Stillbirth
- Intrauterine growth restriction (IUGR)
- Fetal organ anomalies

Which perinatal complications could be observed during the third trimester of pregnancy because of toxoplasmosis infection?
- Usually no clinical signs
- Clinical symptoms may occur in later months or years
- Organ anomalies which are specific to toxoplasmosis
  - Visual disorders related to chorioretinis
  - Hearing loss, deafness
  - Growth restriction

Which findings could be detected in pregnant women with toxoplasmosis by ultrasonography? And cordocentesis in the diagnosis of toxoplasmosis?
- Ultrasonography:
  - Placental thickening (often considered as >4cm)
  - Hydrocephaly or microcephaly
  - Hepatic or intracranial calcification

What are the findings of toxoplasmosis infection proven by cordocentesis?

- Cordocentesis:
  - IgA, IgM, IgE: specific to toxoplasmosis
  - Isolation of *Toxoplasmosis gondii*

What is the treatment for toxoplasmosis during pregnancy?

- Acute infection in pregnant women.
  - Spiramycin, 3 g/day, until the term
- Fetal infection.
  - Sulfadiazine + pyrimethamine, folinic acid
- There is no effect of the treatment, on the fetal transmission and chorioretinitis.
- The rates of the neurological disorders and fetal exitus are decreased by the intrauterine treatment of the congenital toxoplasmosis.

What are the main features of rubella infection and its effects in pregnancy?

- In the group of Togavirus, single-chain RNA.
- Transmitted by respiratory tract.
- Incubation, 2–3 weeks.
- If the pregnant woman is infected in the first 8 weeks of pregnancy, the fetal infection risk is 50%.
- Congenital malformations like microcephaly, microphthalmia, and chorioretinitis are common during this period.
- If rubella is transmitted at the end of the third trimester, pneumonia and encephalitis may occur in the newborn.
- May cause the sensorineural hearing loss.
- Thrombocytopenia is common.
- Congenital heart defects (CHD) are common: Patent ductus arteriosus (PDA) is the most common, atrial septal defect (ASD) is the second.
- Cataract is seen in 30% of all cases.
- IgG concentrations are four times higher.
- Positive IgM.
- Positive rubella culture.
- It can be isolated from the pharynx until 2 weeks and after 1 week before the appearance of skin lesions.

What would you suggest for the prevention of rubella infection?

- All women in reproductive ages who have negative IgG serology must be vaccinated, before planning pregnancy.
- Pregnancy is not recommended in the first month after vaccination.
- Immunoglobulin should be administered to pregnant women who come in contact with rubella.

What are the main features of cytomegalovirus (CMV) infection during pregnancy?

- The most common perinatal infectious agent.
- Ninety percent of all cases are asymptomatic.

- The most common infectious virus which causes neonatal jaundice.
- Microcephaly and hydrocephaly are commonly seen in CMV infections.
- Blindness may occur because of the chorioretinitis.

What are the clinical characteristics of CMV infection?
- Microcephaly
- Growth restriction
- Ventriculomegaly
- Chorioretinitis
- Thrombocytopenia
- Petechiae
- Hepatitis
- Splenomegaly

What would you suggest for the prevention of CMV infection?
- There is no benefits of the antivirals during pregnancy.
- The antiviral treatment decreases the morbidity and mortality rates in symptomatic newborn.
- Prevention:
  - Hygiene, especially hand.
  - Not to use the same items like forks-spoons etc.

What is the treatment for herpes simplex virus (HSV) infection during pregnancy?
- The pregnant women who have active recurrent genital HSV infection must be given antiviral therapy between the 36th week of the pregnancy and birth.
  - Acyclovir 400 mg or Valacyclovir 500 mg
- Caesarean is recommended in cases which have active genital infection at term and with vulvar pain.
- Active genital infection + Premature rupture of membranes (<6 h)→ Caesarean; >6 h, the benefit of a cesarean section has not been determined.

What are the characteristics of varicella zoster virus (VZV) (smallpox) infection?
- VZV is the member of Herpesviridae.
- Transmitted by respiratory tract.
- Ninety percent of women in the reproductive period are immunized.
- Incubation period is 15 days.
- VZV may get latent in the posterior ganglions of the spinal cord after the infection.
- Highly infectious.
- Re-infection: herpes zoster.

What are the main features of congenital varicella syndrome?
- Cutaneous scars in a dermatomal pattern.
- Hypoplasia of the extremities.

- Ocular abnormalities; cataract, chorioretinitis, microphthalmia.
- Low birth weight.
- Cortical atrophy.
- Mental retardation.
- Incidence: 1.3–2%.
- Most cases are related with the maternal varicella infections between the 8th and 20th weeks of gestation.

What are the main features of neonatal varicella syndrome?
- Varicella infection during the last 2 weeks before birth causes neonatal syndrome.
- Vesicular skin lesions and fever in the newborn.
- With the disseminated disease or organ involvement, the mortality risk is 25%.

If a pregnant woman is complaining of skin lesions and is admitted to the outpatient clinic immediately and varicella zoster is considered, what should we do in the management of this patient?
- If VZV IgG negative, VZIG is recommended in the first 96 h.
- VZIG reduces the severity of the disease, but there is no evidence that prevents congenital varicella syndrome.

What is the evidence of intrauterine VZV infection in cordocentesis?
- Presence of VZV-specific IgM antibodies in cord blood

What is the most common clinical manifestation of complicated varicella infection in pregnancy?
- Varicella pneumonia

What are the main symptoms of Zika virus infections?
- Mild symptoms; rash, fever, headaches, arthralgia, and conjunctivitis

What are the congenital anomalies associated with the maternal Zika virus infection?
- Zika virus associated with microcephaly, growth arrest of the cerebrum, partial collapse of the skull, and distinct folds from redundant scalp skin. In pregnant women, this virus is also associated with other fetal disorders such as placental insufficiency, fetal growth restriction, ocular disorders, other central nervous system anomalies, and stillbirth.

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Chapter 8
Prenatal Invasive Procedures

What does prenatal diagnosis mean?

- Prenatal diagnosis is the detection of hereditary diseases, congenital anomalies, and some infections in the early stages of pregnancy after ninth week of gestation.

Which families are recommended to apply prenatal invasive procedures?

- Mothers aged 35 and over.
- If the family has a child with chromosomal anomaly and/or congenital anomaly.
- Family risk for metabolic diseases.
- Stillbirth and/or recurrent miscarriage with unknown cause.
- If one parent has chromosomal translocation.
- If the family has blood diseases such as hemophilia, sickle cell anemia, thalassemia.
- If the mother has anxiety, prenatal diagnosis is performed.
- The probability of fetus with anomaly in pregnant women at risk for genetic diseases varies between 1 and 50%. In these families, the risk is 10–15 times higher than non-risky families.
- All genetic diseases and congenital anomalies cannot be detected by prenatal diagnosis, and no guarantee can be given for a completely healthy child.

What is the meaning of aneuploidy?

- Aneuploidy is defined as having one or more extra or missing chromosomes, leading to an unbalanced chromosome number in a cell.

Acknowledgments The author would like to thank Dr. Büşra Aynalı who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_8

What are the prenatal diagnostic methods?

1. *Noninvasive methods, in maternal blood*
   (a) Double test (11–14 week) {Free Beta human chorionic gonadotrophin (βhCG), Pregnancy associated plasma protein A (PAPP-A), nuchal translucency (NT) measurement}
   (b) Triple test (15–20 or 22 week) {alpha fetoprotein (msAFP), estriol (uE3), and free or total hCG}
   (c) Quadruple test (15–18 or 22 week) {msAFP, uE3, dimeric inhibin A (DIA), and hCG}
   (d) Penta test (15–20 weeks) {msAFP, uE3, DIA, hCG, and hyperglycosylated hCG (HhCG)}
   (e) Extracellular DNA (noninvasive prenatal test-NIPT, cell free DNA)
2. *Invasive methods*
   (a) Amniocentesis
   (b) Chorionic villus biopsy (CVS)
   (c) Cordocentesis
   (d) Fetal biopsy (muscle-skin-liver-kidney)

What is the meaning of preimplantation genetic diagnosis (PGD)?

- PGD is a method for selecting embryos that do not have chromosomal abnormalities and certain genetic diseases for their transfer to the uterus and combine them with in vitro fertilization (IVF).
- PGD can be performed during the cycle of embryo development (IVF) by combining eggs and sperm in the laboratory.

Especially on which situations PGD can be suggested to the families?

- Studies have shown that 50% of spontaneous abortions are caused by a chromosomal abnormality.
- Chromosomal abnormalities may occur by chance in the fetus and may be due to balanced chromosomal abnormalities (translocation, inversion) that have no effect on the mother or father.
- Chromosome analysis and prenatal diagnosis are recommended to these families in their pregnancy.

What are the indications for cell-free DNA (Non invasive prenatal test-NIPT) screening?

- Maternal age greater than 35 years at delivery
- Ultrasonographic findings indicating increased aneuploidy risk
- History of prior pregnancy affected by a trisomy
- Parental balanced robertsonian translocation increasing risk of trisomy 13 or 21
- High-risk first trimester or second trimester aneuploidy screening results

What are the features of alpha fetoprotein (AFP)? In which prenatal tests can we use it?

- AFP: A glycoprotein-oncofetal protein produced in the liver of the fetus that can be detected in the mother's blood from the 12th week of pregnancy. First trimester measurement is not recommended due to low sensitivity. Ideally it is suitable to be measured during 16th–18th gestational weeks. There is no clinical role in measuring AFP in fetal plasma. Fetal AFP is filtered through the kidney and passes to amniotic fluid.
- Neural tube defects (NTDs) such as spina bifida, especially in the nervous system anomalies, AFP levels increase above normal. Since AFP in the fetal serum is easy to pass from the vessels to amniotic fluid through the neural defect, AFP levels increase in the amniotic fluid and then passes to the mother by diffusion through the amniotic membrane. Since this transition is less than transplacental transition, the expected increase in msAFP may not always occur.
- Therefore, measurement of msAFP is a screening test, not a diagnostic test.
- msAFP value $\geq$2.0 or 2.5 multiples of the median (MoM) measurement is interpreted as high. If the measurement is repeated and similar results are obtained, ultrasonography and if necessary AFP and acetyl cholinesterase activity in amniotic fluid is measured by amniocentesis.

What are the conditions that may affect the levels of msAFP?

- Misdating
- NTD
- Fetomaternal bleeding
- Abdominal defects
- Nephrosis
- Intrauterine fetal loss
- Amniotic band sequence
- Cantrell pentalogy
- Dermatological diseases (fetal)
- Chorioangioma
- Cystic hygroma
- Hydrops fetalis
- Sacrococcygeal teratoma
- Triploidy
- Maternal: DM, obesity, hepatoma, teratoma, liver diseases

What are the features of the triple test (TT)?

- Triple test: In maternal blood, msAFP, unconjugated estriol, and hCG are evaluated, and the risk is calculated by adding the age factor. If the value is above 1:250, there is a risk. It is a screening test for Down syndrome. The definitive diagnosis is made by fetal chromosome analysis.

- Triple test of pregnancy performed between 15th and 20th gestational weeks.
- In Down syndrome, msAFP decreased, uE3 decreased and hCG increased

What is the meaning of spina bifida?

- Spina bifida is a congenital malformation in which the spinal column is split (bifid) as a result of failed closure of the embryonic neural tube, during the fourth week post-fertilization.

What is the commonest and most severe form of spina bifida?

- Myelomeningocele (MMC) is the most severe form of spina bifida characterized by protrusion of the spinal cord and the meninges through a defect in the vertebral column and a spectrum of clinical manifestations including hindbrain herniation, hydrocephalus, sensory and motor neurological deficits, bowel dysfunction, and urinary dysfunction.

What is the meaning of lemon and banana signs? In which gestational weeks can we observe those changes?

- The lemon sign: Loss of the convex outward shape of the frontal bones with mild flattening, is present in virtually all fetuses with MMC between 16 and 24 weeks gestation
- The banana sign: Shape of the cerebellum looks like banana and is thought to be due to tethering of the spine with downward traction on the cerebellum (the Chiari II malformation). It can be mostly detected from 14 to 24 gestational weeks.
- Those changes occur due to vacuum effect, namely skull is trying to push the brain matter out of foramen magnum.

What is the probability of exitus of a live born infant with MMC?

- Live born infants with myelomeningocele have a death rate of approximately 10%.

What is the management of MMC?

- Surgery should be performed within 48 h of birth. However, an earlier intervention involving fetal surgery is now considered as a good method with reduced need for shunting and improved motor outcomes. Also another new method, fetoscopic repair is a promising alternative to open fetal myelomeningocele repair with a lower risk of uterine dehiscence.

In which other conditions, prenatal invasive interventions can be used besides cytogenetic analysis?

- Fetal transfusion
- Selective termination
- Balloon atrial septostomy
- Cord strangulation
- Balloon valvuloplasty
- Shunt operations
- Fetoscopy
- Twin-twin transfusion syndrome (TTTS) laser therapy

In which weeks is prenatal invasive interventions performed for cytogenetic analysis?

- CVS: 12 weeks (9–15 weeks)
- Amniocentesis: generally after 15th weeks (early amniocentesis is not preferred; complications like club foot)
- Cordocentesis > 18 weeks (ideal—can be done from 16th week)
- 0.5–1% pregnancy loss rate

Describe amniocentesis, what are the indications?

- Amniocentesis is performed between 15th and 21th pregnancy weeks. A small amount of amniotic fluid is taken with a fine needle with ultrasonography. Cells belonging to fetus poured into amniotic fluid are cultured and produced in special media, and chromosome, enzyme, and DNA analyzes are performed in cells. The risk of abortion is 0.5%. It is called early amniocentesis if administered before 14 weeks, since it is more risky and complications such as club foot (talipes) may occur currently, early amniocentesis is not a preferred method.
- Transvaginal amniocentesis is also possible after 11 weeks, after chorion–amniotic fusion.
- No risk of mosaicism. In addition to culture, enzyme and DNA studies can also be performed.
- Culture success is 97–99%.
- Determination of lung maturation.
- Rh/rh isoimmunization.
- Genetic diagnosis (prenatal diagnosis).
- Diagnosis of amnionitis.
- Amnioinfusion.

What are the complications and disadvantages of amniocentesis?

- Bleeding, infection, amniotic leak-oligohydramnios, and preterm labor are the most important complications.
- The main disadvantage of the procedure is the length of the culture stage, which is 15–30 days after the procedure.

What are the main features of cordocentesis?

- Cordocentesis is the collection of 1–4 mL blood from the umbilical cord of the fetus, karyotyping, whole blood analysis, and blood gas measurement.
- Cordocentesis is performed after the 18th week of pregnancy. Is used in the diagnosis of hereditary blood and metabolic diseases in case of anomaly detection by ultrasound, late admission, failure of previous prenatal diagnostic methods, or in doubtful results.
- It is used in the evaluation of blood gases in infants with cordocentesis developmental retardation, in the diagnosis of infectious diseases (rubella, toxoplasmosis), and to recognize hemolytic anemia in infants of Rh-negative pregnant women during intrauterine period.
- The risk of abortion is 1.5–4.8%.
- Bleeding, infection, and preterm labor are the most important complications.

What are the indications for cordocentesis?

- In hereditary blood and metabolic diseases (hemoglobinopathies, hemophilia, thrombocytopenia)
- Rh/rh Isoimmunization
- Fetal infection
- Karyotyping

What are the main features of the chorionic villus sampling (CVS)? In which situations can it be used?

- CVS is a prenatal test, removal of 5 mg of tissue from the placenta by ultrasound control. It is preferred in diseases that can be diagnosed by DNA analysis (thalassemia, phenylketonuria, cystic fibrosis, Duchenne muscle dystrophy, sickle cell anemia, fragile X send).
- There two methods of CVS: transcervical and transabdominal.
- CVS is performed during 9–15th gestational weeks.
- The risk of abortion is 2–3%. The risk of miscarriage in the transabdominal method is 0.5–1%.
- DNA studies other than chromosome analysis can be done, some enzyme deficiencies can be detected.
- The rate of fetal loss and anomaly (limb deformities) increases in earlier cases (due to vasoconstriction caused by prostaglandins during CVS).
- Adequate material rate is 95%, culture success is 95%.
- The size of the fragment is more important than the total amount of tissue removed during the procedure.
- Direct karyotyping without culturing chorionic villus cells is the most important advantage, but CVS culture is essential for diagnosis.
- The disadvantage of CVS is mosaicism, which is 1%. In the other two techniques (amniocentesis or cordocentesis) this ratio is close to zero.
- Bleeding is the most common complication.
- Infection, especially in transcervical applications, is rare.

How is fetoscopy and fetal biopsy performed? Describe its characteristics.

- Amniotic sac shown with light source and 15–30° optics by fetoscopy.
- Fetal skin, muscle, liver biopsy can be taken.
- Skin biopsy is more common currently.
- It is used in the diagnosis of skin diseases such as ichthyosis, epidermolysis bullosa, Sjögren's syndrome.
- Fetal mortality rate is 3–5%.

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Chapter 9
Hydrops Fetalis

What does hydrops fetalis (HF) mean?

- Hydrops fetalis is a symptom of accumulation of fluid or edema in at least two fetal compartments. Abnormal fluid collection is present in multiple fetal extravascular compartments such as abdominal, thorax, and skin.

In which situations fetal hydrops (HF) is suspected?

- In the ultrasonography, 60% of the cases can be visualized prenatally with the presence of effusion in two or more regions and subcutaneous edema accompanied by effusion in one region.
- HF characterized by generalized skin thickness of >5 mm (skin edema), placental enlargement-thickening (≥4 cm in the second trimester or ≥6 cm in the third trimester), pericardial or pleural effusion, or ascites and polyhydramnios.

In which situations hydrops is called as nonimmune hydrops fetalis (NIHF)?

- NIHF is a symptom of presence of ≥2 abnormal fetal fluid collections in the absence of red cell alloimmunization.

What are the most common cause and other causes of nonimmune hydrops fetalis (NIHF)?

- Fetal cardiovascular disorders: cardiac structural abnormalities, arrhythmias, cardiomyopathy, cardiac tumors, or vascular abnormalities; increased central venous pressure is the most common cause of NIHF.
- Chromosome imbalances.
- Hematologic abnormalities: the most common cause is alpha thalassemia.
- Infections: parvovirus, cytomegalovirus, syphilis, toxoplasmosis.
- Intra-thoracic masses: the most common cause is congenital pulmonary airway malformation (CPAM).
- Lymph vessel dysplasias.

Acknowledgments The author would like to thank Dr. A. Ozan Tekin who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_9

- Twin-to-twin transfusion syndrome and placental causes and syndromes
- Urinary tract malformations: urethral obstruction, prune belly syndrome.
- Inborn errors of metabolism: lysosomal storage diseases like various mucopolysaccharidoses, Gaucher disease, and Niemann-Pick disease.
- Skeletal dysplasias: achondroplasia, achondrogenesis, osteogenesis imperfecta, osteopetrosis, thanatophoric dysplasia, short-rib polydactyly syndrome, and asphyxiating thoracic dysplasia.
- Extra-thoracic tumors: vascular tumors, teratoma, leukemia, hepatic tumors, neuroblastoma.
- Gastrointestinal disorders: diaphragmatic hernia, midgut volvulus, gastrointestinal obstruction, jejunal atresia, malrotation of the intestines, and meconium peritonitis.
- Hepatic disorders: cirrhosis, hepatic necrosis, cholestasis, polycystic disease of the liver, and biliary atresia, due to hypoproteinemia.
- Idiopathic.

What is the most common congenital heart defect related to NIHF?

- The most common congenital heart defects related to NIHF are right sided heart defects, because of increased central venous pressure.

What are the most common chromosomal abnormalities causing NIHF?

- Turner syndrome and Down syndrome

What is the most common infectious cause of NIHF?

- Parvovirus B19

In parvovirus infections, what is the mechanism of HF?

- Parvovirus has an affinity for erythroid progenitor cells, leading to inhibition of erythropoiesis and subsequent anemia.

What are the causes of fetomaternal hemorrhage that may cause maternal sensitization?

- Cordocentesis (umbilical cord sampling, the highest risk of maternal immunization)
  - Abortus (spontaneous or elective)
  - Chorionic villus sampling (CVS)
  - Amniocentesis
  - Ectopic pregnancy
  - Fetal death
  - Vaginal or cesarean delivery (the most common cause of immunization)
  - External cephalic version
  - Ablatio placenta, placenta previa, and vasa previa
  - Trauma
  - Unexplained bleeding during pregnancy

Which cause of fetomaternal hemorrhage is the most risky situation for immunization that can cause maternal sensitization?

- Cordocentesis

Which cause of fetomaternal hemorrhage is the most common situation for immunization that can cause maternal sensitization?
- Vaginal or cesarean delivery

What is measured with an indirect Coombs (IDC) test?
- It is a test used for the determination of free antibody in maternal blood.

What is measured with Kleihauer–Betke test?
- It is a test to calculate the amount of fetal erythrocytes mixed into the maternal circulation.

What is measured with a direct Coombs (DC) test?
- It detects antibodies on fetal erythrocytes. Sample should be collected from umbilical cord via cordocentesis.

What is the primary factor determining the severity of ascites in hydrops fetalis?
- Severity and duration of fetal anemia.

What is the noninvasive diagnostic method of fetal anemia?
- Fetal mid cerebral artery (MCA) Doppler peak systolic velocity (PSV) measurement by US (>1.5 MoM).

Except for the first prenatal visit, in which week the IC repeated and anti-D Ig administered if necessary?
- 28th gestational week, 300 mcg anti-D Ig (Rho(D) immune globulin-RhoGAM $^{(R)}$), IM to Deltoideus muscle.

Explain how fetal hydrops develop in Rh incompatibility.
- First mechanism:
- Fetal anemia → extramedullary hematopoiesis → decreased protein synthesis in the liver → hypoproteinemia → plasma oncotic pressure decreases → fetal edema.
- Second mechanism:
- Fetal cardiac load increases for the maintenance of oxygenation of tissues due to fetal anemia.
  - Fetal cardiac insufficiency.
  - Hydrops.

What is the definition of Mirror syndrome?
- Mirror syndrome (Ballantyne syndrome) refers to serious maternal edema with pulmonary involvement. Mother "mirrors" the edema of fetus and placenta. It represents a form of preeclampsia and is characterized by edema in approximately 90%, hypertension in 60%, and proteinuria in 40% of cases.
- The major maternal morbidity is due to maternal pulmonary edema, which occurred in 21%.

Is there a risk of recurrence of NIHF in subsequent pregnancies?
- It is mostly based on the etiology of original disease. If it is originated from an anatomic cardiac variation or infection, the risk does not change that much. If the

original disease has a genetic basis, then the recurrence risk is considered to be higher compared to the other population.

What are the initial steps in the evaluation of HF?

- Indirect Coombs (IC) test to verify that it is nonimmune
- Evaluate for fetal and placental abnormalities
- Fetal heart rate monitoring, fetal arrhythmia
- MCA Doppler evaluation for anemia
- Fetal karyotype or chromosomal microarray analysis
- In the presence of a family history of an inheritable metabolic disorders: evaluating for storage disorders, enzyme analysis and carrier testing in parents, histologic examination of fetal tissues, maternal thyroid antibodies

What are the treatment options for fetal hydrops?

- In case of
- Fetal anemia (<10 g/dl): in utero transfusion
- Fetal arrhythmia: Digoxin can be considered
- TTTS: fetoscopic laser ablation

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Chapter 10
Amniotic Fluid Anomalies

What are the basic functions of the placenta?

- Transfer of gases: flow-limited passive diffusion.
- Transport of nutrients: Principally glucose (facilitated diffusion), amino acids (active transport), fatty acids (via specific lipoprotein receptors or scavenger receptors), vitamins, and minerals.
- Waste elimination.
- Protection; reservoir of blood for fetus.
- Nutritional: Provides oxygen, glucose, amino acids, and volume (liquid) transfer.
- Immunological: Protects fetus from pathogens and maternal immune system.
- Endocrine: Secretes human chorionic gonadotropin (hCG), Human placental lactogen (hPL), progesterone, estradiol, growth factors, cytokines, and other vasoactive mediators.
- Metabolic: It acts as the respiratory organ and kidneys of the fetus and is responsible for the elimination of carbon dioxide, metabolic acids, and other waste products from the fetus and maintenance of acid–base balance.

How does amniotic fluid volume changes during pregnancy?

- Normal amniotic fluid volume: gradually ↑, approximately 250 mL (16th gestational week) → 800 mL ~ 38 weeks. Then volume ↓ and after term ↓
- All amniotic fluid renovates in term fetus at about 3 h

What are the factors contributing to amniotic fluid balance?

- Amniotic fluid formation: Fetal urine {fluid from the fetal kidneys (hypotonic)} and lung fluid secretions
- Amniotic fluid absorption: Fetal swallowing, amniotic–chorionic interface, and transport within the intervillous range

Acknowledgments The author would like to thank Dr. İ. İlker Arıkan, Dr. Avni Ozan Tekin, Dr. Fadime Dinçer and Dr. Büşra Aynalı who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_10

What is the definition of oligohydramnios?
- Amniotic fluid index (AFI): 5 cm ↓ (standard definition) or 8 cm ↓ (alternative)
- Deepest pocket <2 cm → oligohydramnios

What is the definition of polyhydramnios?
- AFI: 25 cm ↑ (standard definition) or 18 cm ↑ (alternative)
- Deepest pocket ˃ 8 cm → polyhydramnios

What are the fetal and maternal causes of oligohydramnios?

- *Fetal causes*
  - Renal agenesis
  - Obstructive uropathy
  - PROM
  - IUGR
  - Post-term pregnancy
- *Maternal causes*
  - Dehydration, hypovolemia
  - Hypertensive diseases
  - Uteroplacental insufficiency
  - Antiphospholipid syndrome (APS)
  - Idiopathic

What are the causes of the first trimester oligohydramnios?
- Congenital heart anomalies, chromosomal aneuploidy, fetal death, and premature rupture of membranes. It may also be iatrogenic due to CVS. The reason may not be clear.

What are the causes of the second trimester oligohydramnios?
- Congenital urinary system anomalies, preterm PROM, placental causes, amniochorionic separation, early and severe IUGR, indeterminate group (3%)

What are the causes of the third trimester Oligohydramnios?
- Preterm PROM, IUGR, ablation placenta, fetal anomalies, iatrogenic (ACE inhibitors or prostaglandin synthesis inhibitors)

What is the incidence rate of the third trimester oligohydramnios?
- Incidence: 3–5% (late preterm group); (5–11%) 40–42 weeks

Describe the approach to a pregnant woman with oligohydramnios.
- The gestational week is important.
- Fetal anatomical evaluation by ultrasound.
- Fetal biometry is measured.
- Examination of cervico-vaginal fluid to rule out PROM.
- Maternal hydration.
- Amnioinfusion (with informed consent).

- In isolated and persistent oligohydramnios, if the maternal and fetal conditions are stable, the decision is to deliver at 36–37 weeks of gestation. Close fetal monitoring in preterm cases and betamethasone.

Describe the approach to a pregnant woman with polyhydramnios.
- Detailed fetal anatomical examination with ultrasound
- Fetal karyotype analysis?
- Fetal biometry
- Signs of fetal infection (hepatosplenomegaly, liver, and intracranial calcifications) or fetal hydrops.
- MCA Doppler for screening fetal anemia
- Color or power Doppler examination of the placenta (placental hemangioma)
- Maternal DM or Pre- or gestational diabetes screening
- If congenital anomalies and/or IUGR are detected: chromosome analysis or microarray test, serological examination for congenital infections (TORCH)
- If fetal hydrops is detected: if it is immune etiology, indirect coombs test, TORCH serology, investigation of heart failure findings, approach for other causes

Describe the approach to isolated polyhydramnios.
- Perinatal mortality is 3–5 times higher than normal amniotic fluid.
- Fetal movement monitoring and weekly NST.
- Fetal growth monitoring every 3–4 weeks.
- AFI monitoring every 2–3 weeks.
- <32 w: amnioreduction and Indomethacin (4×25 mg orally). >32 w: amnioreduction. After 32 gestational weeks PGI are not used concerning constriction of the ductus arteriosus.

What are the fetal causes of polyhydramnios?
- Central nervous system: neural tube defects (anencephaly, iniencephaly, encephalocele), sacral teratoma
- Gastrointestinal system: Esophageal atresia, diaphramatic hernia, duodenal stenosis atresia
- Respiratory system: Cystic adenomatoid malformation of the lung, chylothorax
- CVS: Ebstein's anomaly, atrioventricular valve regurgitation, arrhythmias, TTTS
- Musculoskeletal system: Skeletal dysplasias, myotonic dystrophy, Pena–Shokeir syndrome, fetal akinesia/hypokinesia syndrome. Polyhydramnios is typically caused by decreased fetal swallowing.

What are the maternal fetal complications of polyhydramnios?
- Maternal respiratory problems
- Preeclampsia (mirror syndrome)
- Preterm birth
- PPROM
- Fetal malpresentation
- Umbilical cord prolapse

- Ablation placenta
- Uterine atony

What are the properties of indomethacin used in the treatment of polyhydramnios?

- Effective in severe symptomatic polyhydramnios
- It acts by reducing fetal urine production (reduction in AFI in the first 24 h)
- Used from 26–27 weeks to 32 weeks of gestation
- 25 mg per os every 6 h
- Long admission is rare, no more than 3 days
- Fetal echocardiography in long-term use (follow-up for duct us arteriosus closure)
- Platelet dysfunction could occur so not to be used in cases with Placental abruption.

Which factors increase fetal cardiac output causing high fetal urine production, which is one of the contributing factors in polyhydramnios?

- Increased urine production may occur in high fetal cardiac output states (e.g., fetal anemia due to alloimmunization, parvovirus infection, fetomaternal hemorrhage, alpha-thalassemia, hemolysis secondary to glucose-6-phosphate dehydrogenase deficiency) or, rarely, from entities such as fetal Bartter syndrome.

Which infections can cause polyhydramnios?

- Infections that may present with hydramnios:
- Cytomegalovirus
- Toxoplasmosis
- Syphilis
- Parvovirus

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Chapter 11
Antenatal Bleeding

What is the definition of antepartum hemorrhage and what are the causes of antepartum hemorrhage?

- Genital tract bleedings, after the 20–24th weeks of gestation.
- Obstetric causes (95%)
  - Abruptio placenta (80%)
  - Placenta previa (10–15%)
  - Vasa previa
  - Cervical dilatation—labor (bloody show)
  - Uterine rupture (very rare)
- Non-obstetric causes (5%)
  - Cervicitis, cervical erosion, and polyps
  - Vaginal laceration, trauma, and varices (vulvovaginal traumas)
  - Vaginal malign/benign neoplasia
  - Cervical malign/benign neoplasia
  - Coagulation disorders
  - Hematuria

What is the meaning of Abruptio placenta?

- Premature detachment (before delivery of the fetus) of normal implanted placenta, in pregnancies >20 gestational weeks, complicates about 1/100 pregnancies.
- Generally it is an emergent situation.

What are the risk factors for abruptio placenta?

- Previous history of abruptio
- Advanced age and gravida

Acknowledgments The author would like to thank Dr. İ. İlker Arıkan, Dr. Avni Ozan Tekin, Dr. Fadime Dinçer and Dr. Büşra Aynalı who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_11

- Preeclampsia
- Chronic hypertension
- Preterm rupture of membranes (PROM)
- Smoking
- Thrombophilia
- Cocaine
- Uterine fibroids
- Trauma, i.e., car crash

What is the strongest risk factor for abruptio placenta?
- Previous history of abruptio; 10- to 15-fold recurrence risk.

What are the clinical symptoms/manifestations/features of abruptio placenta?
- Classically, uterine tenderness, hypertonus and vaginal bleeding
- External (vaginal bleeding is observed) or latent uterine bleeding
- Uterine hypertonus and hyperactivity (due to thrombin and reduced expression of progesterone receptors in decidual cells)
- IUGR (in chronic cases)
- Fetal distress or intrauterine death
- Uterine tenderness or low back pain
- High-frequency uterine contractions
- Idiopathic preterm labor (or due to increased levels of matrix metalloproteinases)
- Disseminated intravascular coagulation (DIC) (final stage): increase in fibrin degradation products

What is the management of abruptio placenta?
- In case of unstable fetus and/or patient, emergent cesarean delivery is the best option. Be ready for blood products, hypovolemia, DIC.
- In case of stable patient and fetus:
  - Gestational age is: <34 weeks → Corticosteroids, tocolysis (avoid indomethacin), $MgSO_4$ (neuroprotective affect <32 weeks); delivery after 36 weeks.
  - Gestational age is: ≥34 weeks → Delivery would be the best option, after corticosteroid application. In cases with normal fetal heart rate observed and bleeding stopped, delivery after 36 weeks would be another option, as well.

What are the complications of abruptio placenta?
- Maternal blood loss leading to hypovolemia, DIC
- Acute fetal distress, stillbirth
- IUGR, in chronic abruptio placenta
- Rh sensitization, in case of Rh incompatibility

What does Couvelaire uterus mean? What is the complication related to this situation?
- Abruptio placenta may be complicated by extensive extravasation into myometrium and serosa of the uterus. This is called Couvelaire uterus.
- Couvelaire uterus is prone to postpartum hemorrhage and atony. However, sole presence of Couvelaire uterus is not an indication for hysterectomy.

What is the definition of placenta previa?
- Placenta is localized over the internal cervical os, diagnosed by transvaginal or perineal ultrasound >20 weeks of gestation. Prevalence is 1/250 births.

What is the classification of placenta previa?
- Total placenta previa: the placenta completely covers the internal os.
- Partial placenta previa: the placenta partially covers the internal os.
- Marginal placenta previa: The placental edge is at border of the internal os.
- Low-lying placenta: The lowest placental edge is <2 cm from the internal os.

What are the risk factors for placenta previa?
- Previous placenta previa (strongest risk factor)
- Advanced maternal age
- Multiple gestation
- Multiparity
- Previous cesarean section
- Smoking, cocaine use
- Infertility treatment
- Previous abortion
- Previous uterine surgeries

What are the clinical symptoms/manifestations/features of placenta previa?
- Asymptomatic, usually diagnosed on routine ultrasound examination.
- Painless vaginal bleeding, some of the patients could have uterine contractions as well, but not hypertonicity of the uterus is observed as in abruptio placenta.

What are the complications of placenta previa?
- Placenta accreta (previous uterine surgeries are important here)
- Maternal hemorrhage
- Fetal distress
- Premature labor or delivery
- Emergent caesarean delivery

What is the management of placenta previa?
- Exclude placenta accreta.
- Actively bleeding previa; in case of unstable fetus and/or patient, emergent cesarean delivery is the best option. Be ready for blood products, hypovolemia, DIC.
- Light bleeding before 34 weeks: Inpatient, NST, observe bleeding, tocolytics, corticosteroids, tranexamic acid.
- (Asymptomatic patient) In case of stable patient and fetus:
  - Gestational age is: <34 weeks → Outpatient.
  - Gestational age is: ≥34 weeks → Inpatient. Corticosteroids 1 week prior to the cesarean.

What is the definition of placenta accreta spectrum, what are the components?
- It develops as a result of placental implantation of the defective decidualization area (i.e., the previous endometrial-myometrial surface defect; previous caesar-

ean section, curettage, myomectomy) resulting from abnormal trophoblastic invasion of the uterine myometrium.
- Defective decidualization is the main problem. Absence of the decidua basalis, incomplete development of the Nitabuch's layer (normally; fibrinoid deposits accumulate and form this layer deeper in decidua basalis, placenta detaches from here at birth)
- Components:

1. Placenta accreta: The placental villi attach to the myometrium, rather than decidua.
2. Placenta increta: The placental villi invade into the myometrium.
3. Placenta percreata: The placental villi invade the myometrium into the serosa or attach to the adjacent organs (mostly urinary vesicle).

What is the most important risk factor for placenta accreta spectrum?
- Placenta previa in pregnant with history of previous cesarean section (prior uterine surgery).
- The risk is higher in women with placenta previa with 3%, 11%, 40%, 61%, and 67% of women with increasing order cesarean deliveries having a placenta accreta.

What are the risk factors for placenta accreta/increta/percreta?
- Advanced maternal age (>35)
- Increased number of previous caesarean deliveries
- History of other previous uterine surgery
- Placenta previa diagnosed prior to delivery
- IVF pregnancy

What is the definition of vasa previa, what type of umbilical cord or placenta can be associated with?
- Vasa previa is the presence of fetal veins on the membranes covering the internal cervical os.
- Vasa previa could be associated with velamentous umbilical cord, membranous umbilical vessels at the placental insertion site (type 1 vasa previa) or bilobe, succentriate placenta (type 2 vasa previa).

What are the risk factors for rupture of uterus without scar?
- High parity
- Trauma
- Labor complications
  - Cephalopelvic disproportion
  - Abnormal presentation
  - Abnormal fetal growth (i.e., hydrocephalus)
- Delivery complications
  - Forceps
  - Breech delivery
  - Internal podalic version and extraction

What are the causes of placentomegaly?

- GDM
- Fetal hydrops
- Placental hemorrhage
- Erythroblastosis fetalis
- Nonimmune hydrops
- Infections (syphilis)
- Chromosomal anomalies
- Hydatidiform mole
- Placental chorioangioma

What are the placental variations?

- Bilobate placenta
- Placenta succenturiata (accessory lobe associated with fetal veins)
- Circumvallate placenta
- Circummarginate placenta
- Placenta membranacea
- The ring-shaped placenta
- Placenta fenestrata

What are umbilical cord insertion abnormalities?

- Marginal insertion (Battledore placenta): Umbilical cord at the edge of the placenta. Generally not associated with an increased risk for adverse perinatal outcomes.
- Membranous insertion (velamentous insertion) increased vasa previa risk (painless vaginal bleeding + severe fetal distress).
- Furcate insertion: an extremely rare abnormality of umbilical cord insertion, in which the umbilical vessels separate before insertion into the placenta.

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Chapter 12
Vaginal Bleeding in Pregnancy

What can be the source of vaginal bleeding in pregnant women?

- Vaginal bleeding can occur in any stage of pregnancy.
- The source is almost always maternal origin rather than the fetus.
- Bleeding may result from decidua or cervical or vaginal lesions (erosions).
- The clinician makes a preliminary diagnosis based on the gestational age and the character of the bleeding (mild or severe, painful or painless, intermittent etc.). Then uses laboratory and imaging tests to confirm or review the initial diagnosis.

Describe the first trimester hemorrhage in pregnancy and its causes.

- Vaginal bleeding is common in the first trimester (0–13 6/7 weeks), which occurs in 20–40% of pregnant women.
- It may be any combination of mild or severe, intermittent or stable, painless or painful.
- The four major sources of nontraumatic hemorrhage in the early stages of pregnancy are:
  - Ectopic pregnancy
  - Abortus (imminence, inevitable, incomplete, complete)
  - Implantation of blastocyst to endometrium
  - Cervical, vaginal, or uterine pathology (e.g., polyps, inflammation/infection, trophoblastic disease)

What is the most common nontraumatic cause of first trimester bleeding?

- Abortion-related bleeding is the most common nontraumatic cause of first trimester bleeding (abortion prevalence: 15–20% of pregnancies).
- Although bleeding is severe, only 1% of the women would require blood transfusion.
- Ectopic pregnancy is much less frequent (prevalence of ectopic pregnancy: 2–5% of pregnancies).

What is the most serious etiology of first trimester vaginal bleeding?

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_12

- The most serious etiology of first trimester hemorrhage is rupture of ectopic pregnancy and poses a major risk for the pregnant woman. Therefore, this diagnosis should be ruled out in every pregnant woman with bleeding.

Describe the issues that should be considered in the anamnesis of the patient presenting with vaginal bleeding during pregnancy.

- The degree and severity of bleeding should be determined: Does she describe spotting or mild bleeding or more than that? Does she feel tired (fatique), or look pale (consider anemia)? Does she have pelvic pain or cramping? Any bleeding with fetal parts expelled? If yes then other abortus-related conditions such as incomplete abortion should be thought rather than implantation bleeding or cervicovaginal disease (e.g., polyps, cervicitis, and cancer). On the other hand, it is important to remember that the presence of only mild, intermittent, painless bleeding does not exclude the possibility of an underlying life-threatening disorder such as ectopic pregnancy.
- A history of ectopic pregnancy or presence of risk factors for ectopic pregnancy (e.g., history of pelvic inflammatory disease, presence of intrauterine device, history of adnexal surgery, smoking) in the patient's medical history increases the likelihood of ectopic pregnancy.
- A history of two or more consecutive abortions (habitual abortions) or a condition associated with abortion risk (e.g., chromosomal translocation, maternal antiphospholipid syndrome -APS, and uterine anomaly).
- The use of assisted reproductive techniques (ART) increases the risk of heterotopic pregnancy (intrauterine and ectopic pregnancy at the same time).

Describe the important factors that should be considered in the physical examination of pregnant women presenting with vaginal bleeding.

- Orthostatic blood pressure or pulse changes (such as tachycardia) are indicative of severe blood loss; supportive care and prompt treatment should be sought. However, it should be kept in mind that although pregnant has massive bleeding, sometimes especially in young patients anemic symptoms do not appear at first admission to the clinic.
- If there is a tissue expelled vaginally, it should be stored for pathological examination.
- Abdominal examination should be performed first. It is best to first examine the quadrant where the patient is experiencing the least pain. Light palpation is preferred because deep palpation causes pain, irritability and defenses. Pelvic-abdominal midline pain is more compatible with abortion related issues, while lateral pain is more compatible with ectopic pregnancy. Non-gynecological causes of pain should be taken into account, as well (diarrhea, constipation, nausea, vomiting, such as classic abdominal pain questions should be asked, remember that the patient may not have a stool discharge for a week, but it may not be described by the patient, if you do not ask it).
- The clinician should determine whether the uterine size is compatible with the estimated gestational age by palpating it (although this is mostly done by ultrasound measurement today). The uterus remains as a pelvic organ until 12 weeks of gestation and then large enough to be palpated just above the pubis.

- Fetal heart beat: fetal heart beats (>120 per min) should be discriminated from the maternal heart beats.
- Speculum examination may be required in lithotomy position to identify the source of bleeding.
  - Vaginal laceration
  - Vaginal neoplasm
  - Vaginal warts
  - Vaginal discharge
  - Cervical polyps, fibroids, ectropion
  - Mucopurulent cervical discharge or bleeding due to sensitivity to cervical os
- Cervical neoplasm
  - Uterus and adnexa should be evaluated by ultrasound (with β-hCG value)
  - Ectopic pregnancy → if β-hCG level is plateau or increases slightly (less than 35% increase in 48 h)? Missed abort?
  - Rhogam(R) (anti-D Ig) should be performed if there is Rh incompatibility between the pregnant and her partner (if indirect coombs result is negative)

Describe the diagnosis and treatment of ectopic pregnancy, which is one of the causes of first trimester bleeding.

- If intrauterine sac cannot be observed with transvaginal ultrasound despite β-hCG > 2000 mIU/ml, ectopic pregnancy should be suspected, but the sac may not be clearly visualized in multiple pregnancies with these β-hCG values.
- β-hCG values that draw a plateau in a week is a more precise finding in ectopic pregnancy diagnosis.
- Methotrexate (MTX) (dose is calculated according to the body surface area-intramuscular 50 mg/m^2) (hemodynamically stable patient, no fetal heart beat in the ectopic sac, renal functions are normal) or surgery (hemodynamic instability, acute abdomen, etc.) is applied. If endometrial thickness is >6 mm, then curettage is also applied not to miss heterotopic pregnancy and avoid MTX teratogenicity.
- If MTX is applied (day 0 is accepted on day of administration), β-hCG values on day 4 and day 7 are checked. MTX is repeated if there is a decrease of less than 15%. Two-dose regimen is also possible. In this regimen, β-hCG values between days 0 and 4 are examined, if there is no clear limit in different sources, if more than 15% increase is present, second dose MTX (IM 50 mg/m^2) is administered, again on day 4 and 7 β-hCG values are compared, and MTX is repeated at the same dose if there is a decrease of less than 15%.
- Surgery: salpingostomy, salpingectomy, milking.

Describe the threatened abortion (abortus imminence).

- The cervical os is closed, positive fetal heartbeat, positive uterine bleeding. If fetal heart beat is present, 90–96% does not result in abortion (7–11 weeks). Mostly, it is caused by the vessels on the maternal placental side and decidual part, these separations are not usually seen by ultrasound, but sometimes it is observed as subchorionic hematoma (accumulation of blood within the folds of

the chorion). When the expectant management is applied, progesterone can also be administered, but there is no clear evidence in improving outcomes. Tranexamic acid is also effective in limiting hematoma in subchorionic hematoma.

Explain the inevitable abortion (abortus incipiens).

- The cervical os is dilated, uterine bleeding increases, accompanying with painful uterine cramps. Gestational tissue may protrude from the cervical os, resulting in abortion in a short period of time. Expectant approach or abortion-inducing approaches (medical or surgery namely curettage) can be applied.

Describe complete and incomplete abortion.

- Complete abortion: If abortion occurs before 12 weeks of age, all contents are usually expelled out of the uterus. With ultrasound, the endometrial thickness appears thin, the uterus is contracted, the cervix is usually closed, and there is little bleeding (because the event is already completed). Observation of chorion in abortion material proves that intrauterine pregnancy has been terminated, β-hCG monitoring should be observed if chorion is not observed (ectopic).
- Incomplete abortion: More frequent at the end of the first trimester or at the beginning of the second trimester. Membranes rupture, and the fetus may be expelled completely, albeit placenta may remain. The cervical os is dilated. Gestational tissues may be observed from the cervix. The uterus is reduced in size, but not fully contracted, as in complete abortion, the patient feels pain since the cervical os is dilated. Bleeding may even be critical to cause hypovolemic shock. Intrauterine tissues are visualized by ultrasound. Medical treatment or curettage is required.

Explain Missed abortion.

- In utero ex embryo or fetus (<20 weeks) has waited for a while, missed. Vaginal spotting may accompany. The cervix is usually closed. By the ultrasound, intrauterine gestational sac (with or without embryonic/fetal pole) and no fetal heart beat observed. Medical or surgical abortion is applied for management of missed abortion.

Explain the vanishing twin.

- While one of the fetus of multiple pregnancy is resorbed and as a result singleton pregnancy is observed (early twin disappearance). It appears more in ART and may manifest itself with bleeding. It continues as a single pregnancy.

Describe the causes of vaginal bleeding in pregnancy other than obstetrical issues.

- Vaginitis, trauma, tumor, warts, polyps, fibroids—Physical examination, speculum, ultrasound.
- Ectropion—Cervical ectropion (columnar epithelium of the endocervix grows towards the ectocervix). No treatment is required.
- Physiological/implantation bleeding—Diagnosis is made by excluding other conditions. Little amount of vaginal spotting is observed. It occurs 10–14 days after fertilization. No intervention is required.

What is the prognosis of first trimester bleeding?

- Prognosis—Studies showed a relationship between first trimester bleeding and pregnancy complications (abortion, preterm delivery, premature rupture of membranes, IUGR, etc.). Prognosis is good if the vaginal bleeding is mild. However, if the bleeding is too much and encountered in the second trimester, its prognosis is worse.
- Also the risk of preterm labor, ablation placenta, and premature rupture of membranes may increase, and the risk of vaginal bleeding also increase in subsequent pregnancy.

What are the causes of second and third trimester bleeding?

- Birth-related (bloody show namely blood-tinged mucus)
- Placenta previa
- Ablation placenta
- Uterine rupture (rare)
- Vasa previa (rare)
- Cervical, vaginal, or uterine pathology (polyps, inflammation/infection, trophoblastic disease) and non-tubal ectopic pregnancies are other causes.

Describe the causes of vaginal bleeding in pregnancies before 20 weeks, second trimester.

- The evaluation is similar to that in the first trimester, but this time the diagnosis of ectopic pregnancy is less likely. The pain is accompanied.
- Only mild, transient, painless bleeding could be observed in cervical insufficiency, small marginal placental separation, or cervicovaginal lesions (polyp, infection, cancer). Excessive bleeding, if accompanied by pain, may indicate risk of abortion or ablation. Hgb/Htc, coagulation values should be evaluated.
- In abdominal examination, pain perception, uterine size, and tenderness are evaluated. At 16th gestational weeks, uterine fundus is palpable in the middle of the umbilicus and pubis and rises to the level of umbilicus in the 20th gestational week.
- In the lithotomy position, external genitals are examined, and the speculum is placed to visualize vagina and cervix. Cervical ectropion, vaginal laceration, and cervical polyps are examined to see if there are gynecological causes for vaginal bleeding. Dilated cervix and gestational parts may be observed and cervical insufficiency is diagnosed if pain and uterine contractions do not accompany to the vaginal bleeding. In the next pregnancy, cervical cerclage is applied after first trimestery Down syndrome screening test is applied, if cervical insufficiency is diagnosed previously.
- Transvaginal ultrasound, the relationship between the placenta and cervical internal os is visualized (bladder should be empty to make that relationship clearly observed) (placenta previa-actual diagnosis → after 20th gestational weeks), or placenta could be detached because of ablation. Cervical length is measured by ultrasound (should be >25 mm; between 16 and 24th gestational weeks; if not then it is called short cervix and correlated with the increasing risk of preterm birth, in those patients it is prudent to advise vaginal progesterone,

which significantly lowers the preterm birth rate and composite neonatal morbidity).

Describe the causes of vaginal bleeding in pregnancies over 20 weeks.

- Bloody show: Mucous plaque occluding the cervical os with mild bleeding may be observed within 72 h before delivery.
- Placenta previa (20%).
- Abruptio placenta (30%).
- Uterine rupture (rare).
- Vasa previa (rare).
- In other cases where there is no cause, marginal bleeding from the placenta, which does not appear on the ultrasound, could be the reason.

What are the important and risky situations that should be taken into account in pelvic examination of pregnant women with vaginal bleeding?

- Manual cervical examination should be avoided. The diagnosis of placenta previa should be ruled out first to perform manual vaginal-cervical examination. In case of accidentally digital examination of the patient with placenta previa; it is a severe malpractice that causes sudden, severe bleeding.

What are the differential diagnoses in third trimester vaginal bleeding?

- Placenta previa—Should be considered in the third trimester bleeding, with out pelvic pain. Classically, distinguished from ablation with the absence of pain and contractions, tetanic and contracted uterus is observed in ablation, though. However, in case of labor contractions in placenta previa hemorrhage, pain could accompany as well. Ultrasound is the most important diagnostic tool (transvaginal ultrasound with empty bladder).
- Abruption placenta (detachment-ablation)—A premature prenatal separation of normally implanted placenta. The most common risk factors are history of ablation in previous pregnancy, trauma, smoking, cocaine, hypertension, and premature rupture of membranes. Ablation is manifested clinically by 80% of cases by vaginal bleeding, 70% by uterine tenderness, and 35% is accompanied by uterine contractions. Uterine tenderness is caused by extravasation of blood from the veins to the myometrium; this appearance (purple uterus) is called the Couvelaire uterus. In severe cases, the blood extends to the peritoneal cavity. The amount of vaginal bleeding may not be an indication of the severity of bleeding, since bleeding may remain in the uterine cavity. Ultrasound may diagnose placental separation as retroplacental hematoma, but <60 percent of ablation cases could be observed on ultrasound. Ablation may be ranged from mild to severe (life-threatening) and may also be chronic-acute (mostly acute). The risk of ablation in trauma patients should be kept in mind, as well.
- Uterine rupture—A rare cause of vaginal bleeding. This possibility should be taken into consideration in patients with hemorrhage with a history of cesarean and myometrial surgery. It usually occurs during labor or with trauma, but it can rarely occur without a specific cause.

- Vasa previa—Observation of fetal blood vessels in membranes covering internal cervical os. Membraneous vessels may be associated with the valementous umbilical cord or caused by the vessel between the bilobulated placenta, and the placenta of the succenturiate lobe. Rupture of vasa previa rupture is an obstetric emergency, which can lead to sudden fetal loss (because bleeding is caused by fetal vessels). Generally because of that risk, cesarean is planned at about 34–35th gestational weeks of the pregnancy.

What is the prognosis of second and third trimester bleeding?

- Like first trimester hemorrhages, second and third trimester bleedings may be associated with pregnancy complications, especially preterm labor.
- In general, these complications are directly proportional to the severity of bleeding, and the cause is also important (in cases without previa, the outcome of pregnancy is worse). Bleeding from unknown origin of the second and third trimesters increases the risk of preterm birth by two to three times.

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Chapter 13
Multiple Pregnancies

What is the definition of Hellin's law?

- Hellin's Law is the principle that one in about 89 natural pregnancies ends in the birth of twins, triplets once in 89^2 births, and quadruplets once in 89^3 births-probability; namely n'lets once in 89^{n-1}.

What is the most serious complication of the multiple pregnancies?

- Preterm delivery (fetal hypothermia, respiratory abnormalities, patent ductus arteriosus, intracranial hemorrhage, hypoglycemia, necrotizing enterocolitis, infection, retinopathy)

What is the meaning of superfetation?

- A situation in which a pregnant becomes pregnant a second time with another (younger) fetus from a different estrous cycle while another embryo or fetus is already present in the uterus (not observed in humans).

What is the meaning of superfecundation?

- In the estrous cycle, two different ova are fertilized by sperm from two different sexual intercourse, which could be encountered in human as well. Sperms do not have to come from the same father. Namely two or more ova, two or more separate sperm at different times, from same father or different fathers.

When is the most appropriate time (trimester) to assess chorioamnionicity? Why is this assessment important?

- First trimester, especially after 7 weeks of pregnancy is the most appropriate period to consider chorioamnionicity.
- Assessing chorioamnionicity is important, since monochorionic fetuses share the same fetoplacental circulation, serious complications could be observed. Such as;
  - TTTS (twin-twin transfusion syndrome).
  - TRAP (twin reversed arterial perfusion).

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https://doi.org/10.1007/978-3-030-29669-8_13

  - TAPS (twin anemia polycythemia sequence).
  - In addition to those complications, monoamniotic fetuses are also at risk for cord entanglement. Also conjoined twin is another complication of monochorionic fetuses, when division occurs >12 days after fertilization.

What does lambda (λ) or twin peak sign on ultrasound indicate?
- Lambda sign: dichorionic/diamniotic.
- It is a triangular-shaped membrane that lies between two layers of the intertwin membrane from a fused dichorionic placenta.
- The lambda sign predicts chorionicity with a high degree of accuracy before 14 weeks of gestation. Presence of the lambda sign indicates dichorionicity, and absence of the lambda sign indicates monochorionicity.

What does T-sign on ultrasound indicate?
- T-sign: monochorionic/diamniotic
- It is a thin T-shaped intertwin membrane extending from the placenta at a 90° angle.
- Those are ultrasound markers being used to distinguish monochorionic and dichorionic placentas.

What are the risk factors for monozygotic twin pregnancy?
- The worldwide prevalence of monozygotic twin pregnancy is fixed: 3–5/1000 births. So, there is not known risk factors for monozygotic twin pregnancies apart from assisted reproductive technologies (ART).

What is the prevalence of monoamniotic twin pregnancy?
- 1/10,000

What are the risk factors for dizygotic twin pregnancy?
- Ethnic predisposition (i.e., 50 per 1000 in Nigeria)
- IVF treatment
- Advanced maternal age
- Multiparity
- Obese and tall mother
- Diet (folic acid)
- A multiple pregnancy history on the mother's side (not paternal)
- Blood group: A
- First cycle after stopping oral contraceptive
- Premenopausal period (high FSH levels, because of low levels of inhibin)

What are the fetal complications encountered in multiple pregnancies?
- IUGR, congenital anomalies, preterm delivery.
- Monochorionic: TTTS, TAPS, TRAP, selective fetal growth restriction (sFGR), single fetal demise, congenital anomalies, conjoined twins, cord entanglement.

What are the criteria for the diagnosis of sFGR? What are the types (stages) of sFGR?

- One of the fetuses should be EFW <10 percentile, discordance in EFW between twins >20–25%, due to unequal placental sharing between twins.
- Classification is made according to Doppler flow in the umbilical artery:
  - Type 1: Positive Doppler flow
  - Type 2: Absent or reversed end-diastolic flow
  - Type 3: Reversed end-diastolic flow

What are the maternal risks and complications encountered in multiple pregnancies?

- Maternal hemodynamic changes: anemia, increased risk of pulmonary edema
- Gestational HT, preeclampsia
- Gestational DM
- Acute fatty liver of pregnancy (AFL)
- Hyperemesis gravidarum (HG), abruptio placenta, thromboembolism, intrahepatic cholestasis of pregnancy, deep venous thrombosis (DVT), placenta previa, vasa previa.

In which type of twins does twin-to-twin transfusion syndrome (TTTS) mostly encountered? What is the rate of incidence of TTTS? How often is the prudent follow-up strategy?

- TTTS is most commonly encountered in diamniotic monochorionic twin pregnancy (based on live born fetuses).
- Fetal bladder volumes, fetal growth assessment, fetal amnion fluids indices are examined after 16th gestational weeks of the pregnancy to see whether there is discordance.
- In terms of twin anemia polycythemia sequence (TAPS), MCA Doppler peak systolic velocity (PSV) is compared between two fetuses (>1.5 MOM; <1.0 MOM).

What are the stages (classification) of TTTS?

- Quintero staging is used.
- Stage 1: There is discordant amniotic fluid, but urine is present in the bladder (oligohydramnios and polyhydramnios, Doppler indices are normal).
- Stage 2: No urine in the bladder of the donor twin. Oligohydramnios and polyhydramnios, Doppler indices are still normal.
- Stage 3: Accompanied by abnormal Doppler finding in umbilical artery, vein, or ductus venosus.
- Stage 4: One of the twins have acid or signs of hydrops.
- Stage 5: Fetal demise of one or both twins.

What is the predictive value of the Quintero staging?

- Staging of TTTS may not progress chronologically. For example, twin pregnancy in stage 1 can progress to stage 4 without passing through stage 2 and 3. In addition, its validity is also questioned, meaning that being in stage 1 does not mean that babies will be born with the best results, namely stage and perinatal outcome is not correlated.

What is the management of TTTS?

- The best method is the fetoscopic laser ablation of placental anastomoses (Solomon technique that coagulates the entire vascular equator) between 16 and 26 weeks of gestational age.
- Serial amnioreduction after 26th week is another method, but it requires repetitive interventions.

What is the absolute intrauterine proof of dizygotic twin pregnancy?

- Two different sex twins (male/female fetus)

What is the absolute intrauterine proof of monozygotic twin pregnancy?

- Single chorion visualized by ultrasound

What is the incidence of conjoined twins and is there any female/male predominance?

- Conjoined twinning occurs in 1 in 100 sets of monozygotic twins, 1 in 50,000 gestations, or 1 in 250,000 live births. A marked female predominance with 72%.

What are the types of conjoined twins?

- There are eight types of conjoined twins.
- They are classified according to the site of fusion. Attachment may be rostral: omphalopagus, thoracopagus, and cephalopagus; caudal: ischiopagus; lateral: parapagus, or dorsal: craniopagus, rachipagus, and pygopagus

What should be the mode of delivery in dichorionic twin pregnancies, what is the determining factor?

- The presentation of the first twin determines the mode of delivery, and if it is cephalic (other obstetric conditions are appropriate), vaginal delivery should be attempted. If the first twin is non-cephalic, the safest delivery mode is the cesarean section.

Which congenital anomalies in monoamniotic twins are more common than in singleton pregnancies?

- Fetal congenital cardiac anomalies are more common.

What is the timing of delivery for normal uncomplicated twin pregnancies?

- Dichorionic: 38 + 0 to 38 + 6 weeks of gestation
- Diamniotic monochorionic: 36 + 0 to 37 + 6 weeks of gestation (ACOG suggests 34 + 0 to 37 + 6 weeks of gestation)
- Monoamniotic monochorionic: 32 + 0/34 + 0 weeks of gestation (generally due to fear of cord entanglement)
- Conjoined twins: 35 + 0 weeks of gestation (even though the literature is inadequate)

Why do we plan delivery of monoamniotic twins before 34 + 0 weeks of gestation?

- Because of the increasing risk of perinatal mortality in the third trimester.
- There are risks such as cord entanglement. Therefore, antenatal steroid is routinely administered at 28 weeks of gestation. If the delivery is not performed after 3 weeks, a single rescue course of steroids is administered.

What are the determining factors of the different types of placentation in monozygotic twins?

- The determining factor is the timing of post fertilization division of the zygote.
  - First 3 days (before morula): dichorionic/diamniotic
  - Day 4–8: diamniotic-monochorionic (most common type)
  - Day 8–12: monoamniotic-monochorionic
  - After the 13th day: conjoined twins.

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Chapter 14
Fetal Growth Restriction, Intrauterine Growth Restriction (IUGR)

What is the definition of intrauterine growth restriction (IUGR)?

- The diagnosis of IUGR is based on ultrasonography biometrical measurements, an estimated fetal weight (EFW) below the tenth percentile for gestational age. Also, the fetus who have failed to achieve genetically predetermined growth potential is called IUGR.

How could we identify the fetus that is not small but growth restricted relative to its genetic potential?

- A normal growth inclination, normal Doppler velocimetry of the umbilical artery, and normal amniotic fluid index suggest a constitutionally small fetus.

What are the risk factors for IUGR?

- Three main risk categories: maternal, fetal, and placental risk factors.
- Diabetes Mellitus (DM), Systemic lupus erythematosus (SLE) (and other autoimmune diseases), cyanotic cardiac diseases, chronic pulmonary disease, hypertensive disorders (preeclampsia), severe chronic anemia, renal insufficiency, antiphospholipid antibody syndrome (but not hereditary thrombophilias), tobacco, alcohol, cocaine, illicit drugs, multiple gestation, teratogen exposure (antineoplastic, antiepileptic, antithrombotic drugs—Warfarin), infectious diseases (malaria, TORCHs), genetic (trisomy 13, trisomy 18) and structural anomalies (like congenital heart disease, gastroschisis), maternal malnutrition, placental and cord anomalies (placental insufficiency, abruption, infarction, circumvallate shape, hemangioma, and chorioangioma, velamentous, or marginal cord insertion) (it is important to remember that generally placenta previa is not considered as a risk factor for IUGR), uterine malformations, pregnancies conceived via assisted reproductive technologies (ART), residing at high altitude, short interval between pregnancies, extremes of maternal age, prior IUGR history, etc.

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https://doi.org/10.1007/978-3-030-29669-8_14

In which situations would you recommend prenatal fetal genetic diagnostic testing (cytogenetic analysis)?

- Early (<24 weeks), severe (<fifth percentile), symmetrical growth restriction.
- Major fetal structural abnormalities (i.e., cardiac).

What is the recurrence risk of IUGR in the subsequent pregnancy?

- The recurrence risk of IUGR is about 20%.

What are the main IUGR types?

- Asymmetric IUGR: Uteroplacental insufficiency is affected by cell size. The abdominal circumference (AC) is first affected, since subcutaneous adipose tissue and liver glycogen stores are used primarily. The head circumference (HC) is closer to normal (also biparietal distance-BPD), since the brain is spared until the last moment.
- Symmetric IUGR: Both cell number and cell size decrease due to factors happened in early stages of gestation. Teratogenic exposure, intrauterine infections (CMV, toxo plasmosis, rubella, varicella, malaria, syphilis, listeria, etc.) (5%), congenital fetal anomalies (1–2%), metabolic disorders and genetic anomalies.

What does ponderal index (PI) used for? How is it calculated?

- The ponderal index (PI) is used for IUGR, especially in fetuses with asymmetric IUGR.
- PI = [weight (in grams) × 100] ÷ [length (in cm)]^3.
- PI of less than the tenth percentile reflects fetal malnutrition; PI of less than the third percentile indicates severe wasting.

What methods do we use for follow-up of patients with IUGR? What is our main goal and drawback?

- We need to be sure about the LMP date (re-dating with the previous ultrasound reports-12th gestational week US report is better to estimate LMP). After that; Serial ultrasound evaluation of fetal growth velocity (2–3 weeks apart), also we need to compare the current fetal biometry-US report with 2–3 weeks previous US report, fetal biophysical profile (BPP), and Doppler velocimetry represent the key elements of fetal assessment and guide pregnancy management decisions.
- The purpose is to identify those fetuses that are at highest risk of in utero demise and neonatal morbidity who may benefit from preterm delivery.

What are the Doppler assessment and its importance of the fetus with IUGR?

- The general sequence of Doppler changes in IUGR is:
  - A reduction in umbilical venous flow is the initial hemodynamic change.
  - Umbilical artery Doppler index increases (diminished end-diastolic flow) due to increased resistance in the placental vasculature.
  - Middle cerebral artery peak systolic velocity increases (also in anemic fetuses), and end-diastolic flow velocity increases (reflected by a low PI) in the middle cerebral artery (brain-sparing effect).

  - Increasing placental vascular resistance results in absent and then reversed end-diastolic flow in the umbilical artery.
  - As cardiac performance deteriorates absent or reversed end-diastolic flow in the ductus venosus, and pulsatile umbilical venous flow may develop, end stage, critical stage.

What are the fetal complications of IUGR?

1. Fetal death
2. Asphyxia
3. Meconium aspiration
4. Neonatal hypoglycemia
5. Hypothermia
6. Hypocalcemia
7. Polycythemia
8. Hyper viscosity
9. Advanced motor and neurological insufficiency

How would you determine the timing of delivery of an IUGR fetus (optimal timing of delivery)?

- Umbilical artery Doppler can guide assessing the timing of the delivery. If the umbilical artery Doppler and the antepartum course are reassuring, delivery of fetuses with IUGR may be postponed until 38–39 weeks, in case of umbilical artery Doppler and other obstetrical issues remain normal.
- For pregnancies complicated by IUGR with absent end-diastolic umbilical artery flow, and fetal surveillance has remained reassuring, delivery at 34 weeks should be considered after corticosteroids applied.
- For IUGR with reversed end-diastolic umbilical artery flow, antenatal corticosteroid administration followed by delivery at 32 weeks should be considered.
- In case of decreased diastolic umbilical flow, fetal surveillance has remained reassuring, frequency of Doppler testing is increased, and delivery at about after 37 weeks should be considered.

What is the suggested proven medical therapy of IUGR?

- Antenatal steroids (<34 weeks)
- $MgSO_4$ (<32 weeks).

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Chapter 15
Normal Vaginal Labor

What is the definition of normal labor?
- A clinical process characterized by expulsion of fetuses and placenta after 20 weeks and over 500 g with concomitant contractions causing cervical dilatation, effacement and gradually increasing its severity.

What is the definition of the situs (lie)?
- The position of the longitudinal axis of the fetus according to the mother's longitudinal axis.
- It is 99% longitudinal.
- Transverse lie: It is seen in mostly multiparity, placenta previa, hydramnios, uterine anomalies.

What is the meaning of presentation of the fetus?
- Fetal part which is close to cervical os
  - E.g. Head, breech, shoulder.

What is the definition of the habitus, posture (attitude)?
- The position of the fetal parts relative to each other and also to the uterine walls. Such as longitudinal, transverse and oblique.

What is the definition of the presentation?
- The portion chosen as reference in the presented fetal part is to the right/left and anterior/posterior according to the maternal birth canal.
- Occiput in the presentation of vertex.
- Sacrum in the presentation of breech.
- Face in the presentation of mentum.
- Acromion in the presentation of shoulder.

Acknowledgments The author would like to thank Dr. Ülkü Özmen who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_15

What are the four Leopold maneuvers?

1. The week of pregnancy is determined by the height of the fundus. After the third month, uterus begins to rise on the pubis per month. Uterus is between the umbilicus and symphysis pubis in the fifth month. Uterus is at umbilicus in the sixth month. In the seventh month, uterus is between umbilicus and sternum. In the 8th month, uterus is 4 cm under the sternum. In primiparous women, uterus descends 2–3 cm under sternum at the term.
2. Examination of the sides of the abdomen to locate the child's back and limbs. This examination determines the baby's posture.
3. This maneuver determines whether the presenting part is head or breech.
4. It is done to understand how much of the presenting fetal part has entered the pelvis.

What are the anatomical structures that limit pelvic inlet?

- Sacral promontorium
- Linea terminalis
- Symphysis pubis

What are the anatomical structures that limit the middle pelvis?

- Sacrum S3–S4
- Os ischii-spina
- Lower part of symphysis pubis.

What are the anatomical structures that limit pelvic outlet?

- Caudal end of sacrum
- Os ischii-tuberocity
- Lower part of symphysis

What are the main types of female pelvis according to the Caldwell-Moloy?

	Gynecoid	Android	Anthropoid	Platypelloid
Pelvic access (anterior-posterior)	11 cm	11 cm	12 cm	10 cm
Pelvic access (transverse)	12 cm	12 cm	12 cm	12 cm
Fore-pelvis	Generous	Narrow	Narrow	Wide
Side walls	Straight	Convergent	Divergent	Divergent
Ischial spines	Blunt	Prominent	Blunt	Blunt
Subpubic angle	**90°**	**<90°**	**>90°**	**>90°**
Pelvic outlet	10 cm	>10 cm	10 cm	10 cm
Bone structure	Normal	Thick	Normal	Normal

Describe the clinical evaluation of the pelvis.

1. Obstetric history
2. Diagonal conjugate >11.5 cm
3. Evaluation of sacrum
4. Spines
5. Subpubic angle and distance between tuberocities

What are the possible mechanisms for initiating birth?
- Progesterone withdrawal
- Premature decidual activation
- Increase in oxytocin secretion
- Prostaglandin synthesis
- Placental CRH increase → COX2 activity increase → prostaglandins increase
- Placental CRH increase → Fetal ACTH increase → fetal adrenal activity increases → cortisol increase

What is the effect of progesterone on delivery?
- Progesterone contributes to the system that protects myometrial contractile response.

What is the effect of estrogen on delivery?
- Increases the myometrium's capacity to contract and respond to contracting agents.

What are the uterine phases of labor?
- Phase 1: myometrial silence
- Phase 2: preparation
- Phase 3: active labor and birth
- Phase 4: involution

What are the possible changes occurring at the phase 1?
- Uterine relaxation and silence period
- Cervical softening
- Reduction of cross-linking between collagen fibrils
- Reduction of lysyl oxidase activity
- There are significant increases in the activity of the enzymes that stop or inhibit the activation of uterotonics:
  - Prostaglandins–Prostaglandin dehydrogenase
  - Endotelines–encephalinase
  - Oxytocin–oxytocinase
  - Histamine–diaminoxidase
  - Catecholamines–Catechol-O-Methyltransferase
  - Platelet-activating factor (PAF)–PAF acetyl hydrolase

How is the transition from phase 1 to phase 2 occur?
- Increased sensitivity to uterotonics
- Increase in myometrial oxytocin receptors
- Increase in gap junction between myometrial cells
- Cervical softening, ripening
- Oxytocin
- Prostaglandins E_2 and F_2-alfa
- PAF: PAF stimulates fetal membranes to produce PGE_2
- Endoteline-1
- Serotonin (5-hydroxytryptamine)
- Histamine

What are the main features of the uterine phase 2 of labor?

- Actin–myosin bonds increase in number.
- Contraction associated proteins (CAPs): oxytocin receptors, prostaglandin F receptors, connexin 43 (gap junction alpha-1 protein) (it is only exist in pregnant women).
- RU 486-antiprogesteron—increases connexin 43 receptors and causes preterm labor.
- These receptors increase in gap junction in near term.
- Increases their response to uterotonics.
- Oxytocin receptors less activated at lower uterine segment-isthmus

What are the myometrial and cervical changes of phase 2, preparation for labor?

- Increases in binding between actin–myosin.
- Increases in intracellular cytosolic calcium concentration.
- PGF2α and oxytocin ligand activated calcium channels.
- Calcium is released in the internal stores of the sarcoplasmic reticulum.
- The cervix is mostly composed of connective tissue.
- Proteoglycans and glycosaminoglycans are activated and are affected by hormones that activate myometrium.
- Percentage of cervical glands increases in endocervical epithelium.
- Cervical dilatation can be achieved with prostaglandin E2 and F2α.

What are the characteristics of endocervical epithelium?

- Mucosal epithelium has a protective effect against bacterial and viral agents during pregnancy
- Claudin 1 and 2 tight k-junction proteins serve as protective role
- Collagen I, III, and IV are present in the cervix
- Hyaluronic acid (also called hyaluronan) increases in cervical effacement

What is the feature of the uterine phase 3 of labor?

- Uterine contractions that cause progressive cervical dilatation and the birth of the baby

What are the stages of labor?

- First stage: Time from the beginning of regular pain to complete dilatation.
- Second stage: Time from complete dilatation of cervix to birth of the fetus.
- Third stage: Expulsion of placenta and fetal membranes.
- Puerperium period

What are the characteristics of contractions of uterus?

- Unlike other smooth muscles, uterine contractions are painful.
- Contractions are involuntary and cannot be controlled extrauterine.
- Decrease in pain does not stop contractions.

What are the changes in the pelvic floor at labor?

- The most important structure is the levator ani muscle and the overlying fibromuscular structures.
- Levator ani muscle in the non-pregnant woman is 3–5 mm.

- Thickness increases during pregnancy and wraps vagina.
- Perineum is wedge-wed during labor and goes down to a thin layer (1 cm).
- Anus becomes dilated.

Describe the first stage of labor.
- Latent phase
  - It starts with the feeling of contractions at regular intervals and ends with the increase in cervical opening.
  - The cervix becomes softer, displaced forward, wiped, slowly opening up to 3–4 cm.
- Properties of active phase
  - The frequency and intensity of uterine contractions increase.
  - Acceleration of cervix opening.
  - Average lasts about 3–5 h.
  - When cervical opening reaches 10 cm, the second phase of labor begins.

Describe the second stage of labor
- Time from complete dilatation to expulsion of the fetus
  - >2 h in nulliparas and >1 h in multiparas is considered prolonged

What are the characteristics of real labor pains and contractions?
- Contractions and pain come at regular intervals.
- Contraction does not exceed 1 min and increasingly intensified.
- Pain is felt in the waist and abdomen.
- The cervix is gradually opened and wiped.
- Contractions do not stop with sedation.

What are the characteristics of a false labor?
- Contractions and pain come at irregular intervals.
- Contraction time is long and irregular.
- Pain is felt in the pelvic area.
- Contractions are felt as a generalized abdominal tightening.
- Contractions do not cause progression of labor and dilate cervix.
- Contractions stop with sedation.

What are the changes in the uterus during labor?
- The upper part of the uterus thickens as the labor progresses, and the lower part is passively thinned.
- The upper part contracts, retracts, and pushes the fetus.
- The cervix becomes dilated and like a fibromuscular tube in which the fetus descends.

Which parameters are evaluated in cervical examination (BISHOP)?
- Dilatation and effacement
- Level of the portion that is being presented

- Evaluation of membranes
- Cervical position

How is follow-up done in the first phase of labor?
- Fetal electronic monitoring-Cardiotocography (CTG)
- Contraction follow-up
- Follow-up of vital signs of mother every 4–6 h
- A pelvic examination of every 2–3 h
- Oral intake is stopped, according to recent researches this advise becomes obsolete.
- IV Fluid 60–120 mL/h (electrolyte and 5% dextrose)
- Providing analgesia
- Amniotomy, artificial rupture of membranes, if necessary to accelerate labor

How is follow-up performed in the second stage of labor?
- Duration is important.
- Close fetal monitoring should be performed. FHR should be monitored every 15 min.
- The mother should be taught how to push.

How is follow-up done in the third stage of labor?
- Never pull the placenta. Slow clockwise tractions.
- Consider whether the placenta and its parts are complete.
- Repair of episiotomy and other lacerations.

Explain the detachment findings and types of placenta.
- Uterus becomes round, hard.
- A sudden blood discharge.
- Uterus descends to pelvis after placental detachment.
- Cord length increases as placenta comes down.

There are two types of placental detachment
1. Duncan type: come with maternal side (Dirty-Duncan)
2. Schultze type: Separation of fetal side (Shiny-Schultze)

Describe the cardinal movements of the fetal head during labor.

- **Engagement**
  - The greatest transverse diameter of the head, biparietal diameter, is located pelvic inlet (boundaries: superior border of pubic symphysis, pubic crest on either side, laterally by arcuate lines, posteriorly by sacral promontory)
  - Fetal head enters pelvis transversely (most commonly in occiput transverse-OT, LOT more common than ROT) or enters obliquely at 45° angle to pelvic inlet (right occiput anterior ROA or left occiput anterior LOA; does not enter as direct OA or OP)
  - Leading edge of the spine is at/or below station 0.

- **Descent:** Fetal head descends to pelvic floor. In nulliparas descent occurs during second stage of labor, but generally in multiparas it happens while fetal head engages to pelvic inlet.
- **Flexion:** Chin is brought towards the chest by flexion of the fetal head.
- Fetus enters the maternal pelvis with suboccipitobregmatic diameter which is shorter than occipitofrontal diameter (9.5 cm versus 12 cm).
- **Internal rotation:** The occiput portion of the head normally stays transverse position then occiput rotates from the transverse position towards anteriorly to symphysis pubis.
- Rotates into direct OA position (more common) or direct OP.
- **Extension:** The head which is flexed, extends to out of the symphysis pubis, delivery of the fetal head. The fetal chin turns downwards to lie over maternal anus.
- **External rotation (restitution):** The head that has completed its birth does the opposite of its internal rotation movement.
- **Expulsion:**
  - The front shoulder is delivered then the back shoulder. The rest of the body is born easily.

What is synclitism?
- Normal position of the fetal head in pelvic inlet, sagittal suture lies halfway between pubic symphysis and sacral promontory

What is anterior asynclitism?
- Asynclitism: oblique malpresentation of the fetal head in labor
- Fetal head's sagittal suture deflects towards sacral promontory, anterior parietal bone is designated the point of presentation.

What is posterior asynclitism?
- Fetal head's sagittal suture deflects towards pubic symphysis, posterior parietal bone is designated the point of presentation.

What is Ritgen maneuver?
- The Ritgen maneuver is defined as one hand on the emerging occiput to control the speed of delivery and keep flexion of the fetal head while with the other hand the fetal chin was reached behind the anus and lifted forward.
- This prevents damage to the urethra and protects the perineum.

What is the definition of the episiotomy?
- Episiotomy, a surgical cut of the vagina and perineum carried out by a skilled birth attendant to enlarge the vaginal opening, is sometimes used in an attempt to prevent serious perineal damage caused by tearing and to facilitate the birth of the baby.
- When the fetus head comes to the perineum in the labor and causes the perinea to rise, it is applied to break the perineum resistance and prevent possible tears.
- It is approximately 4–5 cm incision in the vulva.

What are the main types of episiotomy?

- Actually there are seven ways of performing an episiotomy, with "median" and "mediolateral" being the two main types of episiotomy in the literature and medical practice
- **Median:** Midline episiotomy. A vertical incision from the posterior fourchette and runs along the midline through the central tendon of the perineal body. Less bleeding is seen, easier to repair, but may extend to anal sphincter. Postoperative pain is rare. Cosmetically better.
- **Mediolateral:** An incision beginning in the midline and directed laterally and downwards away from the rectum, there is more bleeding, it is less likely to reach the anal sphincter, and repair is more difficult than median, postoperative pain is frequent.

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Chapter 16
Operative Births and Cesarean Section

What is the definition of cesarean section (C/S)?

- Delivery of the living fetus older than 20 weeks, and 500 g, by abdominal incision through the uterine wall.

What are the indications for C/S?

- Previous cesarean delivery, relative indication, since vaginal birth after cesarean (VBAC) is another option, but VBAC is contraindicated in classical vertical uterine incision.
- Failed induction
- Prolonged and obstructed labor (protracted labor)
- Fetal distress
- Dystocia, suspected fetopelvic disproportion
- Fetal malpresentation
- Very low birth weight
- Placenta previa
- Placental abruption
- Multiple pregnancy
- Cord prolapse
- Severe pre-eclampsia, HELLP syndrome or eclampsia
- Maternal infections (e.g., HIV (in case of high viral load), active genital herpes simplex)
- Fetal coagulation defects

What are the C/S types in terms of skin incisions?

- The skin incision may be vertical (midline or paramedian) or transverse lower abdominal (Pfannenstiel, Joel-Cohen, Pelosi, Maylard, Mouchel, or Cherney).
- Transverse incision is usually preferred about 2–3 cm above the pubis in the abdominal wall.

Acknowledgments The author would like to thank Dr. Aykut Barut who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_16

What are the advantages of transverse skin incisions?
- Less bleeding
- Less postoperative pain
- Less wound infection
- Anatomical
- Easier recovery in the postoperative period
- Esthetic concerns

What are the C/S types in terms of uterine incisions?

1. Incisions in the upper segment of corpus uteri:
   - Classic incision: Vertical incision in the upper segment of the uterus, generally preferred in cases with placenta previa.
2. Incisions in the lower segment of the uterus: These incisions are made in the lower segment of the uterus and require the bladder to be pushed down to expose the lower segment.
   - Lower segment transverse incision (Munro Kerr): The most common incision type in C/S. 2–3 cm below the upper edge of the uterovesical fold of peritoneum
   - Lower segment vertical incision: Rarely preferred method, generally for large fetuses, not to extend laterally to the uterine arteries as in vertical incision.

What are the early complications of C/S?
- Early complications: intraoperative damage to organs such as the bladder or ureters and general postoperative complications
- Various complications including fever, endometritis, wound infection, bleeding, aspiration atelectasis, urinary tract infection, thromboembolism, pulmonary embolism may be observed.
- Maternal mortality is about 1–2/1000. About 25% of these are related to anesthesia complications.
- Febrile morbidity, need for blood transfusion, thromboembolic complications, anesthesia-related complications, pyelonephritis, pneumonia, and sepsis are more common in cesarean than vaginal delivery
- When elective cesarean and vaginal delivery are compared in perinatal death and neurological sequelae, the risk is doubled in C/S.

What are the late complications of C/S?
- Bowel obstruction due to adhesions.
- Dehiscence of uterine incision in next pregnancy, cesarean scar pregnancy.
- These complications are more common in classical vertical caesarean section.

What is forceps?
- Forceps is an instrument used to facilitate delivery or accelerate the progression of the presenting fetal head (stage 2 of birth) without causing trauma to the mother and fetus.

What are the properties of forceps?
- Consists of two lockable parts at the articulation.
- Blades (branches), body, lock, handle.
- Cephalic curvature of the fetal head and pelvic curvature of the pelvic axis.
- 15–18 cm.
- They are basically composed of two pieces that cross each other.
- Each blade has two curves, cephalic, and pelvic.
- The cephalic curvature adapts to the shape of the fetal head, while the pelvic curvature fits the shape of the birth canal.

What are the types of forceps?
- Classic
  - Simpson
  - Tucker-Mclaine
- Special
  - Piper: Used for breech presentation to facilitate delivery of the after coming fetal head. Since the blades have no pelvic curve, a deep episiotomy should be performed to prevent damage to the vagina and perineum.
  - Kjellant: Used for occiput posterior and occiput transverse presentation
  - Barton: Used for rotation especially in deep transverse arrest in a platypelloid pelvis, occiput transverse delivery of the fetus.

What are the conditions for forceps application?
- Bladder and rectum should be empty.
- Fetal head position should be well evaluated.
- Fetal position is compatible with vaginal delivery, cephalopelvic disproportion should be assessed.
- The head must be engaged in the pelvis.
- Head or anterior face of the mentum should be present.
- Cervical patency and wiping should be complete.
- Membranes should be ruptured.

What are the indications of forceps?
- Maternal indications, conditions that make pushing, straining difficult
- Heart disease
- Pulmonary insufficiency
- Specific neurological conditions
- Excessive fatigue
- Prolonged second phase of the action
  - In nulliparous women, prolonged second stage of labor is defined as failure of progress more than 4 h when epidural analgesia is used and more than 3 h when not used.
  - In multiparous women, prolonged second stage of labor is defined as failure of progress more than 3 h when epidural analgesia is used and more than 2 h when not used.

What are the types of forceps?

- Outlet forceps
  - The fetal head must have reached the vaginal introitus, scalp is visible at the introitus (crowning).
  - Sagittal suture, pelvic outlet should be in the anteroposterior plane.
  - Rotation does not exceed 45°.
- Low forceps
  - Fetal head is at +2 station or above, and not reaching the pelvic floor.
  - No restriction on rotation.
- Mid forceps
  - Fetal head is above +2 station, but fetal head is engaged.
- High forceps
  - Fetal head is not engaged, not used in current obstetrics practice.

What are the maternal complications of forceps?

- Tears in the perineum, vagina, and cervix
- Anal sphincter injury
- Vesicovaginal, rectovaginal fistula
- Postpartum infection: metritis
- Uterine rupture
- Increased recovery time

What are the fetal complications of forceps?

- Laceration of the head and face
- Abrasions
- Facial nerve injury
- Fracture of the scalp, clavicle
- Intracranial hemorrhage

What does vacuum extraction mean in obstetric practice?

- Tools used to apply traction and suction to the fetal scalp to assist the birth of the fetus are called vacuum extractors.
- An applicator is applied to the fetal scalp by applying negative pressure, and it helps to deliver the fetus without harm to the mother and fetus by traction.

What are the appropriate conditions for applying the vacuum?

- The fetal head must be engaged in the maternal pelvis.
- Membranes must be ruptured.
- Cephalopelvic disproportion should be ruled out.
- Bladder and rectum should be empty.
- Fetal head position should be well evaluated.
- Complete cervical dilation should be confirmed.

What are the advantages of vacuum extraction over forceps?

- Avoiding steel blades lacerations in the vagina

- Allowing rotation of the fetal head without damaging the maternal tissues
- Less intracranial pressure encountered during traction with vacuum

What are the fetal complications of the vacuum?
- Most often called chignon
- Intracranial hemorrhage
- Subgaleal hematoma
- Subconjunctival bleeding

What are the complications of episiotomy?
- Infection, hematoma, cellulitis, abscess
- Perineal laceration, dehiscence
- Rectal incontinence
- Pudendal nerve injury
- Necrotizing fasciitis
- Rectovaginal fistula

What are the risk factors for birth trauma?
- Cephalopelvic disproportion (CPD)
- Preterm birth
- Prolonged or rapid delivery
- Malpresentation
- Macrosomia

What is the most frequently injured fetal nerve at birth?
- Facial nerve.
- It develops as a result of forceps or spontaneous birth. Prognosis is good.

Describe the Erb-Duchenne paralysis.
- C5, C6, C7 nerve roots are affected. The most commonly involved root is C5.
- Obstetric brachial plexus palsy.
- Waiter's tip (biceps damage).

Describe the Klumpke paralysis.
- C8, T1 nerve roots are affected.
- Obstetric brachial plexus palsy.

What are the risk factors for fetal Erb-Duchenne and Klumpke paralysis?
- Macrosomia
- Shoulder dystocia
- Forceps–vacuum births
- Breech delivery
- Prolonged or rapidly progressive birth
- Previous birth history of brachial palsy
- Male fetus
- Maternal DM

Which injuries can accompany dystocia?
- Clavicle fractures
- Humerus fractures

- Fracture, subluxation of shoulder girdle
- Torticollis
- Facial nerve paralysis
- Phrenic nerve paralysis (C3–C5)
- Horner's syndrome (ptosis, miosis, enophthalmos)

What is the prognosis of nerve paralysis at birth in infant?
- 95% spontaneous recovery.
- 92% of them recover in the first 3 months.
- Physiotherapy for the first 3–6 months.
- If not resolved, surgery is applied, usually after 6 months.

What are the internal organ hemorrhages in the infant at birth and how do they occur?
- Especially after breech births.
- Most commonly liver damage is encountered.
- Splenic rupture and rarely adrenal hemorrhage.

What is the most easily broken fetal bone at birth?
- Clavicle

What is the incidence of birth fracture of the clavicle in vaginal births?
- Birth fracture of the clavicle occurs in approximately 0.4–10% of vaginal births.

What is the most common symptom of clavicle fracture in newborns?
- The most common symptom is decreased movement of the ipsilateral arm.

What is sternocleidomastoid hematoma?
- Swelling appears in the middle of the muscle 2–4 weeks after birth.
- Head inclined to the lesion side (congenital torticollis).
- Prognosis is good.

What is the caput succedaneum?
- Edema or swelling of the skin of the fetal scalp.
- Bleeding below the scalp and above the periosteum, crossing sutures.
- It develops as a result of vaginal birth.
- Resolves in 2–3 days.
- Most commonly in the parietal and occipital regions.
- The event is above the periosteum.
- In addition to edema, hemorrhage may occur.
- It usually develops secondary to vacuum or instrument deliveries.

What is cephalic hematoma?
- Subperiosteal bleeding.
- Since bleeding occurs slowly, swelling does not occur at birth but occurs several hours after birth.
- May cause anemia and jaundice.
- Does not cross the sutures
- No color change in the scalp
- Hematoma may be infected; Abscess, osteomyelitis, and meningitis may develop.

- Hematoma resorbs within 1–2 months.
- Skull fractures may accompany

What is the importance of subconjunctival hemorrhage in the fetus?
- It is common after difficult births and has no clinical significance. It resolves spontaneously.

Describe fetal subdural bleeding.
- Hemorrhage below the dura mater and above the arachnoid membrane due to mechanical trauma.
- Since superficial veins do not develop in preterm fetuses, this type of bleeding is more common in term newborns.

Describe fetal epidural bleeding.
- Usually the dura vessels are torn; medial meningeal artery or its branches. Sinus sagittalis superior can also be torn.
- Since dura is loosely attached to the bones, the dura is separated from the bones and a true epidural space is formed when bleeding occurs between dura mater and the skull of the fetus.
- In these hemorrhages, intracranial pressure increase, herniation and oculomotor paralysis are common because the hematoma is above the tentorium cerebelli.

Describe fetal intraventricular hemorrhage.
- Most commonly seen in preterm fetuses. Bleeding in germinal matrix.
- Bleeding may spread to the subarachnoid space.

Describe fetal subarachnoid hemorrhages.
- It usually develops after asphyxia and coagulopathy rather than birth trauma. It presents with bloody CSF and convulsions.
- May cause hydrocephalus.

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Chapter 17
Preterm and Postterm Pregnancies

Describe these situations: preterm labor, preterm birth, prematurity, low birth weight.

- Preterm labor
- Contractions that occur more frequently than 10 min or more after the 20th week of gestation and before the 37th gestational week are accompanied by one of the following:
  - Progressive cervical change.
  - 80% or more of the cervical effacement.
  - Dilation of cervix 2 cm or more.
- Preterm birth
  - Births before 37th gestational week (viable gestational age is minimum 24 week).
  - Delivery starts after gestational viability begins (20–28 weeks) but before 37 weeks of completion.
  - Preterm birth is 7–10% of all births.
  - 75–85% of neonatal deaths without anomalies.
- Prematurity
  - Babies born before 37th gestational week.
- Low birth weight
  - Babies born below 2500 g. If it is below 1500 g, it is called a very low birth weight.

Acknowledgments The author would like to thank Dr. Mehmet Can Nacar who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_17

What are the diagnostic criteria of preterm delivery?

- Uterine contractions (at least twice in 20 min or 6 times per hour) and
- Rupture of fetal membranes or
- 2 cm or more cervical dilatation and/or
- Cervical length is less than 1 cm in ultrasound (US)
- Eighty percent or more cervical wiping
- If there is less clearance and wiping in the first examination, progression in clearing and wiping is also sufficient for the diagnosis of preterm labor at least 30 min and 2 h later, preferably by the same doctor.

What are the symptoms of preterm labor?

- Suprapubic pressure sensation.
- Increased vaginal discharge.
- Backache.
- Menstrual-like cramps.
- These symptoms may also occur in normal pregnancies, but most are nonspecific.
- Prospective studies have shown that these symptoms have low predictive value for the diagnosis of preterm labor.

What are the risk factors for preterm labor?

- Dehydration.
- Premature rupture of membranes (PROM).
- Cervical insufficiency.
- Infections.
  - Urinary tract infections.
  - Cervical and vaginal infections.
- Group B streptococcus (GBS).
- Bacterial vaginosis (BV).
- Stretched and large uterus.
  - Polyhydramnios.
  - Multiple pregnancy.
- Uterine anomalies.
  - Myoma uteri.
  - Septate uterus, etc.
- Placental problems.
- Smoking, cocaine use.
- There is no reason for the majority of preterm patients.

What are the risk factors for preterm labor?

- Maternal
  - Age <18 and >35
  - Genetic, racial
  - Weight (<50 kg)

  - Alcohol/cigarettes
  - Previous genital infections
  - Illicit Drug use
- Obstetric history
  - History of preterm birth (35%)
  - Second trimester miscarriages
  - Uterine cervical anomalies
- Socioeconomic factors
  - Low social status, poor economic situation
  - Insufficient antenatal care and support

What are the risk factors for preterm birth?

- **Fetal and placental**
  - Bleeding in first or second trimester
  - Antepartum hemorrhage with placenta previa
  - Intrauterine infection
  - PROM
  - Intrauterine growth restriction (IUGR)
  - Congenital fetal anomalies
  - Multiple pregnancies
  - Polyhydramnios
  - Congenital uterine anomalies
- **Maternal**
  - Severe maternal diseases
  - Preeclampsia
  - Urinary tract infections with asymptomatic bacteriuria
  - Maternal infections
  - Lower genital infections
  - Psychological stress
  - Cervical insufficiency
  - Myoma uteri
- **Idiopathic**
  - In fact, when this group is examined thoroughly, true idiopathic preterm birth is 1%.
  - This group is associated with intrauterine infection, placental ablation, placenta previa, uterine factors, polyhydramnios, cervical insufficiency, immunological factors, maternal factors, and trauma.

Describe the problems seen in preterm babies.

- Acute complications
  - Respiratory distress syndrome (RDS)
  - Intraventricular hemorrhage (IVH)

  - Necrotizing enterocolitis (NEC)
  - Sepsis
  - Convulsions
  - Jaundice and kernicterus
- Long-term sequelae
  - Bronchopulmonary dysplasia (BPD)
  - Retrolental fibroplasia
  - Cerebral palsy (CP)
  - Developmental problems

What is the main purpose of treatment of patients with preterm labor?
- Prevention of contractions
- Prevention of fetal complications
  - Lung maturation
    - Corticosteroids
    - TRH (thyrotropin-releasing hormone)
    - Ambroxol
  - Intraventricular bleeding
    - Phenobarbital
    - Vitamin K
  - Magnesium sulfate (neuroprotective effects)

What is respiratory distress syndrome, which is a complication of preterm delivery in infants?
- This results from immature lungs that are unable to sustain necessary oxygenation. Resulting hypoxia is an underlying associated cause of neurological damage such as cerebral palsy. In addition, hyperoxia, a side effect of RDS treatment, contributes to morbidities such as bronchopulmonary dysplasia, pulmonary hypertension, necrotizing enterocolitis, periventricular leukomalacia, and retinopathy of prematurity.

In which situations treatment of preterm labor is contraindicated?
- If the labor is in the late stage
- If the fetus is mature (lung maturation is shown or over 34 weeks)
- Presence of fetal anomaly
- Presence of chorioamnionitis symptoms objectively
- Presence of severe vaginal bleeding
- Presence of fetal distress status
- Presence of maternal factors
- Stillbirth

What are the tocolytic agents that can be used to prevent contractions in the treatment of preterm labor?
- Hydration

- Beta-mimetics (ritodrine, terbutaline)
- Calcium channel blockers (nifedipine)
- Magnesium sulfate
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Atosiban (an inhibitor of oxytocin)
- Nitric oxide donors

What is the main purpose of tocolytic agents in preterm labor?
- Save time for corticosteroids to work, generally 48 h.

Describe beta-sympathomimetics—beta-agonists (ritodrine, salbutamol, and terbutaline).
- They show their effects by increasing intracellular cAMP.
- Reduce myometrial contraction by reducing intracellular Ca.
- Continuous administration limits receptor agonist detachment and receptor number within 24 h and causes desensitization (downregulation).
- Beta-adrenergic can be given with IV, IM, SC, oral routes.
- Dextrose should be used instead of NaCl to reduce pulmonary edema risk.
- Start with low dose and adjust dose according to uterine contraction and maternal tachycardia.

What is the mechanism of action of magnesium sulfate in preterm labor?
- Reduces intracellular Ca, reduces Ach release and nerve sensitivity.
- Actin and myosin activation is inhibited.

Do you know any other neuroprotective agents for preterm pregnancies?
- Few specific treatments have been identified to reduce or prevent brain injury in the vulnerable preterm newborn. One potential neuroprotective therapy is with erythropoiesis-stimulating agents (ESAs) such as erythropoietin and darbepoetin. In addition to stimulating erythropoiesis, ESAs are protective in the developing brain in animal models. Preliminary clinical studies are encouraging, and large trials are now underway.

What is the mechanism of action of calcium channel blockers in preterm labor?
- Reduce intracellular Ca^{++} by blocking Ca^{++} channels in myometrial cells.
- The most effective is nifedipine; prevents Ca from entering the cell through voltage-gated channels in the cell membrane.

What is the mechanism of action of prostaglandin (PG) inhibitors in preterm labor?
- Decrease prostaglandin synthesis by inhibiting cyclooxygenase enzyme, reducing cervical maturation and uterine contractions.
- Most commonly used agent is indomethacin.
- PG synthesis inhibitors pass from mother to fetus, prolong bleeding time, show cardiopulmonary side effects (early closure of ductus arteriosus or complete obstruction as a result of persistent fetal circulation).

- May cause renal dysfunction or decrease in urine output, so it is also used in the treatment of polyhydramnios.
- It is recommended to use for a short time between 32nd and 34th weeks, because of the risk of early closure of the ductus arteriosus.

What is the mechanism of oxytocin antagonist, atosiban (IV route) in preterm labor?

- Competitively inhibits oxytocin receptors
- Reduces the frequency of contractions when infused for 2 h
- Very low side effects
- Very few amount of it passes through the placenta

What are the fetal adverse effects of beta-sympathomimetics?

- Beta-sympathomimetic agents can cross the placenta and affect distressed fetuses with fetal tachycardia and other possible side effects.
- Although the information is not sufficient, there is some information about intracranial hemorrhage.

What are the fetal adverse effects of magnesium sulfate?

- Magnesium sulfate can also cross the placenta and cause difficulties in fetal cardiac activity. They decrease the variability of basal fetal heartbeat, in nonstress test (NST).
- There may be hypotonicity and hypocalcemia due to hypermagnesemia.

Which type of delivery is preferred for preterm labor?

- Generally, vaginal route should be preferred in the delivery of fetuses which have not completed 24 weeks.
- Evaluation between 24 and 34 weeks is no different than that of more than 34 weeks, but usually if the fetus is less than 2500 g, namely low birth weight, elective cesarean is preferred in order to improve fetal survival by reducing hypoxic stress, asphyxia, and intraventricular hemorrhage, albeit it is not strongly evidence based.
- Electronic monitoring and fetal presentation are important:
  - Vacuum extraction should be avoided for variability reduction and late decelerations. C/S should be performed to reduce intracranial complications under breech arrivals and under 1750 g.

Describe fibronectin, the only biochemical marker with predicted value for preterm labor today.

- Extracellular matrix protein normally found in fetal membranes and decidua.
- Detection of fibronectin up to 20 weeks is possible because the amniochorion is not fully fused with the decidua.
- Presence after 20 weeks indicates destruction in the chorion-decidua region and seen as a precursor to preterm labor.
- Normally reappears in cervicovaginal secretions near term period.
- It has high sensitivity and negative predictive value in determining preterm labor.

Describe the transvaginal sonography of the cervical length in predicting preterm labor.

- Can be used in all three trimesters of pregnancy.
- Unlike transabdominal ultrasound, it is not affected by bladder fullness and patient position.
- Cervical length over 30 mm is proof that there is no significant effacement.
- An objective method of evaluating the cervix (evaluation of the internal os is not possible, especially if the external os is closed).
- Changes in cervical length begin 10 weeks before birth, while changes that can be detected in the examination can be noticed 3–4 weeks before.
- Measurement between internal and external os.
- Funneling of membranes into the cervical canal: high risk of preterm birth.

What is the role of amniocentesis in the determination of fetal pulmonary maturation?

- Diagnosis of subclinical amniotic fluid infection.
- Pregnant women with amniotic fluid culture (+) have a high risk of membrane rupture and delivery within 48 h.
- Amniocentesis culture was positive in 20% of preterm pregnant women whose membranes were intact and had no signs of clinical infection.
- Routine amniocentesis is not recommended.

What is the meaning of preterm premature rupture of the membrane (PPROM)?

- PPROM is the rupture of membranes before the 37th week of pregnancy (amniorrhexis)
- If there is no delivery within 24 h following membrane rupture, this is defined as prolonged premature rupture of membranes.

How is PROM diagnosed?

- Careful history and physical examination
- Sterile speculum examination: Clear fluid flow from cervix, fluid pooling in posterior fornix
- Nitrazine test
- Formation of fern image in microscopic examination
- Ultrasound: Does oligohydramnios exist?
- Amnioinfusion staining: In cases of doubt, the release of 100–200 mL of lactated Ringer's solution or indigo carmine dye (1 mL of dye in 9 mL of isotonic solution) to be given in the form of amnioinfusion, and these dyes discharging from the vagina are used in the diagnosis.
- Follow-up for intrauterine infection:
  - Maternal blood:
    - ESR >60 mm/h
    - WBC >15,000/mm^3
    - CRP ≥2 mg/dL

- Amniotic fluid
  - Glucose <17 mg/dL
  - WBC ≥20 cells/mm^3
  - IL-6 >7.9 ng/mL

What is the first test to be affected in a third trimester fetus with intrauterine infection?

- The first test to be affected is the reactivity of NST, followed by a decrease in respiration in biophysical profile of the fetus.

What are the increased risk of infection and findings related to chorioamnionitis?

- Increased risk of infection in extreme oligohydramnios with ultrasonographic measurements with deepest amniotic fluid pocket <1 cm.
- On Doppler ultrasonography, a 15% increase in umbilical artery S/D ratio compared to the first measurement is associated with histological chorioamnionitis.
- Nonreactive fetal heart rate and fetal tachycardia are closely related to intrauterine infection.
- Fetal respiratory movements are reported to decrease from 90% to 65% after PPROM, and if there is infection, this value is reported to be as low as 35%.

What are the definitions of postterm and postmature pregnancies?

- Postterm pregnancy
  - The most commonly used definition is the 42nd gestational week (or 294 days) and above according to the last menstrual period.
  - Pregnancies that have completed the 42nd gestational week or exceed 294 days are defined as postterm or prolonged pregnancies.
  - The incidence in all pregnancies is 3–12%. Pregnancy longer than 43 weeks 4%.
- Postmature pregnancy
  - It is called the clinical appearance of a newborn baby showing a pathologically prolonged pregnancy, sometimes called dysmaturity syndrome.
  - Postmaturity occurs in 10% of postterm pregnancies; infant wrinkled, partially peeled skin, long thin body structure, elongated nails are typical in postmaturity syndrome, and some are born with serious problems such as asphyxia and meconium aspiration.

How is the fetal mortality rate increase in postterm pregnancies?

- Perinatal mortality increases in pregnancies older than 42 weeks.
- Two times in 43 weeks.
- 4–6 times in 44 weeks.

What are the etiologic factors, risk factors of postterm pregnancies?

- Anatomical or biochemical abnormalities in the fetus or amniotic fluid
- Maternal pituitary dysfunction
- Congenital anomaly in the fetus (adrenal hypoplasia)
- Anencephaly

- Deficiency of placental sulfatase, low E3
- NSAID medications
- Postterm delivery of previous birth

What are the fetal and placental outcomes of postmaturity?

- Fetal
  - Weak and old appearance due to decreased subcutaneous adipose tissue
  - Dry, wrinkled, and occasionally peeled skin due to decreased vernix caseosa
  - In case of meconium, green/yellow painted nails, skin, membranes
  - Long nails
  - Thin limb
  - Skin peeling
  - Macrosomia: more frequently
  - Shoulder dystocia
  - Trauma to birth brachial plexus palsy
  - Cephalic hematoma
  - Compared to 40 weeks of gestation
    - The possibility of meconium amniotic increased from 19 to 27%
    - Meconium aspiration from 0.6 to 1.6%
    - Increases in oligohydramnios
- Placental
  - Calcification
  - Villous edema
  - Syncytial pseudo-hyperplasia-syncytial nodes
  - Fibroid degeneration of villi
  - Placental microinfarcts

Describe a baby who has diagnosed with postmaturity syndrome.

- The postmature newborn is unique, and features include wrinkled, patchy, peeling skin; a long, thin body suggesting wasting; and advanced maturity in that the infant is open-eyed, unusually alert, and appears old and worried.

What is the management of postterm pregnancies?

- Birth induction if Bishop score is above/or 8. Weekly cervical examination after 41–42th week.
- C/S ratio increases in postterm pregnant women
- Biophysical profile (BPP)
  - BPP: twice a week after 40 weeks
  - Zero or two points for each category.
    - Most important is amnion fluid measurement (AFI)
    - NST
    - Fetal body movements
    - Respiratory movements
    - Flexion

Describe general information about the histological features of fetal membranes.

- The epithelium of the amniotic membrane is unilamellar, 0.02–0.05 mm thick and without vein, and the underlying connective tissue contains dense collagen fibers.
- The chorion membrane is composed of 4–6 cubic cell layers of 2–10 mm thickness, adhering to the decidua and showing dense veining.

What are the risk factors for PROM?

- Infection (cervico-vaginitis); microorganisms cause the release of proteolytic enzyme (proteases). Proteases facilitate rupture formation by reducing membrane strength and elasticity.
- The most important microorganisms are chlamydia, mycoplasma, and group B streptococci.
- Membrane rupture occurs mostly in the lower pocket because the infection is caused by ascending infection.
- Cervical insufficiency; increased risk of infection and PROM in the presence of silent cervical dilatation.
- The risk of PROM and chorioamnionitis increases as a result of cervical cerclage operation.
- Smoking.
- Invasive procedures applied to the cervix.
- Placenta, low-lying.
- Ehlers Danlos syndrome (X-linked recessive connective tissue disease).
- PROM in obstetric history.

Explain the approach to PROM after 36th gestational week.

- In case of: 3 cm cervical dilatation.
- Suspected chorioamnionitis.
- Presence of group B streptococci in vagina.
- Nonreactive NST.
- Poor biophysical profile (<6).
- Oligohydramnios.
- Meconium-containing amniotic fluid.
- IUGR.
- Preeclampsia, it is not expected; birth is induced.
- If these situations are not the case
  - There are many centers that accept this waiting time as 12 h. Conditions beyond 12 h are considered prolonged PROM.
  - In these pregnant women, 50% of delivery starts in the first 12 h and 95% starts in 48 h.
  - The most important risk factor is infection, namely chorioamnionitis.
  - Fetal tachycardia, nonreactive NST, uterine tenderness, high fever, malodorous vaginal discharge, leukocytosis, sedimentation. and elevated CRP are in favor of clinical chorioamnionitis.

Describe the approach to PPROM between 32 and 36 weeks.
- If fetal lung maturation can be evaluated well at 32–36 weeks, expectant approach can be tried.
- Waiting increases the length of hospital stay and the risk of infection.
- If pulmonary maturation test cannot be performed, corticosteroid should be administered and appropriate antibiotic therapy should be initiated and followed closely.
- When evaluating, mature cases should be managed as mature term pregnancy.

Describe the approach to PPROM between 23 and 31st gestational weeks.
- The most challenging group, we sought to extend the gestational age as long as possible.
- High risk of perinatal mortality and morbidity.
- Abruptio placenta, infection, and umbilical cord compression are possible complications.
- Bed rest is recommended (although not proven); recurrent digital pelvic examination should be avoided.
- Antibiotics (prevention of chorioamnionitis).
- Corticosteroid and $MgSO_4$.

Describe the approach to PPROM cases before 23rd gestational week.
- Approximately 50% give birth in 1 week
- One out of five pregnancies lasts for 1 month
- Risks such as chorioamnionitis, endometritis, rest placenta, postpartum hemorrhage, and sepsis are life-threatening risks.
- Motor development problems, cerebral palsy, chronic lung diseases, hydrocephalus, and mental retardation may be very important in newborns whose latent period is prolonged and can survive after follow-up.
- In addition to the wait-and-see method, new modalities are being tested on a study basis such as amnioinfusion, fibrin/cryoprecipitate/platelet infusion.

Explain antibiotic therapy in PROM.
- Penicillin can prevent GBS complications.
- 4 × 1 (2.5 M) iv penicillin or 4 × 1 g ampicillin during delivery following an initial dose of five million units.
- Erythromycin or clindamycin is used in patients with penicillin allergies.

Describe corticosteroid treatment and positive effects in PPROM.
- The most commonly used protocol is betamethasone, two doses of 12 mg given intramuscularly 24 hours apart, namely 2 × 6 mg other day again 2 × 6 mg. Dexamethasone is another method that not preferred as betamethasone, applied four doses of 6 mg given intramuscularly 12 hours apart.
- Reduction in the incidence of respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), and Necrotizing enterocolitis (NEC)

What is the purpose of tocolysis in PROM?
- Tocolytic therapy can be tried for a short time to save time for the effectiveness of corticosteroid (48 h) and antibiotic therapy.

What are the fetal pulmonary maturation tests?

- Lecithin sphingomyelin (L/S) ratio > 2/1 (if the pregnant woman has diabetes, Rh incompatibility and fetal asphyxia, no exact result can be obtained—Phosphatidylglycerol -PG is more reliable)
- Phosphatidylglycerol (PG) determination >3%
- Fluorescence polarization (TDXFLM II) total surfactant activation test: >70
- Determination of lamellar bodies
- Phosphatidylinositol
- Desaturated lecithin >1500 in nondiabetic patients, >2000 in diabetic patients

Describe adverse maternal and perinatal outcomes associated with postterm pregnancy

- Maternal:
  - Fetal macrosomia
  - Oligohydramnios
  - Preeclampsia
  - Cesarean delivery
    - Dystocia
    - Fetal jeopardy
  - Shoulder dystocia
  - Postpartum hemorrhage
  - Perineal lacerations
- Perinatal:
  - Stillbirth
  - Postmaturity syndrome
  - Neonatal intensive care unit (NICU) admission
  - Meconium aspiration
  - Neonatal convulsions
  - Hypoxic-ischemic encephalopathy (HIE)
  - Birth injuries
  - Childhood obesity

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Chapter 18
Pregnancy and Diabetes Mellitus

What is the definition of gestational diabetes (GDM)?
- It is a form of glucose tolerance disorder that starts in pregnancy or is noticed for the first time in pregnancy.

What are the prevalence and characteristics of gestational diabetes?
- The most common medical problem during pregnancy.
- 7% diabetes + pregnancy.
- Diabetes during pregnancy increases over the years, the rate of type 2 diabetes increases due to obesity.
- Fetal fat cells increase due to hyperglycemia exposure in the womb, insulin resistance, and obesity increase in adult life.

What are the features of the patients who are strongly suspected of having diabetes?
- Strong family history of diabetes
- Maternal age > 25
- History of having a large (macrosomia) baby
- Persistent glycosuria
- Obesity
- Unexplained stillbirth or fetal death history

What is the pathophysiology of GDM?
- GDM is similar to type 2 diabetes (DM).
- 90% resistance of insulin receptors.
- Increased fat in the abdomen.
- 10% insufficiency in insulin production
- Carbohydrate intolerance
- Estrogens increases insulin and cortisol levels

Acknowledgments The author would like to thank Dr. Mehmet Can Nacar who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_18

- Progesterone increases insulin usage
- Human placental lactogen (hPL) blocks insulin receptors
- Growth hormone, as well.
- Placental insulinase

What are the metabolic changes associated with carbohydrates in pregnancy?
- Fasting hypoglycemia
- Postprandial hyperglycemia
- Hyperlipidemia
- Hypoaminoacidemia

How would you make a diagnosis of GDM?
- 50 g OGTT should be performed between 24 and 28 weeks of gestation not requires the patient to be fasting.
- 50 g glucose test after 1 h should be less than 140 mg/dL.
- Fifteen percent positive result.
- If fasting blood glucose (FBG) is 126 mg/dL or blood sugar is 190–200 mg/dL at any time, it is diagnosed as diabetes.
- 100 g OGTT is performed if 50 g glucose test of 1 h is above 140 mg/dL:
  - 0 h, 105 mg/dL, or 95 mg/dL
  - First hour, 190 mg/dL, or 180 mg/dL
  - Second hour, 165 mg/dL, or 155 mg/dL
  - Third hour, 145 mg/dL, or 140 mg/dL
- Diagnosis is made if two values are high.
- If one value is high, OGTT is repeated after 1 month.

What are the limit values of 75 g oral glucose test?
- Fasting: 5.3 mmol/L (92 mg/dL)
- Hour 1: 10 mmol/L (180 mg/dL)
- Hour 2: 8.6 mmol/L (153 mg/dL): diagnosis of GDM is done when one glucose value is elevated

What are the types of diabetes detected during pregnancy?
- Type I (IDDM) (insulin dependent)
- Type II (NIDDM) (insulin independent)
- Type III (GDM)
- Type IV (Secondary DM) (drug-chemical-induced steroids, etc.)

Explain the types of diabetes according to the White classification.
- Class A1: Diet controlled GDM (FBG <105 or toughness <120)
- Class A2: Abnormal fasting and postprandial glucose levels by abnormal glucose tolerance test; GDM required insulin (GDM complicated by hypertension, polyhydramnios, macrosomia or stillbirth)
- Class B: Insulin-treated diabetic patients who develop diabetes after the age of 20 or have diabetes for less than 10 years
- Class C: Diabetic patients between the ages of 10–19 or 10–19 years with diabetes

- Class D: People with diabetes starting under 10 years of age or for more than 20 years
- Class E: Pelvic arterial calcification
- Class F: Nephropathy (>500 mg/day proteinuria)
- Class H: Arteriosclerotic heart disease (ASHD)
- Class R: Proliferative retinopathy or vitreous hemorrhage
- Class T: Renal transplantation

What are the complications of diabetes during pregnancy?

- Hypertension
- Preeclampsia
- Urinary infections
- Increased rate of caesarean section
- IUGR
- Increased congenital malformations (2–6 times more)
- Increase in maternal mortality by ten times
- Diabetic nephropathy
- Diabetic retinopathy
- Diabetic ketoacidosis
- Diabetic neuropathy
- Birth trauma, shoulder dystocia
- Intrauterine exitus
- Neonatal hypoglycemia
- Hypocalcemia
- Hyperbilirubinemia
- Polycythemia
- Respiratory distress syndrome
- Fetal macrosomia
- Cardiomyopathy

What are the congenital malformations related to diabetes?

- In patients without diabetes control (especially increase in values above 7.9% of Hb A1c).
- If Hba1c > 10%, 23% major fetal malformations are observed.
- Situs inversus increases by 84 times.
- Duplex ureter increases by 23 times.
- Sacral agenesis-caudal dysplasia increases to 252.
- Anencephaly (10×).
- Open spina bifida (10×).
- Holoprosencephaly (10×).
- Microcephaly, encephalocele, and meningomyelocele increase.
- Heart anomalies (VSD and transposition of the great arteries 5×), ASD, hypoplasic left ventricle, situs inversus, and aorta anomalies.
- Agenesis of kidney, polycystic kidney, double ureter, tracheoesophageal fistula, intestinal atresia, and imperforated anus increase.

How could complications of diabetes on pregnancy be detected in previous trimesters?

- On 16th week: msAFP can be used for neural tube defect screening.
- Neural tube defects should be suspected for AFP values greater than 2.5 times the mean values.
- AFP and acetylcholinesterase should be evaluated in targeted ultrasound and amniotic fluid.
- Fetal echocardiography performed between 20 and 22 weeks of age gives an idea about major structural cardiac malformations.

What are the fetal outcomes in pregestational diabetes?

- Perinatal loss 2–4%.
- Abortion rate increases.
- Preterm labor may increase 2–5 times.
- Diabetes does not increase chromosomal abnormalities, but increase congenital malformations.
- Mostly DM is related to Macrosomia but it also causes IUGR, because of vasculitis.
- Unexplained fetal death—cause unknown.
- Polyhydramnios increases.

What is the treatment of diabetes during pregnancy?

- Treatment should be started in the preconception period.
- HbA1C should be kept within normal limits (<5%).
- Insulin dosage and diet monitoring are important.
- All patients should be seen by the dietician.
- Exercise increases the crucial insulin response within 24 h (increased sensitivity).
- Short-acting insulin (regular and semilente) peak effect 2–4 h after injection.
- Peak effect 5–12 h in medium-acting insulins (lente and NPH).
- Peak effects in long-acting insulins (protamine, zinc, and ultralente) last for 12–24 h.
- 28 kcal/kg + 300 cal diet is recommended or ADA recommends 30/kcal/g—for nonobese patients.
- 30% calorie reduction is recommended in obese patients.
- 50–60% carbohydrate, 20% protein, 35% fat.
- 25% of daily calorie in breakfast.
- 30% lunch.
- 30% evening.
- 15% bedtime.

What are the blood values that require the initiation of insulin in the treatment of diabetic pregnant women?

- Fasting plasma glucose ≥105 mg/dL.
- Plasma glucose ≥155 mg/dL at postprandial first hour.
- Postprandial second hour plasma glucose ≥130 mg/dL.

- In these cases insulin treatment is started.
- Oral antidiabetics cross the placenta (but not proven).
- Are oral antidiabetics teratogens? (but not proven).

How is insulin treatment of diabetic pregnant women regulated?
- 0.7 U/kg/day within 6–18 weeks.
- 0.8 U/kg/day in the weeks 18–26.
- 0.9 U/kg/day in 26–36 weeks.
- 1.0 U/kg/day in 36–41 weeks.
- 2/3 in the morning (NPH/regular insulin ratio 2/1).
- 1/3 in the evening (NPH/regular insulin ratio 1/1).
- If the dose is increased, it is not increased by more than 20%, and the old dose is continued for at least 3 days.

Which oral antidiabetics (OAD) can be used in pregnancy?
- A limited number of studies with glyburide and metformin have shown that fetal effect is similar to insulin and is effective in regulating blood sugar.

What are the targeted blood plasma glucose levels in the treatment of diabetic pregnant women?
- Fasting blood glucose level 60–90 mg/dL.
- Pre-lunch and evening glucose levels 60–105 mg/dL.
- Maintaining a postprandial 1-h glucose level below 140 mg/dL.
- Postprandial 2-h glucose level should be kept below 120 mg/dL.

What are the parameters examined in the follow-up of diabetic pregnant women?
- Preeclampsia will occur in 25% of patients; blood pressure, protein, and edema follow-up are important.
- Ophthalmologic examination.
- Cardiac functions.
- Renal functions.
- Urine culture, microprotein in urine.
- Weight gain.

What are the main features of poorly controlled diabetic pregnant women and its outcome?
- Patients with poor hypertension
- Macrosomia
- IUGR
- Polyhydramnios
- Induction, delivery or cesarean section at 37–40 weeks

What are the targeted blood glucose values during the labor induction of diabetic pregnant women?
- Maternal euglycemia (the condition of having a normal concentration of glucose in the blood) during delivery (80–100 mg/dL).
- Postpartum glycaemia can be increased up to 200 mg/dL.

What are the maternal complications of DM?
- Hypoglycemia
- Retinopathy
- Diabetic nephropathy
- Atherosclerosis
- Spontaneous abortion
- Polyhydramnios
- Chronic hypertension
- Preterm labor
- Diabetic ketoacidosis:
  - 50% cause infection
  - 20% of the cause is neglected or forgotten insulin doses
  - No reason found for up to 30%
  - Antenatal steroid to facilitate fetal lung maturation in pregnant women with diabetes

What are the fetal complications encountered in DM?
- Macrosomia
- Hypoglycemia
- Hypocalcemia and hypomagnesemia
- Polycythemia
- Hyperbilirubinemia and neonatal jaundice
- Respiratory distress syndrome (RDS)
- Cardiomyopathy
- Birth trauma and perinatal asphyxia

What is the risk of GDM and DM in terms of subsequent pregnancies of pregnant women diagnosed with GDM?
- Lifestyle changes are crucial, as diabetes develops in about 50% of patients with gestational diabetes within 20 years.
- Approximately 40% of patients diagnosed with GDM in subsequent pregnancies.

What is the recommendation for a woman with DM in terms of birth control?
- Patients diagnosed with gestational diabetes may use low-dose COC.
- If there is a risk of embolism, only progesterone-containing methods such as LNG-IUD may be recommended.

What is the postpartum evaluation of patients with DM?
- Recommendations for postpartum evaluation are based on the 50% likelihood of women with GDM developing overt diabetes within 20 years. The Fifth International Workshop Conference on Gestational Diabetes recommended that women diagnosed with GDM undergo postpartum evaluation with a 75-g OGTT.
- Postdelivery (1–3 days): Fasting or random plasma glucose
- Early postpartum (6–12 weeks): 75-g, 2-h OGTT
- 1-Year postpartum: 75-g, 2-h OGTT

- Annually: Fasting plasma glucose
- Triannually: 75-g, 2-h OGTT
- Prepregnancy: 75-g, 2-h OGTT

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Chapter 19
Pregnancy and Gastrointestinal Disorders

What is observed as a result of gastro-intestinal system (GIS) smooth muscle relaxation with progesterone?
- Reduced intestinal motility
- Reflux esophagitis
- Decreased gastric acid secretion, increased mucus secretion
- Increased gastric volume

Which changes can be observed on the laboratory findings in hyperemesis gravidarum (HG)?
- Prerenal azotemia due to severe dehydration
- Hypokalemia due to hydrochloric acid loss
- Hyponatremia, hypocalcemia
- Ketonemia, ketonuria
- High creatinine level
- Hyperbilirubinemia and deterioration in liver function tests

What are the complications of HG?
- Mallory Weiss tears/lacerations
- Vitamin K deficiency (coagulopathy, epistaxis)
- Wernicke's encephalopathy (due to thiamine deficiency)

What is the treatment of hyperemesis gravidarum?
- Fluid-electrolyte replacement
- Dietary recommendations
- Ginger

Acknowledgments The author would like to thank Dr. Hasan Yüksel who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_19

- Pharmacological treatment
  - Vitamin B6 + doxylamine
  - Antiemetics (promethazine, chlorpromazine, metoclopramide; if necessary ondansetron)
- Hospitalization

What are the recommendations for the treatment of gastroesophageal reflux (GER)?

- Adjustment of maternal head position
- Antacids
- Histamine H2-receptor antagonists (H2 receptor blockers)
- Proton pump inhibitors (PPI)

What are the most common causes of abdominal surgery during pregnancy? Explain.

- The frequency of appendicitis in pregnancy does not increase, even decreases. However, it is difficult to diagnose because the appendix changes its position.
- Therefore, complication rates and mortality increase.
- Especially in the last trimester the risk of perforation is much higher.

What are the main features of the intrahepatic cholestasis of pregnancy?

- Itching is the most common symptom, especially occurs in the third trimester and then jaundice develops.
- Hyperbilirubinemia is moderate (<4–5 mg/dL).
- AST, ALT, and LDH levels are elevated.
- ALP is elevated.
- Bile acid levels increase by tenfold.
- The exact cause is unknown.
- Preterm delivery, meconium staining of amniotic fluid, fetal demise.
- More common in second trimester, the risk increases near term.
- Deliver at 38th week.

Explain the treatment of intrahepatic cholestasis of pregnancy.

- Antihistamines
- Cholestyramine (bile acid-binding resin)
- Phenobarbital
- Dexamethasone
- S-Adenosyl methionine
- Ursodeoxycholic acid (UDCA) relieves pruritus, but a favorable effect on fetal/neonatal outcome has not been demonstrated.
- Itching disappears 3–7 days after birth

What are the main features of the acute fatty liver (AFL) of pregnancy?

- The most common cause of acute hepatic failure in pregnancy.
- Although the cause is not known, sometimes “3OH acyl coenzyme A dehydrogenase” deficiency may be detected.

- There are fat micro vesicles, small collections of *fat* within the *liver* cells.
- No tendency to recur.
- Nulliparity, multiple pregnancy, and male fetus are factors related with increased risk.
- Occurs in the third trimester or early postpartum period.
- Consider in unexplained liver failure near term.
- It often accompanies signs and symptoms of preeclampsia, and its clinic presentation can be very similar to HELLP syndrome especially.
- Hypoglycemia and hepatic coma may develop rapidly.
- The definitive treatment is delivery.
- If no complications are developed, no sequel is expected.

What is the prognosis of acute fatty liver (AFL) in pregnancy?
- Maternal mortality rates may reach to 75%.
- Fetal mortality is about 90%.

Which type of hepatitis have worse prognosis in pregnancy?
- Hepatitis E

What should be given to the newborn to HbsAg-positive mother?
- Hepatitis vaccine (to every baby) and hepatitis immunoglobulin (within 12 h of *birth)*

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Chapter 20
Hematological Disorders in Pregnancy

What are the physiological changes in hematological parameters during pregnancy?

- Neutrophil → Increase
- Red Blood Cell (RBC) → Increase
- Erythrocyte fragility (propensity of erythrocytes to hemolyze under stress → Increase
- Sedimentation → Increase
- Leukocyte → Increase
- Mean erythrocyte volume → Slightly increases
- Mean erythrocyte hemoglobin concentration → Unchanged
- Lymphocytes → Unchanged
- Basophile → Decrease
- Hemoglobin → Decrease
- Hematocrit → Decrease
- Platelet → Decrease

What are the Hemoglobin concentrations for the diagnosis of anaemia during pregnancy?

- Pregnant women with hemoglobin levels less than 11.0 g/dL in the first and third trimesters and less than 10.5 g/dL in the second trimester are considered anemic.

What are the two most common causes of anemia in pregnancy and puerperium?

- Iron deficiency anemia (IDA) and acute blood loss

Which tests are used to diagnose iron deficiency anemia (IDA)?

- Hemoglobin and hematocrit
- Erythrocyte indexes

Acknowledgments The author would like to thank Dr. Hasan Yüksel who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_20

- Peripheral smear
- Low Serum iron and ferritin levels (< 12 ng/mL), increased iron-binding capacity and transferrin saturation

Explain the treatment of iron deficiency anemia.

- Correction of anemia and replenishment of iron stores can be achieved by simple iron compounds (ferrous sulfate, fumarate, or gluconate) by providing about 200 mg of elemental iron per day.
- Parenteral treatment (ferrous sucrose, iron dextran) is given to pregnant women who cannot tolerate oral forms.
- In order to replenish the iron stores, 3 months oral treatment should be continued after anemia has been corrected.

In which cases anemia due to acute blood loss can be observed and how to manage?

- In early pregnancy; it may occur in cases with abortion, ectopic pregnancy, hydatidiform mole, or postpartum hemorrhage.
- At least 3 months of iron therapy is a more useful treatment option than blood transfusion in patients with hemoglobin levels ≥7 g/dL, with stable general condition, with no risk of serious bleeding, and no dizziness, feeling of falling when standing.
- Blood transfusion should be performed if the hemoglobin level is less than 7 g/dL.

What is the most common cause of megaloblastic anemia during pregnancy and its treatment?

- Folic acid deficiency is the most common cause.
- Usually found in women who do not consume fresh green leafy vegetables, or animal proteins.
- In the treatment, folic acid, a nutritious diet, and iron are given
- Folic acid is administered orally, up to 1 mg per day, and provides an effective hematological response.
- Common approach is to take 0.4 mg of folic acid per day before and during the first trimester.
- Megaloblastic anemia due to vitamin B12 deficiency during pregnancy is quite rare
- Vitamin B_{12} deficiency occurs more likely after partial or total gastric resection. The other causes are Crohn's disease, ileum resection, and excessive proliferation of bacteria in the intestines.

Describe sickle cell anemia hemoglobinopathies observed during pregnancy.

- HbS occurs as a result of the substitution of valine for glutamic acid at the sixth position of the β-globulin chain.

  Pregnancy in sickle cell anemia (homozygote HBS) adversely affects the course of the disease.

- Maternal mortality rate is about 2% and morbidity rate is about 80%.

- Sickle cell carriage is generally well tolerated during pregnancy.
- Maternal complications: Sickle cell crisis, pyelonephritis, severe anemia, pneumonia, neurological deficit.
- Fetal complications: Fetal demise and IUGR.
- Asymptomatic bacteriuria and pyelonephritis are particularly important in these pregnancies.
- In patients with pyelonephritis, destruction of erythrocytes passing through the kidney is increased and the disease is exacerbated.
- These patients should be vaccinated for pneumococcus and influenza.
- During labor, adequate oxygenation and hydration should be given to the mother.
- HbS-containing erythrocytes become sickle when deoxygenated, and hemoglobin aggregates are formed.
- Ischemia and infarct periods occur in many organs in sickling crises.
- These produce many clinical symptoms, predominately pain, which is called the *sickle-cell crisis.*
- The management of the *crisis* includes IV hydration, in case with severe pain parenteral meperidine or morphine can be given.
- The diminished oral intake secondary to pain and fever which may frequently accompany crisis worsens hypovolemia
- At the capillary level, the concentration of sickling decreases with oxygenation.
- Erythrocyte transfusion may not relieve pain or shorten the duration.
- Diagnosis: pain, fever, and reduction in hemoglobin concentration (exclude the other causes that may lead to these findings).
- Labor: epidural analgesia should be preferred.
- Necessary blood products should be prepared.
- If hematocrit level is <20%, then hemoglobin concentration should be improved by erythrocyte transfusion.

Explain the thalassemia and its management during pregnancy.

- During pregnancy 1/500.
  - **α-Thalassemia**
    - Hb H disease, only one α chain is synthesized
    - HbBart, there is no α chain
  - **β-Thalassemia**
    - Thalassemia minor
    - Thalassemia major
- Pregnancy prognosis in minor forms of disease is good. Prophylactic iron 60 mg/day and folic acid 1 mg/day.
- Anemia should be closely followed up because of various reasons for hemoglobin decreases.
- Thalassemia trait couples must undergo chorionic villous sampling (CVS) for prenatal diagnosis or PGD in IVF.

Describe gestational thrombocytopenia. How is it managed?

- Hemodilution and pooling of platelet causes a decrease in platelet levels in the third trimester.
- Gestational thrombocytopenia is diagnosed when platelet count <150,000/μL.
- Incidence is between 4 and 7%.
- Thrombocytopenia is usually mild and platelet count >70,000/μL.
- Generally asymptomatic, no bleeding problem, it is usually determined by routine screening.
- No history of thrombocytopenia before pregnancy.
- Returns to a normal platelet count within 2–12 weeks postpartum.

What are the main features of the immune thrombocytopenic purpura (ITP) during pregnancy?

- Caused by antibodies to platelets.
- The platelets coated with antibodies are destroyed by the reticuloendothelial system, particularly by the spleen.
- Acute ITP: usually known as a disease that develops after a viral infection in children.
- Many cases recover spontaneously, but 10% of cases become chronic.
- In young women, the disease begins chronically and very rarely resolves spontaneously.
- There is no evidence that pregnancy increases the episodes or exacerbates the active disease in patients with ITP diagnosed before pregnancy.
- Four keys decisive for ITP:
  - Ongoing thrombocytopenia
  - No splenomegaly
  - Megakaryocyte counts in the bone marrow may be normal or increased.
  - Exclusion of other causes of thrombocytopenia

Explain the management and treatment of ITP during pregnancy.

- Treatment is required when platelet counts are below 50,000/μL.
- Corticosteroid 1 mg/kg/day may be given.
- IV immunoglobulin may be given in resistant cases.
- In cases that do not respond to steroid and immunoglobulin therapy, splenectomy may be effective.

What are the fetal effects of ITP?

- IgG antibodies can pass through the placenta and cause thrombocytopenia in the fetus and neonate
- About 12% of babies born to mothers with ITP have severe thrombocytopenia (<50,000/μL).
- There is an increased risk of intracranial hemorrhage during labor and delivery of a fetus with severe thrombocytopenia.
- There are no clinic or laboratory tests to predict the platelet count of the fetus.
- Caesarean or vaginal delivery preference depends on obstetric indications.
- Prophylactic cesarean section does not reduce the risk of fetal and neonatal bleeding.

What is the course of hemophilia in pregnancy, what is the risk of postpartum hemorrhage?

- The course of hemophilia in pregnancy does not change, but the probability of postpartum hemorrhage is 20%.

What is the course of von Willebrand disease (vWD) in pregnancy, what is used in the treatment, what is the risk of postpartum hemorrhage?

- The most common hereditary bleeding disorder.
- There is no change in the course of the disease during pregnancy; however, 50% of these patients will have postpartum hemorrhage.
- Desmopressin, fresh frozen plasma, and cryoprecipitate are used in the treatment.

What are the obstetric conditions that are at increased risk because of placental vasculopathy?

- Preeclampsia, eclampsia
- IUGR, low birth weight
- First trimester abortions
- Intrauterine fetal deaths
- Preterm labor and delivery
- Placental abruption

What is disseminated intravascular coagulation (DIC)?

- It is a thrombo-hemorrhagic condition where coagulation and fibrinolytic systems are activated together.

What are the most common causes of DIC in obstetrics?

- Placental abruption
- Preeclampsia
- Septic abortion

What is the treatment for DIC?

- The most important step in the treatment is the treatment of the underlying cause
- Besides, depending on the phase of DIC, AT III preparations, fresh frozen plasma, cryoprecipitate, blood and other blood products, subcutaneous low-dose heparin can be used.

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Chapter 21
Pregnancy and Hypertensive Disorders

What is the classification of hypertensive disorders during pregnancy?

- Preeclampsia-eclampsia
- Chronic hypertension
- Chronic hypertension with superimposed preeclampsia
- Gestational hypertension
- Transient hypertension

How would you diagnose chronic hypertension during pregnancy?

- Before pregnancy or before 20th week of pregnancy
  - Systolic ≥140 mmHg
  - Diastolic ≥90 mmHg
- Chronic hypertension which persists for 12 weeks postpartum

What are the diagnostic criteria of preeclampsia?

- After the 20th week of pregnancy in a previously normotensive patient; on at least two occasions, at least 4 h apart; systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg; and the presence of newly onset one or more of the following criteria:
  - Proteinuria ≥0.3 g/24-h urine or protein/creatinine ratio ≥0.3 (mg/mg) (30 mg/mmol) (in random urine specimen) or dipstick ≥2+ (when quantitative measurement is not possible)
  - Platelet: <100,000/μL
  - Serum creatinine >1.1 mg/dL (97.2 μmol/L) or doubling of baseline creatinine value in the absence of renal disease
  - Elevated liver transaminases to twice the upper limit of normal levels

Acknowledgments The author would like to thank Dr. Hasan Yüksel who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_21

- Pulmonary edema
- Cerebral or visual disturbances (e.g., new onset—persistent headache and unresponsive to analgesics, blurred vision, scotoma, flashing lights, or sparks)

What is the gold standard of diagnosing proteinuria in preeclampsia?

- Twenty-four-hour urine collection is considered as the gold standard of diagnosing proteinuria in preeclampsia, in case of the correctly collected. Also according to recent researches 24-h urine P/Cr ratio could be used to diagnose proteinuria.

What are the risk factors for preeclampsia?

- Nulliparity
- Multifetal pregnancies
- Chronic hypertension ≥4 years
- A past history of preeclampsia
- A family history of preeclampsia and kidney disease

How Does Smoking Reduce the Risk of Preeclampsia?

- Cigarette smoke reduces fm-slike tyrosine kinase-1 (sFlt-1) and increases placental growth factor (PlGF), namely Carbon Monoxide (CO) may act by inhibiting placental production of antiangiogenic proteins, such as sFlt-1, and by inhibiting placental apoptosis and necrosis, but not because of nicotine.

What kind of clinical findings should be accompanied for the diagnosis of superimposed preeclampsia in a pregnant woman with chronic hypertension?

- If proteinuria is present already, two- to threefold sudden increase of previous levels.
- Sudden worsening hypertension
- Thrombocytopenia
- AST and ALT elevation

Describe gestational hypertension.

- Gestational hypertension refers to hypertension (at least 2 occasions) without proteinuria that develops after 20 weeks of gestation.

What is the most common cause of hypertension in pregnancy?

- Gestational hypertension

How to distinguish between transient hypertension and chronic hypertension?

- It is diagnosed retrospectively. Blood pressures return to normal by postpartum 12 weeks in transient gestational hypertension, but not in chronic hypertension.

What is the basic pathophysiology of preeclampsia?

- Vascular endothelial disease
- Abnormal trophoblast invasion: trophoblasts' myometrial invasion deficiency
- The muscular layers of myometrial fragments of the spiral arterioles remain intact → vasoconstriction → high resistance → low blood flow
- TXA2 and PGF2 (vasoconstrictor, platelet aggregation) ↑
- PGI2 and PGE (vasodilator, platelet disaggregation) ↓

- Excessive release of vasoactive substances, genetic predisposition, oxidative stress, diet, coagulation disorders, cardiovascular maladaptation, immunologic factors are also blamed

What are the effects of preeclampsia on kidneys and its pathognomonic findings?

- GFR↓, renal blood flow↓, acute tubular necrosis, acute renal failure, glomerular capillary endotheliosis, uric acid clearance↓ uric acid↑, proteinuria, oliguria

What is the effect of preeclampsia on liver and its pathognomonic findings?

- Hepatic hemorrhage (sub capsular hematoma), periportal necrosis, transaminases ↑, hyperbilirubinemia

What is the effect of preeclampsia on fetoplacental unit?

- IUGR, oligohydramnios, placenta ablation, fetal distress

What is the purpose of magnesium sulfate treatment in preeclampsia, what is the mechanism of action?

- The aim is prophylaxis for eclampsia. Calcium channel blockage may increase the seizure threshold by acting on the *N*-methyl-D-aspartate (NMDA) receptors.

What are the contraindications of magnesium sulfate treatment?

- Myasthenia gravis, renal insufficiency, and pulmonary edema

What are the side effects of magnesium sulfate (Which symptoms may occur in the patient)?

- Diaphoresis, redness, flushing, peripheral vasodilatation, nausea, vomiting, headache, muscle weakness, vision problems, and palpitations

What is the most commonly used antihypertensive agent in pregnancies?

- Alpha-methyldopa

What are the commonly used antihypertensive drugs in pregnancy?

- Alpha-methyldopa
- Hydralazine
- Beta-blockers
- Nifedipine
- Sodium nitroprusside
- Nitroglycerin
- Labetalol, clonidine

What is the drug of choice in order to prevent recurrent preeclampsia in subsequent preeclampsia?

- According to recent research, universal aspirin administration is associated with fewer cases of preeclampsia and fewer costs relative to no aspirin administration and aspirin administration based on serum and ultrasound measures or clinical risk factors. Generally it is advised to prescibe 60–150 mg low dose Aspirin, which diminishes platelet thromboxane synthesis while maintaining vascular wall prostacyclin synthesis.

Is there a condition in which diuretics can be used in preeclampsia?
- Pulmonary edema; urine output must be monitored with urinary catheter

Describe a typical eclamptic attack.
- Typical eclamptic seizure lasts for 75–90 s and it has two phases:
  - Facial tics occurs for 15–30 s before general rigidity lasting 60 s.
  - This is followed by tonic-clonic activity lasting 60 s.

How would you monitor magnesium infusion in preeclampsia?
- Patellar deep tendon reflex (DTR)
- Respiratory rate
- Diuresis
- Blood Mg level

What is the therapeutic blood level range of magnesium sulfate?
- 4–8 mg/dL

What is used as an antidote in the toxicity of magnesium sulfate treatment?
- Calcium gluconate 10%, 10 mL amp, over 15 min IV infusion

What to do if the patient has seizure while taking $MgSO_4$?
- Magnesium sulfate, 2 g IV bolus over 5 min (airway open)
- Sodium amobarbital 250 mg IV over 3 min
- Diazepam 5–10 mg IV
- Phenobarbital 125 mg IV, first stabilize the patient then perform C/S.

What are the components of HELLP syndrome?
- Hemolysis:
  - Abnormal peripheral blood smear findings
  - Total bilirubin >1.2 mg/dL
  - LDH ≥600 IU/L
- Elevated liver enzymes:
  - AST >72 IU/L
  - LDH ≥600 IU/L
- Low platelet count
  - Platelets <100,000/mm^3

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Chapter 22
Cardiovascular Diseases in Pregnancy

What are the physiological changes in cardiovascular system during pregnancy?

- At the last trimester, the apex of the heart gets pushed upward and toward the left horizontal axis with the elevation of the diaphragm due to the uterus.
- Pregnancy is associated with vasodilation of the systemic vasculature (increased levels of estrogen and progesterone).
- Cardiac output (about 40%) and heart rate (10–20 bpm) increases throughout pregnancy.
- The first heart sound is louder (S1).
- The third heart sound (S3) becomes clear and detected in 80%.
- An ejection systolic murmur is normal until the third degree.
- Diastolic murmur is not normal.
- Diastolic pressure decreases slightly in the first two trimesters but returns to the normal level in the pre-pregnancy period.
- Renin, angiotensin II, and aldosterone levels increase.
- Atrial natriuretic peptide (ANP) levels do not change.

What are the clinical manifestations of heart disease during pregnancy?

- Progressive dyspnea or orthopnea
- Nocturnal cough
- Hemoptysis
- Syncope
- Chest pain
- Cyanosis
- Persistent venous distention in the neck -appears to bulge
- ≥Third-degree systolic murmur
- Diastolic murmur

Acknowledgments The author would like to thank Dr. Müge Harma who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_22

- Cardiomegaly
- Persistent arrhythmia

Explain the New York Heart Association (NYHA) Classification and association with the maternal and fetal risk.
- Class I: No restriction in physical activity.
- Class II: There is minimal limitation in physical activity.
- Class III: There is significant limitation in physical activity.
- Class IV: Symptomatic at rest.
- I and II. Maternal and fetal risk is low in this group.
- However, in III and IV, the risk increases significantly, and pregnancy is not recommended for these patients.
- Reduced peripheral resistance during pregnancy reduces backward flow in valvular insufficiencies and therefore creates less risk in pregnancy.

What are the situations where pregnancy is not recommended because of cardiovascular risks?
- Pulmonary arterial hypertension
- Severe systemic ventricular dysfunction (EF <30%, NYHA III-IV)
- Previous peripartum cardiomyopathy with any residual left ventricular dysfunction
- Severe mitral stenosis
- Severe symptomatic aortic stenosis
- Systemic right ventricle with moderate to severely decreased ventricular function
- Severe aortic dilation (>45 mm in Marfan syndrome or other Heritable Thoracic Aortic Diseases; 0.50 mm in bicuspid aortic valve; Turner syndrome Aortic size index (ASI) >25 mm/m^2; Tetralogy of Fallot >50 mm-aortic diameter)
- Vascular Ehlers-Danlos
- Severe (re)coarctation
- Fontan circulation with any complication

Explain the relationship between mitral stenosis (MS) and pregnancy.
- It is the most common heart disease during pregnancy.
- Generally the main cause is Rheumatic fever. MS causes obstruction to left ventricular inflow.
- Pregnancy is contraindicated in severe mitral stenosis.

Explain the relationship between aortic stenosis and pregnancy.
- The prominent symptom is angina and syncope.
- Be aware of sudden death due to hypotension.

Explain the relationship between left to right shunt diseases and pregnancy.
- Shunt degree does not change significantly during pregnancy.
- However, maternal mortality increases to 50% in patients with pulmonary hypertension (Eisenmenger syndrome) with shunt reversal.

Explain the relationship between right-to-left shunt diseases and pregnancy.
- This group of patients is classified as cyanotic heart disease.
- Fallot tetralogy is the most common.

Explain the relationship between tetralogy of Fallot and pregnancy.
- It is usually diagnosed in childhood, and corrective surgery is performed.
- Patients who have corrective surgery do not experience any problems in their pregnancies.
- If a patient with tetralogy of uncorrected Fallot becomes pregnant; the risk of heart failure, IUGR, and abortion is increased.

Explain the relationship between atrial septal defect (ASD) and pregnancy.
- In the adult, bicuspid aorta is the most common congenital hearth disease (CHD) after aortic valve.
- It does not require any special treatment in pregnant women without complication.
- Endocarditis risk is low and does not require prophylaxis.

Explain the relationship between ventricular septal defect (VSD) and pregnancy.
- It is usually self-closing or surgically corrected.
- In pregnant women with untreated VSD, pulmonary hypertension and Eisenmenger syndrome may develop due to severe left to right shunt.
- Endocarditis risk is high, and prophylaxis is required.

Explain the relationship between patent ductus arteriosus (PDA) and pregnancy.
- Maternal mortality due to pulmonary hypertension is high in the presence of significant PDA.
- Endocarditis prophylaxis should be performed.

What is the prognosis of coarctation of the aorta during pregnancy?
- If coarctation of the aorta is without correction, the prognosis is very poor.

What is the prognosis of Eisenmenger syndrome during pregnancy?
- In the left-to-right shunted lesions, it means the reversal of the shunt as a result of the development of pulmonary hypertension.
- It is the most serious cardiovascular condition during pregnancy.
- Maternal and fetal mortality is more than 50%.

What is the prognosis of Marfan syndrome during pregnancy?
- Autosomal dominant transition.
- Mitral valve prolapse (MVP) is present in 90% of cases.
- Patients with severe aortic involvement have aortic dissection and a high risk of maternal mortality.

How is the prognosis of mitral valve prolapse (MVP) in pregnancy?
- Generally no adverse effects on pregnancy
- If there is regurgitation, endocarditis prophylaxis should be performed.

Explain the main features of peripartum cardiomyopathy and its clinical importance.
- Cardiomyopathy occurring in the last month of pregnancy or within the first 5 months of the postpartum period in women without previous history of heart disease and congestive heart failure.

- Etiology is unknown (could be autoimmune).
- Treatment with bromocriptine to improve myocardial recovery in peripartum cardiomyopathy remains investigational, so breastfeeding should not be discouraged.

What is the most common cause of heart failure during pregnancy?
- Superimposed preeclampsia

In which conditions is prophylaxis of infective endocarditis provided?
- Use of prosthetic heart valve or prosthetic material
- Previously infective endocarditis
- To have one of the following congenital heart diseases:
  - Corrected cyanotic heart disease
  - First 6 months after correction with prostatic material

How is prophylaxis of infective endocarditis provided?
- Ampicillin 2 g or cefazolin or ampicillin and gentamycin 30 or 60 min before delivery.
- In patients with penicillin allergy, clindamycin may be given.
- If enterococcal infection is suspected, vancomycin is given.
- In high-risk conditions, the same dose may be repeated 6 h after delivery.

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Chapter 23
Pregnancy and Renal Diseases

What is the most common bacterial infection during pregnancy? Why?
- Urinary tract infection.
- Most frequently asymptomatic bacteriuria. Most frequently; cystitis and pyelonephritis are seen as symptomatically.
- Increased bladder residual volume caused by pregnancy and vesicoureteral reflux due to dilatation due to progesterone are risk factors.

What is asymptomatic bacteriuria? How the diagnosis is made? What is the treatment?
- It is the condition of proliferation of bacteria in the urinary system without causing any symptoms.
- It is seen in 2–7% during pregnancy.
- Diagnosis; In case of sterile urine specimen, 100,000 or more of the same uropathogenic bacteria reproduction per milliliter is considered.
- The gram-negative bacteria of *Escherichia coli* and *Klebsiella pneumoniae* were the most common uropathogenic bacteria.
- If untreated, 30% of them develops complicated upper urinary tract infection.
- Treatment with ampicillin, nitrofurantoin, and cephalosporins for 7–10 days is reliable and effective.

Describe the characteristics and clinical features of acute pyelonephritis
- It is seen in 2% of pregnancy, infection of the upper urinary tract and kidneys.
- It is a leading cause of septic shock in pregnancy.
- It is the most common serious urinary complication of pregnancy.
- It is more common in the later weeks.
- Unilateral and right-sided in half, and one fourth of pregnancies in bilateral.

Acknowledgments The author would like to thank Dr. Adile Yeşim Akdemir and Dr. Büşra Aynalı who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_23

- Clinic:
  - Fever
  - Shivering
  - Flank pain, costovertebral angle tenderness
  - Nausea
  - Vomiting

What would you do in order to achieve a diagnosis in case of those symptoms above are observed?

- I would check a urinalysis and urine culture, in order to diagnosis pyelonephritis.

What can acute pyelonephritis cause in pregnant women?

- Preterm labor/preterm birth (tocolysis and steroids application are prudent to attempt to prolong the pregnancy; <34 weeks, patient without sepsis)
- Sepsis
- Pulmonary edema and acute respiratory distress syndrome

What is the treatment and management of acute pyelonephritis?

- Hospitalization
- Urine and blood cultures
- Measurement of hemogram, serum creatinine, and electrolyte levels
- Close monitoring of vital signs with urinary output
- Intravenous crystalloid replacement to provide urine output of >30 mL/h
- Intravenous antimicrobial therapy (broad spectrum beta-lactams; intramuscular ceftriaxone for 2 days followed by oral cephalexin for 10 days or an inpatient regimen consisting of IV cefazolin followed at discharge by oral cephalexin for 10 days)
- Control urine culture 1–2 weeks after antibiotic treatment

What are the symptoms of cystitis (symptomatic infection of the bladder)?

- Dysuria.
- Frequent urination.
- Urgency.
- Sometimes it is a clinical entity accompanied by some systemic findings.
- While hematuria is frequently detected, pyuria and bacteriuria are an inseparable finding of cystitis.

What is the empiric therapy of cystitis in pregnancy?

- Beta-lactams, nitrofurantoin, and fosfomycin

What are the main features of the nephrolithiasis in pregnancy?

- 1/2000–3000
- There is no data indicating that pregnancy increases stone formation.
- It does not affect the course of pregnancy but increases the frequency of urinary tract infections during pregnancy.
- 80% calcium oxalate stones are seen.

- The most common predisposing factor is familial idiopathic hypercalciuria.
- Diagnosis:
  - The most common symptom is flank pain in 90%.
  - Gross hematuria in one third of patients.
  - Ultrasonography is useful in diagnosis, but hydronephrosis (especially right sided, grade 1–2) associated with pregnancy can lead to confusion.

Explain the treatment of nephrolithiasis in pregnancy.
- It varies according to the duration of the symptoms and the week of pregnancy.
- Intravenous hydration and analgesic are given.
- There is a urinary tract infection that needs to be treated severely in half of those with symptomatic stone.
- In 75% of the patients, improvement is achieved with conservative treatment and the stone decreases spontaneously.

Explain acute renal failure (ARF) during pregnancy.
- Preeclampsia and eclampsia are the most common causes of ARF in pregnancy.
- Other reasons; postpartum hemorrhage, abruptio placenta, sepsis, sickle cell anemia, etc.
- It is usually corrected with appropriate treatment after pregnancy.
- In case of renal cortical necrosis, permanent damage is caused by the amount of necrosis.
- Oliguria is one of the important findings of ARF.
- Hemodialysis should be performed in the presence of azotemia and serious oliguria without deteriorating the general condition.

What are the factors leading to chronic renal failure (CRF) during pregnancy?
- The most common cause is DM.
- Other common causes; HT is glomerulonephritis and polycystic kidney.

How is chronic renal failure (CRF) in pregnancy classified according to creatinine level?
- According to creatinine level:
  - Mild disorder: <1.5 mg/dL
  - Central insufficiency: 1.5–3 mg/dL
  - Severe insufficiency: >3 mg/dL

What are the most common complications and other complications of chronic renal failure (CRF) in pregnancy?
- Hypertension is the most common complication of pregnancy in CRF.
- Anemia; responds to recombinant erythropoietin.
- Pregnancy is adversely affected, and preeclampsia, preterm labor, and development retardation may occur.
- If necessary, hemodialysis can be done.

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Chapter 24
Pregnancy and Respiratory Diseases

What is the most common pulmonary disease observed in pregnancy?
- Asthma
- Incidence rate in pregnancy is between 1 and 4%

Explain the features of asthma in pregnancy
- Chronic inflammatory airway disease and reversible airway obstruction due to bronchial smooth muscle contraction.
- Excessive mucus secretion and mucosal edema.
- In one third of the patients, a period of pregnancy is expected to worsen, while the rest will be improved or there will be no change.

In which period of pregnancy, asthma exacerbations are encountered more commonly and the route of labor could affect these exacerbations?
- 20% of asthma exacerbations are intrapartum, and delivery by cesarean increases the risk of asthma exacerbation by 18 times than normal spontaneous vaginal labor.

What are the complications of pregnancy with asthma?
- Preeclampsia, preterm labor, IUGR, low birth weight, ablation placenta, premature rupture of membranes, and perinatal mortality may occur.

Explain the treatment of acute attack and chronic asthma during pregnancy?
- During the acute attack; oxygen, steroid, theophylline, itratropium bromide, and beta agonist can be given.
- Treatment of chronic asthma; systemic and inhaled corticosteroids, chromolines, theophylline, and beta agonists.

Acknowledgments The author would like to thank Dr. Büşra Aynalı who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_24

Does asthma have an effect on delivery, what are the considerations regarding the drugs used?

- Does not change the route of delivery. Also it is important to remind that C/S increases the risk of asthma exacerbation by 18 times than normal spontaneous vaginal labor.
- Hydrocortisone is given during the delivery.
- Preparations of oxytocin, PG E1–2 can be given.
- PG F2 alpha and ergotamines should not be used in patients with asthma because they have bronchoconstrictor effects.

Explain the incidence of pneumonia in pregnancy and its effect on pregnancy

- Incidence of pneumonia is 1/600.
- There is inflammation affecting the lung parenchyma and alveoli.
- Less tolerable during pregnancy.
- Hypoxemia and acidosis may affect the fetus.
- It triggers preterm labor after second trimester.
- Every pregnant woman with suspected pneumonia should have a chest X-ray (posteroanterior and lateral views).
- 2/3 of pneumonia is bacterial.

Describe bacterial pneumonia

- *Streptococcus pneumoniae* (*S. pneumoniae*) is the most common.
- Typical symptoms; shortness of breath, cough, fever, chest pain, dyspnea, tachycardia, tachypnea.
- Proper antibiotics (macrolide, penicillin, and cephalosporin) are given.
- Clinical improvement occurs in 48–72 h.
- Fever may continue for 2–4 days.

Describe viral pneumonia

- The influenza A viruses are the most common viral cause of pneumonia.
- In order to prevent the disease, influenza vaccination should be applied to all pregnant women at any period of pregnancy (no matter which gestational week).
- Amantadine and rimantadine can be given according to the risk/benefit ratios.

Describe tuberculosis and its effects on pregnancy

- It is caused by inhalation of *Mycobacterium tuberculosis*.
- Inadequate treatment and in the presence of advanced or extrapulmonary tuberculosis; preterm labor, low birth weight, growth retardation and perinatal mortality rates are increased.
- Isoniazid + rifampicin + ethambutol is used in pregnancy.

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Chapter 25
Pregnancy and Thyroid Diseases

What are the most common causes of hyperthyroidism during pregnancy and how is it diagnosed?

- Graves' disease is the most common cause of hyperthyroidism during pregnancy.
- Diagnosis:
  - Decrease in TSH
  - Increase in FT3–4
  - Detection of thyroid-stimulating antibodies
- An autoimmune disease characterized by the presence of thyroid stimulating antibodies.
- It often enters remission during pregnancy and decreases the level of autoantibodies.
- It is exacerbated in postpartum period.
- Since circulating thyroid-stimulating antibodies can pass through the placenta, there is a risk of developing hyperthyroidism in the fetus (2–10%).

What are the maternal and perinatal complications of hyperthyroidism?

- Maternal complications:
  - Preeclampsia: 11–17%
  - Heart failure: 1–8%
  - Death: 1%
- Perinatal complications:
  - Preterm birth: 8–32%
  - IUGR: 7–17%
  - Still birth: 1–18%

Acknowledgments The author would like to thank Dr. A. Ozan Tekin who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_25

Explain the treatment of hyperthyroidism in pregnancy. What are the side effects of the treatment?

- The first choice for the treatment of hyperthyroidism during pregnancy is the propylthiouracil (PTU) (oral).
- It is the drug that blocks the synthesis of thyroid hormones.
- It also inhibits the transformation of T4–T3.
- It crosses through placenta less than methimazole (thiamazole, oral).
- The most important clinical side effect is agranulocytosis.
- A complete blood count is required when the patient has fever.
- In the treatment of PTU, fetal goiter and hypothyroidism may develop in 1–5% of fetuses.
- Methimazole may cause aplasia cutis, esophageal, and choanal atresia (methimazole embryopathy).
- If PTU is used for a long time, it is recommended to use PTU in the first trimester and methimazole in the second trimester due to hepatotoxicity.

What is the treatment that cannot be used in the treatment of hyperthyroidism during pregnancy?

- Radioactive iodine therapy is absolutely contraindicated in pregnancy.

When surgical treatment is to be planned in the treatment of hyperthyroidism during pregnancy?

- Surgical treatment is avoided if possible during pregnancy, but the best time is second trimester if operation is mandatory.

Describe hypothyroidism in pregnancy.

- Thyroid pathology is more common in pregnancy.
- The most common cause of hypothyroidism during pregnancy is Hashimoto's thyroiditis.
- In general, hypothyroidism is characterized by infertility and abortions.

What are the maternal and perinatal complications of hypothyroidism in pregnancy?

- Maternal complications:
  - Preeclampsia: 16–31%
  - Cardiac dysfunction: 2–3%.
- Perinatal complications:
  - Low birth weight: 32–33%
  - Still birth: 3–9%
  - Ablatio placenta: 1–8%

How would you diagnose and treat hypothyroidism in pregnancy?

- Diagnosis:
  - High TSH with low free T4 and T3 values.
  - Antimicrosomal and antithyroglobulin antibodies increase.

  - These antibodies can pass through the placenta and rarely cause neonatal hypothyroidism.
  - Levothyroxine treatment should be initiated, and the TSH value should be kept between 0.5 and 2.5 mU/L.

What are the main features of the postpartum thyroiditis?

- Temporary autoimmune thyroiditis is detected in 5–10% of women during the first year after birth.
- Postpartum thyroiditis develops in 16% of pregnant women with type 1 diabetes.
- For diagnosis, a TSH abnormality should be present except for thyroid-stimulating antibody positivity or presence of a toxic nodule within 1 year of delivery.
- Lymphocytic infiltration is observed and there are two defined clinical phases:
  - Resistant-induced thyrotoxicosis stage; glandular destruction is due to excessive hormone release.
  - Hypothyroid stage; postpartum occurs in 4–8 months.
- There is a 3.6% progression per year and 30% permanent hypothyroidism risk. There is a risk of 69% recurrence in the next pregnancy.

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Chapter 26
Ectopic Pregnancy

What is the definition of the ectopic pregnancy?
- The implantation of the fertilized ovum to any location other than the endometrial cavity.

What is the incidence of ectopic pregnancy in all pregnancies?
- 2% of all pregnancies

What is the most common cause and percentage of maternal mortality in the first trimester?
- Ectopic pregnancy. Five percent of all maternal deaths

What are the risk factors of ectopic pregnancy?
- Maternal age of >35
- Previous history of ectopic pregnancy
- Previous tubal, abdominal, pelvic surgery
- Pelvic inflammatory disease (PID)
- Smoking
- Endometriosis
- Infertility and assisted reproductive techniques (ART)
- Contraception failure (most commonly intrauterine device-IUD)

What is the most common clinical presentation of ectopic pregnancy?
- First trimester vaginal bleeding, abdominal pain as sharp or stabbing. Hemorrhagic shock may also occur if bleeding is excessive. Or it could be asymptomatic as well.

In which anatomical locations can ectopic pregnancy be observed?

1. Tubal (99.4%)
   - Interstitial

Acknowledgments The Author would like to thank Dr. Aykut Barut who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_26

- Isthmic (25%)
- Ampulla (55%) are the most common part

2. Uterine:
   - Rudimental horn
   - Cervical
   - Cesarean scar pregnancy
3. Intraligamentous
4. Ovarian
5. Abdominal

Which clinical findings are encountered in ectopic pregnancy?
- Lower abdominal, pelvic pain (often unilateral)
- Cervical tenderness, pain
- Irregular bleeding
- Menstrual delay and amenorrhea
- Adnexal mass

What are the diagnostic methods in ectopic pregnancy?
- β-hCG levels checked
- Progesterone levels checked
- Ultrasound
- Culdocentesis (currently not preferred method)
- Laparoscopy (gold standard)
- Other markers: VEGF, CK, Disintegrin, metalloprotease-12 (ADAM-12), SP-1

How would you monitor β-hCG levels in diagnosis of ectopic pregnancy?
- Plateau of serial β-hCG levels for 1 week.
- An increase of β-hCG less than 63% every 2 days. (It is also done in some centers, not doubling in 3 days.)
- β-hCG levels exceeding 3500, but no intrauterine gestational sac on transvaginal ultrasound is visualized.

How would progesterone monitoring help in diagnosis of ectopic pregnancy?
- Progesterone levels are lower in ectopic pregnancy.
- In normal intrauterine pregnancy, serum progesterone level is >25 ng/mL, with a sensitivity of 97.5%.
- Serum progesterone levels <5 ng/mL strongly marks abnormal pregnancy, but also in abortion as well.
- Because of that progesterone measuring is not much helpful in diagnosis of ectopic pregnancy.

What are the ultrasound findings in ectopic pregnancy?
- No visible intrauterine gestational sac by transvaginal ultrasound, although hCG level is above 1500 mIU/mL.
- Tubal ring (in non-ruptured ectopic pregnancy—ring of fire).
- Free fluid (bleeding) in pouch of Douglas.

- Adnexal mass.
- Detection of heart rate in adnexal sac.

What causes intrauterine pseudogestational sac in ectopic pregnancy?
- Decidual endometrium and small amount of intrauterine fluid, simulating early intrauterine pregnancy

In which β-hCG levels intrauterine gestational sac is expected to be visualized by ultrasound?
- Suprapubic ultrasound: β-hCG > 6000 mIU/mL
- Transvaginal ultrasound: β-hCG > 1500 mIU/mL

How does endometrial curettage help in differentiating between abortion and ectopic pregnancy?
- Decidual reaction (Arias-Stella) without trophoblastic tissue.
- Diagnosis if chorionic villus is seen: abortion.
- If the tissue taken by curettage is put into saline, chorionic villi generally appear fern-like, floating in saline but decidual tissue does not float.

How is ectopic pregnancy diagnosed by culdocentesis?
- The aspiration of nonclotting, bloody fluid has a positive predictive value of about 85% for the presence of EP.

What are the differential diagnoses of ectopic pregnancy?
- Normal intrauterine pregnancy.
- Ruptured ovarian cyst: difficult to distinguish by ultrasound, preoperative β-hCG levels should be checked in order to determine ectopic pregnancy, laparoscopy should be performed.
- Bleeding corpus luteum: difficult to distinguish by ultrasound in very early stages of pregnancy, preoperative β-hCG levels may not help, laparoscopy should be performed.
- Spontaneous abortion: Loss of intrauterine pregnancy, β-hCG levels decrease steadily.
- Salpingitis: Usually, there is no menstrual delay. Tenderness is bilateral, whereas in tubal pregnancy unilateral, fever exceeding 38°, white blood cells 15,000–30,000, sedimentation rate increases.
- Appendicitis: Cervical examination is less painful than ruptured tubal pregnancy, pain localized at McBurney point, WBC: 10,000–18,000, sedimentation rate slightly increased.
- Adnexal torsion.
- Endometriosis.

How is ectopic pregnancy diagnosed in a patient with IUD?
- Diagnosis of ectopic pregnancy is more difficult in a woman with IUD
- Pelvic pain and uterine bleeding may be due to IUD
- β-hCG levels should be checked

What are the treatment modalities of ectopic pregnancy?

- Expectant management, follow-up
- Medical treatment
- Surgical treatment
  - Methotrexate

    Local (salpingocentesis)
    Systemic (oral-parenteral)
  - Local injection of potassium chloride (KCl) ultrasound-guided local injection

    Laparotomy
    Laparoscopy

    - Milking
    - Salpingostomy: Linear incision into tube and not sutured
    - Salpingotomy: Linear incision is made and sutured to the tube
  - Radical (salpingectomy)

    Laparotomy
    Laparoscopy

What are the contraindications of methotrexate (MTX)?

- Hemodynamically unstable
- Signs of active bleeding, ruptured ectopic pregnancy
- Sensitivity to MTX.
- Intrauterine pregnancy.
- Breastfeeding
- Active pulmonary disease
- Renal disease
- Chronic liver disease
- Preexisting blood dyscrasia
- Immunodeficiency
- Peptic ulcer disease
- Unable to comply with visits and follow-up

Explain how MTX treatment is monitored in ectopic pregnancy.

- Day 0 curettage is done to the patient, β-hCG level does not decrease on the first day, the diagnosis of ectopic pregnancy is strengthened (if intrauterine, we would expect a decrease after curettage), and on day 1 the first dose of MTX (50 mg/m^2/IM) is given. On day 4, β-hCG level is measured. When two doses of MTX protocol is preferred, if there is more than 15% increase in β-hCG levels on day 1 and day 4, the second dose of MTX is administered on day 4. On day 7, β-hCG level is checked again and compared with the β-hCG level of fourth day, if more than 15% decrease is not achieved than MTX is applied again as day 1 and applied until 15% decrease in β-hCG level is encountered.

- If the decrease in β-hCG levels is above 15% between days 4 and 7, weekly follow-up until β-hCG level is <10.
- If there is no decrease in β-hCG levels, if the ectopic mass persists, if there is any evidence of intraperitoneal bleeding, treatment fails: Surgery is performed.

What are the contraindications of laparoscopy in the surgical treatment of ectopic pregnancy?

- Shock
- More than 2 L hemoperitoneum
- Uncontrollable massive bleeding

What are the indications for salpingectomy in ectopic pregnancy?

- Fertility is not sought
- Planning and requesting IVF
- Fallopian tubes are severely damaged
- Uncontrollable bleeding after conservative treatment
- Hemodynamic instability

What are the symptoms of ectopic pregnancy rupture?

- Abdominal and pleural pain
- A feeling of weakness, dizziness, and fainting

What is heterotopic pregnancy?

- The diagnosis of intrauterine and ectopic pregnancy at the same time is a rare situation, but it has become more common today with the frequent use of ART. Therefore, this possibility should not be ignored, especially in patients receiving IVF treatment.

What is the clinical importance of Cesarean scar pregnancy (CSP)?

- CSP is a rare type of ectopic pregnancy. The gestational sac is implanted in the myometrium at the site of a previous cesarean section. Mothers with CSP are faced with risks of unpredictable massive bleeding or more fatal complications.

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Chapter 27
Malpresentation and Dystocia

What is the meaning of malpresentation, malposition; what is the rate of it in term fetuses?

- 96% of fetuses in term are in vertex presentation.
- All non-vertex presentations are called malpresentation.
- The fetus is in an abnormal position or presentation that may result in prolonged or obstructed labor.
- This rate increases in preterm labor.
- Malpositions are abnormal positions of the vertex of the fetal head (occiput as the reference point) (i.e., occiput posterior position).

What is the classification of the malpresentation?

- Breech presentation (1/33)
- Face presentation (1/600–800)
- Brow presentation (1/1400)
- Compound presentation (1/1500)

What are the risk factor of dystocia?

- Due to relatively narrow maternal pelvic
  - Narrow pelvic inlet

    Pelvic anterior posterior diameter less than 10 cm
    If the transverse diameter is less than 12 cm
    BPD of the fetus is important
    Bandl's ring occurs when engagement is not proper
    Uterine and cervical response is important
  - Narrow mid-pelvis

    Transverse diameter, distance between spines <10.5 cm
    Anterior-posterior diameter <11.5 cm
    Distinct spines

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- Narrowing of pelvic outlet

  Tuberous distance between the angles is less than 8 cm
  Alone is rare
  Pubis fracture
  Perineal tears

- Generally narrowed pelvis

- Due to uterine contractions
  - Hypotonic uterine dysfunction

    Oxytocin
    Amniotomy
    Cervical prostaglandin E2
    Intra-cervical balloon laminate

  - Hypertonic dysfunction

    Precipitate labor
    Hydration
    Oxygen
    Tilting the patient to the left

- Causes of fetus
  - Presentation anomalies
  - Position anomalies

    Head deflections
    Facial: mentum anterior and mentum posterior
    Forehead
    Vertex
    Large fontanel
    High straight posture
    Straight posture
    Asynclitism: anterior and posterior
    Occiput posterior

  - Fetus development abnormalities

    Macrosomia
    Hydrocephalus
    fetus with increased AC
    Others (conjoined twins, sacral teratomas, etc.)

What are the presentation anomalies?

- Breech presentation: Breech presentation occurs in 3–4% of all term pregnancies.
  - Flank

  - Complete
  - Incomplete

- Transverse presentation
- Compound presentation

What are the reasons of breech presentation?

- Grand multiparity
- Poly- and oligohydramnios
- Placenta previa
- Uterine anomalies (i.e., septum, uterine didelphys)
- Multiple pregnancy
- Macrosomic fetus
- Hydrocephalus
- Anencephaly
- Short umbilical cord
- Fetuses with chromosomal anomaly
- Preterm gestation
- Previous breech presentation

What are the indications for C/S for breech delivery?

- Babies with weight below 2500–4000 g
- Hyperextended head
- Uterine dysfunction
- Healthy fetus at 26–30 weeks
- Other obstetric causes

Should shoulder dystocia be predictable and preventable at birth?

- No. With antenatal and intrapartum monitoring and imaging methods, it is unpredictable to prevent shoulder attachment. Preventive cesarean section for pregnancies with risk factors, early gestational age should be remembered, even if at least 50% of pregnancies with shoulder implants do not have these risk factors.

What are the risk factors for shoulder dystocia at birth?

- Macrosomic fetus is the most important risk factor. However, the birth weight of babies was found to be less than 4 kg in approximately 50% of pregnancies with shoulder dystocia.
- Maternal DM, fetal macrosomia, and fetal shoulder region are larger than non-diabetic mothers.
- Having a history of shoulder dystocia at previous birth.
- Postterm pregnancies.
- Male fetal sex.
- Advanced maternal age.
- Unusual progression of labor (fast or slow).
- Operative vaginal delivery, especially vacuum.
- Abnormal pelvimetry.

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Chapter 28
Postpartum Bleeding

What is the definition of postpartum hemorrhage (PPH)?

- 500 mL after vaginal delivery.
- Defined as more than 1000 mL of blood loss after cesarean (C/S).
- Or according to American College of Obstetricians and Gynecologists (ACOG): defined as a cumulative blood loss of greater than or equal to 1000 mL or blood loss accompanied by signs or symptoms of hypovolemia within 24 h after the birth process.
- Historically, a 10% difference between the initial and postpartum hematocrit values define PPH.
- Need of blood transfusion.

What is the classification of PPH?

- Early/primary PPH: Postpartum bleeding occurring the first 24-h period. It is the common type
- For instance; 88% of deaths in Egypt during this period (first 4 h)
- Late/secondary PPH: Postpartum 24 h to 6 weeks

What is the primary etiology of PPH?

- Uterine atony: constitutes 70–80% of PPH. It occurs in 1/20 of births. Risk factors: excessive tension of the uterus (polyhydramnios, multiple pregnancy, macrosomia), atonic uterus (rapid or prolonged birth, chorioamnionitis, prolonged oxytocin use, high parity), the failure to contract (tocolytic use, general anesthesia), or fibroids. All women who experienced PPH in a previous pregnancy should be considered to be at risk of PPH in subsequent pregnancies.
- Placental retention (Succenturiate placenta)
- Lower genital system lacerations (Cervical, vaginal, and perineal lacerations)

Acknowledgments The Author would like to thank Dr. Mehmet İ. Harma who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_28

- Uterine rupture
- Morbid adhesion of placenta (i.e., accreta)
- Uterus inversion (i.e., excessive umbilical cord traction)
- Coagulopathy (i.e., Disseminated intravascular coagulation (DIC), acute coagulopathies, hemophilia)

What is the secondary etiology of PPH?
- Placental site subinvolution
- Retained products of conception
- Infection
- Inherited coagulation defects (e.g., factor deficiency such as von Willebrand)

What is the most common etiology PPH?
- Uterine atony: constitutes 70–80% of PPH

What are the risk factors for PPH?
- It is important to remember that although there are risk factors, obstetric hemorrhage is unpredictable.
- Postpartum bleeding history.
- Prolongation of the third stage of labor, dysfunctional labor, rapid labor.
- Chorioamnionitis.
- Obesity.
- Macrosomia.
- Multiple pregnancy.
- Labor induction (Prolonged use of oxytocin). Also as an additional information; according to recent research, immersion in water (water birth) during labor seems to facilitate uterine contractions more efficiently following vaginal delivery.
- Antepartum bleeding.
- Operative labor.
- Uterine anomalies.
- Uterine fibroids.
- Trauma.
- Multiparity.

Describe the three components of active management of the third stage of labor, to reduce the probability of PPH.
- The three components of active management are:
  - Oxytocin administration (10 units, 2 ampoules, diluted IV infusion or IM; most effective medication for prophylaxis of postpartum hemorrhage)
  - Uterine massage
  - Umbilical cord traction

What are the complications of PPH?
- Maternal death
- Hypovolemic shock

- DIC
- Renal failure
- Hepatic failure
- Acute respiratory distress syndrome (ARDS)
- Sheehan syndrome (hypopituitarism)

Describe the management of PPH.

- In most cases of primary PPH, most common causes are uterine atony and lacerations.
- Pay attention to the globe vesicale (urinary bladder overdistension).
- Bimanual uterine massage, apply uterotonics (first-line treatment).
- Check placental integrity, succentriate lobe.
- If there is no uterine atony but bleeding persists, perform a vaginal examination to check—laceration of the genital system, retention of the placental fragments.

Explain medical treatment methods of postpartum hemorrhage

- Fluid replacement
  - Colloids (dextran, gelatin, hydroxyethyl starch-HES): They have no superiority than crystalloid. They should not be the first choice. If it is to be used, it should not exceed 1000–1500 mL in 24 h.
  - Crystalloids (Ringer's lactate-RL, SF): These are the first solutions for fluid replacement. The contribution of 1000 mL RL to plasma volume is 200 mL and 80% out of the vessel.
- Blood transfusion
- Blood products (the recommended massive transfusion protocol for packed red blood cells: fresh frozen plasma: platelets = 1:1:1; to mimic whole blood).
  - If DIC is suspected or bleeding persists, platelet and fresh frozen plasma transfusion can be used empirically.
- Uterotonics
  - Oxytocin (10–40 units infusion in 500–1000 mL crystalloid as continuous infusion or IM: 10 units) (Do not apply IV push, hypotension can result).
  - Methylergonovine maleate (Methergine® 0.2 mg IM, repeating every 2–4 h) (do not apply IV, severe hypertension could result).
  - 15-methyl PGF2a (IM: 0.25 mg, Intramyometrial: 0.25 mg).
  - Carbetocin (long-acting oxytocin receptor agonist).
  - Misoprostol (PGE1 analog) (600–1000 μg oral, sublingual, buccal, or rectal).
  - Dinoprostone (PGE2).
- Hemostatics
  - Tranexamic acid (antifibrinolytic agent IV)
  - Prothrombin complex concentrates (plasma-derived concentrates of vitamin K-dependent clotting factors) and fibrinogen concentrates (should be used only after multiple rounds of the standard massive transfusion agents)

  - Recombinant factor VII (should be reserved for extenuating circumstances after multiple rounds of the standard massive transfusion agents)
  - Intraoperative cell salvage (autologous blood transfusion; limited availability of appropriate staff and equipment)

Postpartum bleeding: explain the surgical treatment methods.

- External aortic compression: on the one hand, the abdominal aorta is punched and the femoral artery pulsation is controlled.
- Manual reposition of uterus—in case of inversion.
- Intrauterine tamponade and packing (4-in. gauze, can be soaked with 5000 units of thrombin in 5 mL of saline then insert from one cornua to the other with ring forceps.)
- Uterus tampon-gas compress, Foley catheter, Sengstaken–Blakemore tube, Bakri Balloon.
- Uterus tourniquet application: effective in reducing intraoperative bleeding.
- Suturing the placental bed.
- Bilateral uterine artery ligation (O'Leary sutures).
- Internal iliac/hypogastric artery ligation (requires a retroperitoneal approach).
- Vaginal ligation of uterine arteries.
- Cervical hemostatic suture.
- Triple ligation of Tsirulnikov: the round ligament, utero-ovarian ligament, and uterine arteries are bilaterally attached. Used in atony.
- Stepwise devascularization.
- Uterus compression sutures (i.e., B-Lynch, Cho square, Hayman, Pereira, U-type sutures).
- Uterine artery embolization (in hemodynamically stable patients).
- Intra-aortic balloon occlusion.
- Hysterectomy: Subtotal/Total (final option when all conservative and surgical treatments fail).

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Chapter 29
Diseases of the Puerperium

What is the meaning of puerperium, how long is the puerperium period?
- Puerperium is a process beginning with the conclusion of birth and reversion of physiological and anatomical changes that occur during pregnancy.
- Begins with the conclusion of birth.
- Physiological and anatomical changes return to normal.
- The reversal of changes that occur during pregnancy is considered to be 6 weeks on average.

What is the involution of the uterus, what are causes of involution?
- At term uterus is 1000 g 5–6 weeks later decreases to 100 g due to diminishing of myometrial cell sizes
- After delivery, the uterus is palpated at the level of the umbilicus
- By the end of second week, uterus becomes a pelvic organ
- Cervix uteri thickens and cervical canal regenerates (cervical tears resulting delivery called Emmet)
- A large wound forms in the area where the placenta is detached, reparation begins, endometrial regeneration begins in the decidua
- Endometrium regenerates rapidly (16th day) however, the placental site shows slower regeneration

What is the subinvolution of the uterus? Depends on what?
- Delayed or ceased involution; the most common cause is placenta retention and infection (most likely causative agent is chlamydia)

What is the mechanism of uterine involution?
- Decidua is separated in two within 2–3 days
- Superficial layer lochia

Acknowledgments The Author would like to thank Dr. Aykut Barut who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_29

- Basal layer is the resource of new endometrium
- The placental area (10 × 15 cm) is halved with contraction, within 2 weeks 3 × 4 cm. Full regeneration 6 weeks

What is Lochia? What are the types of lochia?
- Postpartum vaginal excretion
- Red in first 3–4 days, lochia rubra
- Turns brown with hemostasis, lochia fusca
- It becomes serous within the sixth day, lochia serosa
- It turns to gray with epithelization within 3 weeks, lochia alba
- Normal secretion, within 4 weeks

Which changes are observed in the vagina, pelvic floor, and ligaments after childbirth?
- At the end of fırst week cervical opening is one finger width; transverse; full recovery within 6–12 weeks
- Pelvic tonus and vulva return to normal within 6–8 weeks
- Vaginal tonus is achieved after 3–4 weeks
- Hymen: carunculae myrtiformes (remnants of the hymen after parturition)
- Ligaments return to normal tonus and length at 6 weeks

What are the terms related to lactation?
- Mamogenesis: breast development, growth
- Lactogenesis: initiation of milk secretion
- Galactogenesis: continuation of milk secretion

What are the hormones related to mammogenesis, lactogenesis, and lactopoesis?
- Mammogenesis (mammary development): Estrogen, prolactin, progesterone, growth hormone, glucocorticoids
- Lactogenesis (initiation of lactation): Prolactin, insulin, glucocorticoids, decreasing of estrogen-progesterone and human placental lactogen
- Lactopoesis (maintenance of lactation): Oxytocin, prolactin, sucking of the infant, growth hormone, thyroxin, insulin, glucocorticoids

At the end of pregnancy, with which hormones decrease in plasma initiates lactation?
- Estrogen
- Progesterone
- HPL

Describe postpartum physiological changes
- Leukocytosis: up to 30,000; neutrophils increases; is not an indicator of infection. Eosinopenia take places
- Acetonuria: due to starvation
- Venous return increases, patients with heart failure may need diuretics
- Diuresis: increased extracellular fluid is quickly excreted by diuresis
- Weight: following birth at first 6 kg, then with diuresis 2–3 kg reduces

What is the definition of postpartum infection? Which infections are most common encountered?

- Fever >38 °C, at least two consecutive days, within 10 days after the first 24 h of delivery
- Most common genital, urinary, breast infection. At first, genital infection is considered until proven otherwise
- First 24 h; atelectasis and pneumonia

What are the risk factors for postpartum infection?

- Early membrane rupture (PROM)
- Prolonged labor
- Operative births
- Multiple vaginal examination
- Manual removal of the placenta

Describe endometritis

- The most common cause of puerperal fever
- Second to third day; fever higher than 38 °C
- Tachycardia
- Foul-smelling lochia
- Uterine tenderness
- Beta-hemolytic streptococcus, Bacteroides fragilis

What is the treatment of endometritis?

- Double antibiotics: clindamycin + gentamicin
- Single: second or third generation cephalosporin
- Parenteral until afebrile for 48 h
- Abscess, wound infection, septic pelvic thrombophlebitis are considered if there is no response to triple treatment for 48 h.

What is the diagnosis and treatment of episiotomy infection?

- 90% *Staphylococcus aureus*
- Leave open, debridement is done
- Antibiotic, hot seat bath
- Allowed to secondary healing

What is the diagnosis and treatment of parametritis?

- Frequent after C/S
- The most common cause of persistent fever in puerperal infection despite antibiotic therapy
- Usually localized at the base of the ligamentum latum and unilateral
- Treatment; antibiotic, drainage, supracervical hysterectomy

Describe the diagnosis and treatment of pelvic abscess

- A complication of delayed treatment
- Fever, impairment of general status
- Pelvic tenderness
- Tenderness in uterine movements

- Defense rebound
- May be mortal if ruptured
- Antibiotic + laparotomy
- Most common cause B. fragilis

Describe the diagnosis and treatment of septic pelvic thrombophlebitis
- Most often right V. ovarica is involved
- Pain is cardinal symptom, with or without fever on fifth to sixth day
- Develops in 1–5% after C/S
- Can progress to V. cava
- Can be considered with denial of diagnosis of wound infection and exclusion of pelvic abscess with unexplained fever that not respond to antibiotic therapy
- Ultrasound has no place in diagnosis, CT—MRI

Describe the diagnosis and treatment of Puerperal Mastitis
- Fever
- Myalgia
- Pain in the breast
- Redness
- The causative agent is staphylococci
- Breastfeeding should continue during treatment
- In cases of treatment failures, it progress to abscess

When the first menstruation is observed in breastfeeding and non-breastfeeding in the postpartum period?
- First menstruation in non-breastfeeding seventh to ninth week, this period can be extended to 36th week in breastfeeding

Describe the hormonal and hematological changes in the postpartum period
- Prolactin levels return to normal at 3 weeks in non-breastfeeding.
- Estrogen levels immediately return to normal.
- Thyroid sizes return to normal at 12 weeks.
- Pulse, stroke volume, and cardiac output return to normal at 8 weeks.
- Hematological values return to normal at 8 weeks.
- Fibrinolytic activity increases first to fourth days, return to normal on the seventh day. Fibrinogen gradually returns to normal at 2 weeks.
- Renal size, creatinine clearance, and GFR return to normal at 8 weeks.

Describe early postpartum follow-up
- Vital signs, uterine size and tonus, and vaginal bleeding should be followed every hour after birth.
- Postpartum blood pressure, fever, pulse, respiratory rate are strictly controlled for the first 4–6 h.
- Body temperature is usually 0.5 °C elevated in labor and delivery due to progesterone.
- Body temperature returns to normal after 12–24 h.
- Shivering occurs in one-third of cases due to vasomotor changes.

How is the diet regulated in the postpartum period?

- Mild nutrition recommended on the first postpartum day.
- Foods rich in protein, including fruit juice and milk are provided.
- Calorie needs is 2600 Cal in breastfeeding, and about 2000 Cal in non-breastfeeding.
- Fluid requirement is about 3000 cc.
- Micturition (urination) should be at postpartum first 4–6 h; if urine stasis occurs, catheter should be inserted and urine output should be monitored.
- Moderate ileus occurs due to reduced feeding during labor and antepartum enema.
- A laxative may be used on the second postpartum day.
- Postpartum hemorrhoidal complaints should be treated.

Describe the ambulation of the puerperia in the postpartum period

- The puerperia should walk in the first 12 h after delivery
- Early ambulation prevents stasis in the lower extremities and thromboembolic disease
- Supports uterine involution
- Provides lochia drainage
- During this period, heavy weights should not be lifted, stockings for varicose should be dressed
- Good nutrition should be recommended

What does breast engorgement mean, when can it be expected, and in which patients is it more common?

- After birth, lactation begins with the withdrawal of placental hormones.
- On postpartum second to fourth days, the mammary glands become fully activated and the breast is edematous and painful.
- The causes of breast engorgement are the filling of breast alveoli and small breast canals with milk, dilatation of capillary vessels, edema, and lymphatic stasis.
- It is more common in primiparous than multiparous.

What are the recommendations for puerperal hygiene?

- To prevent infections, vulva and perineal hygiene is very important.
- If there is pain in the perineum after delivery, cold compression should be performed.
- After urination and defecation, the perineum can be washed with warm water and soap.
- Antibiotic and antiseptic solutions should be given in the presence of infection.
- Bath can be done without sitting.

When should postpartum discharge be planned?

- If the patient does not have any problems after normal delivery, within **first and third day** postpartum can be removed from hospital.
- However, very close follow-up the puerpera should be done. Many complications may occur within 3–12 days after delivery.

When can sexual life begin in the postpartum period?

- Sexual activity (intercourse) should not start earlier than 4–6 weeks after delivery

What are the emotional status that can be observed in the postpartum period?

- Postpartum blues: 50–70%
- Postpartum depression: 10–15%
- Postpartum psychosis: 0.14–0.26%

At the end of the puerperium what should be done at the control?

- Postpartum examination is done at sixth weeks
  - Body temperature, body weight, and blood pressure should be examined
  - Hemoglobin and urine examination should be done
  - Breast, nipple examination should be done
  - Abdominal examination should be done
  - Varicose veins and edema in the legs should be controlled
  - Perineal scar, laceration, fistula
  - Cytological smear of vagina and cervix
  - Uterus, endometrium
  - Second postpartum control should be performed within 3–6 months

What are your recommendations for postpartum contraception?

- High prolactin levels in lactating women inhibit ovulation by suppressing gonadotropins and directly affecting ovary.
- Amenorrhea in lactating women may persist for months; 5% of these cases have ovulation at 6 weeks, 25% at 12 weeks, and 65% at 24 weeks.
- In non-breastfeeding women, ovulation occurs 15% at 6 weeks, 40% at 12 weeks, and 75% at 24 weeks.
- Contraception is recommended immediately after the abortion, after delivery at the latest fifth to sixth week.
- Non-breastfeeding mothers can choose oral contraceptives, intrauterine devices, tubal sterilization, or barrier methods for contraception.
- Combined oral contraceptives, although they pass to milk very little, should be used with caution in breastfeeding women.
- IUDs can be administered at 6 weeks postpartum or immediately after delivery.

In which localizations can postpartum hematoma be observed and how is it managed?

- Postpartum hematomas can be encountered as complications of labor and delivery.
- Mostly seen in operative deliveries.
- Most hematomas arise around the vulva, at the base of the perineum, in the ischiorectal fossa, under the levator ani muscle.
- Hematoma is rarely encountered in the broad ligament and retroperitoneum.

- In the treatment, hematoma is drained, bleeding vessel is ligated, and tampon is placed.
- Surgery may be required for abdominal hematomas.

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Chapter 30
Contraception

What is the definition of family planning?

- Family planning allows individuals and couples to anticipate and attain their desired number of children and the spacing and timing of their births, according to World Health Organization (WHO).

What are contraceptive methods for women?

1. Contraceptive pills
   (a) Combined oral contraceptives (COCs) or "the pill"
   (b) Progestogen-only pills (POPs) or "the minipill"
2. Injectable methods
   (a) Monthly injectable or combined injectable contraceptives (CIC)
   (b) Progestogen-only injectable (every 2 or 3 months)
3. Intrauterine device (IUD)
4. Cervical cap and contraceptive sponge
5. Diaphragm
6. Implants (Implanon/norplant)
7. Female sterilization (bilateral tubal ligation)

What are contraceptive methods for men?

1. Condoms (male)
2. Male sterilization (vasectomy)

What are the benefits of family planning?

- Protects against unwanted and unplanned pregnancies
- Protects mother and child health

Acknowledgments The Author would like to thank Dr. Aykut Barut who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_30

- Provides sexual intercourse without fear of pregnancy
- Protects the economy of the family

What are the factors that prepare maternal mortality?
- Early marriage
- Deliveries at early ages (20 ↓)
- Deliveries at advanced ages (35 ↑)
- Frequent deliveries (more frequent than 2 years)
- Plenty of deliveries
- Undesired pregnancies
- Pregnancy and childbirth without medical staff support
- Unhealthy pregnancies

What is the definition of natural family planning?
- Planning of pregnancy by observing natural signs and symptoms during fertile and infertile periods of menstrual cycle or avoidance of sexual intercourse during the fertile period if pregnancy is not desired

What are the types of natural family planning?
- Cervical mucus method (the quality of the cervical mucus varies throughout the menstrual cycle)
- Basal body temperature (progesterone 0.2–0.5 °C↑)
- Symptothermal method (cervical mucus method + basal body temperature)
- Calendar method or rhythm method
- Withdrawal (Coitus interruptus)
- Vaginal washing (douche)
- Breastfeeding and pregnancy prevention; lactation amenorrhea

What are barrier contraceptive methods?
- Condom (male/female)
- Diaphragm
- Spermicides tablet-ovule/cream-gel/foam

What is the mechanism of action of combined oral contraceptives (COCs)?
- Ovulation suppression
- The cervical mucus thickens to prevent the transition of sperm
- Slows transport of the ovum
- Effectiveness: 99.9%

What are the positive aspects of combined oral contraceptives (COCs)?
- They are effective and easy to use
- Reduces dysmenorrhea, regulates menstruation and reduces menstrual blood loss, reduces risk of anemia
- Reduces the risk of pelvic infection
- Reduces the risk of ectopic pregnancy
- Reduces the risk of endometrial and ovarian cancer
- Reduces the risk of benign breast disease
- Reduces the risk of endometriosis and osteoporosis

- Reduces the risk of acne and hirsutism
- Prevents functional ovarian cyst formation

What are the negative aspects of Combined Oral Contraceptives (COCs)?
- Necessity to take pills every day as a reliable prevention of pregnancy
- Use of postpartum in the first 6 months can reduce the amount of breast milk
- Nausea, breast tenderness, weight change, migraine and intermediate bleeding, vaginal discharge, depression may be encountered
- Increased risk of deep vein thrombosis
- Remembering taking pills every day
- To get weight (in some women)
- Occasionally intermenstrual bleeding and spotting
- Interaction with some drugs (barbiturates, phenytoin, phenylbutazone, rifampicin)
- Can increase blood pressure

What are the rules in use for combined oral contraceptives (COCs)?
- Use should be started on the first day of menstruation; protection provided at first cycle
- Physical examination including blood pressure measurement and breast examination should be performed
- Pills should be taken daily, preferably at the same time

What are the side effects of combined oral contraceptives (COCs)?
- Nausea
- Breast sensitivity
- Reduction of menstrual blood or intermenstrual spotting
- Headache
- Dizziness
- Weight gain
- Amenorrhea
- Acne

What are the contraindications for combined oral contraceptives (COCs)?
- >35 years, more than 15 cigarettes per day
- Migraine headaches with focal neurological signs (aura)
- Pregnancy
- Vaginal bleeding of unknown cause
- Existing breast cancer
- Uncontrolled moderate to severe hypertension 160/100 mmHg
- Diabetes with severe vascular complications
- Current/history of thromboembolism
- Cerebrovascular accident
- Complicated valvular heart disease
- Surgical operation requiring long-term immobilization
- Active viral hepatitis
- Benign, malignant liver tumors

- Severe fibrosis of the liver
- Severe decompensated cirrhosis

What are the important warning signs for the patient using COCs?
- Severe abdominal pain
- Severe chest pain, shortness of breath
- Severe headache, dizziness
- Loss of strength or sensation
- Severe thigh or leg pain
- Sudden loss of vision, blurred vision, speech impairment
- Jaundice of skin and sclera

What is mini pills, what is the mechanism of action?
- They contain only progestin.
- Effectiveness: breastfeeding 98.5%, 96% in non-breastfeeding.
- Usage: it is taken on the first day of the period and taken continuously at the same time every day.
- Indications: breastfeeding, advanced age, estrogen contraindicated women.
- Contraindication: pregnancy.
- Mechanism of Action:
  - Thickens cervical mucus
  - Inhibits ovulation 40–60%
  - Reduces tubal motility
  - Thins endometrium
  - Reduces the possibility of implantation.

What is the mechanism of action and effectiveness of injectable contraceptives?
- Inhibition of ovulation
- Thickens cervical mucus
- Inactivates the endometrium
- Effectiveness: 99.9%

What are the contraindications to Injectable Contraceptives?
- Mesigyna: Same contraindications of COCs
- Depo-provera:
  - Pregnancy
  - Vaginal bleeding of unknown cause
  - Existing breast cancer

Describe the general features of intrauterine device (IUD)
- Suitable for women of all ages.
- It is a very effective method.
- Inserted into the uterus by trained personnel.
- It's a small plastic device. Fertility returns when removed.
- Prevents pregnancy unless removed.

- Inert IUDs: Polyethylene (Lippes Loop) or stainless steel.
- Copper IUDs: Cu T-380 A, Cu T 220 C, Multiload (Cu 250 and 375) and Nova T.

What are hormone-containing IUDs?
- *Progestasert* containing 38 mg of progesterone in the body and 1 year effective
- *LevoNova and Mirena*; LNg-20, 5 years effective, containing 20 mg levonorgestrel

How does IUD provide contraception? What is its effectiveness?
- Creates spermicidal effect by creating sterile inflammation environment
- Prevents sperm passage and embryo implantation
- Progesterone-containing IUDs also suppress ovulation and thicken the cervical mucus
- Effectiveness of the method 97–99%

What are the positive features of the IUDs?
- IUDs are easy to use, effective, safe, and convenient
- Fertility returns when removed
- No systemic and metabolic side effects, (except copper allergy for Copper IUD)
- No possibility of forgetting, independent of sexual intercourse
- Can be administered immediately after delivery and abortion and is suitable for lactating women

What are the disadvantages of the IUDs?
- Require trained personnel for administration
- Dysmenorrhea and cyclic disorder during the first 3 months
- During administration, a small risk of uterine perforation
- Causes pain when thrown into vagina or dislocated into cervix

What are the contraindications for IUDs?
- Pregnancy or suspicion of pregnancy
- Existing active or recurrent pelvic infection or active sexually transmitted disease (STD), including purulent cervicitis
- Unexplained uterine bleeding
- Genital malignancy
- Congenital uterine anomalies or uterine fibroids that deforming uterine cavity
- Subsequent sepsis after miscarriage or delivery
- Pelvic tuberculosis

What are the relative contraindications of IUD that should not be considered as the first choice?
- Painful or excessive bleeding during menstruation
- Patients with a history of ectopic pregnancy
- Increased risk of STD (having more than one sexual partner of herself and/or her partner)
- Immune system depression
- In the presence of deep anemia

- With coagulation disorders
- Copper allergy or Wilson's disease

Classify according to IUD Application period

- Interval application
- Post-abortion application
- Postpartum application: In 10 min after the placenta removed (or in first 48 h) or sixth weeks postpartum

What is the meaning of emergency contraception? What are the options?

- Emergency contraception (EC) is using a drug or copper intrauterine device (Cu-IUD) to prevent pregnancy shortly after unprotected intercourse. It should be offered to all women requesting this service. Women should start the method as soon as possible to maximise effectiveness, preferably within 72 hours of intercourse. Options for EC are: Yuzpe (estradiol-levonorgestrel combination), Levonorgestrel (1.5 mg single or standart 2 x 0.75mg dose), mid-dose mifepristone (25 mg to 50 mg), Ulipristal acetate (UPA) (30–50 mg), Cu-IUD.

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Chapter 31
Painful Conditions in Gynecology

How would you classify acute pelvic pain?
- Complications of pregnancy (ectopic pregnancy, abortion)
- Acute infections
- Adnexal pathologies
- Cyclic pelvic pain (dysmenorrhea, mittelschmerz, premenstrual symptom)
- Gastrointestinal
- Genitourinary
- Musculoskeletal

What is the most common cause of non-gynecologic acute pelvic pain?
- Appendicitis

Explain the primary dysmenorrhea
- There is no pelvic pathology associated with painful menstruation.
- The primary reason is the increase in the synthesis of endometrial prostaglandins during menstruation.
- Primary dysmenorrhea always occurs with ovulatory cycles.
- The pain is colic and is particularly suprapubic.
- Starts a few hours before menstruation or with menstruation, lasting about 48–72 h. Also back pain, nausea, vomiting, diarrhea, and rarely attacks of syncope may accompany with dysmenorrhea.
- Generally cervical motion tenderness is not present, but there may be uterine sensitivity.
- Erythrocyte sedimentation rate is normal (can be used in the differential diagnosis of salpingitis).

Explain the treatment and management of primary dysmenorrhea
1. Prostaglandin synthetase inhibitors or nonsteroidal anti-inflammatory drugs (NSAID) (mefenamic acid, naproxen).
2. Combined oral contraceptives (OCSs) (ovulation inhibition); NSAIDs are indicated when no response to drugs is observed.

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https://doi.org/10.1007/978-3-030-29669-8_31

3. If the symptoms are not relieved with 4–6 cycles, diagnostic laparoscopy (L/S) is performed.

Describe secondary dysmenorrhea

- Pain starts 1–2 weeks before the menstruation and continues for few days after the cessation of menstruation.
- The primary treatment is the eradication of primary pathology.
- There is a pelvic pathology associated with painful menstruation and usually occurs in older ages than primary dysmenorrhea.
- Endometriosis is the most common cause of secondary dysmenorrhea, followed by adenomyosis and copper intrauterine device (IUD) usage.
- Secondary dysmenorrhea is also seen in patients with subacute endometritis, pelvic inflammatory disease (PID), ovarian cyst, pelvic congestion, myoma uteri, uterine polyps, Asherman syndrome, congenital pelvic malformations, cervical stenosis, imperforate hymen, and transverse vaginal septum.

What is the meaning of "Mittelschmerz"?

- Mittelschmerz (German for "middle pain" or "pain in the middle of the month").
- It occurs due to the reaction of follicle fluid or bleeding to peritoneum at ovulation.
- The pain is acute, short-term, generally mild and unilateral, and lasts for a few hours to a couple of days.

Describe the premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD)

- PMS is a syndrome that occurs in a way to interfere with daily activity, including physical and psychological findings, and occur in the luteal phase.
- Premenstrual dysphoric disorder (PMDD) is a severe subtype of premenstrual syndrome. It is seen in 3–5% of women in reproductive ages. In addition to the classical PMS, severe psychological findings are also evident:
  - Edema
  - Weight gain
  - Headache
  - Breast tenderness
  - Weakness
  - Irritability
  - Pelvic pain
  - Sleep disturbances
  - Emotional-state changes
  - Lack of concentration

What is the ACOG diagnostic criteria for PMS?

1. PMS is diagnosed if at least one of the affective and one of the somatic symptoms that listed below are reported.
2. Affective symptoms: Depression, angry outburst, irritability, anxiety, confusion, social withdrawal.

3. Somatic symptoms: Breast tenderness, abdominal bloating, headache, swelling of extremities

- Diagnosis made if there is a report of at least one of these affective and somatic symptoms in the three prior menstrual cycles during the five days before the onset of menses.
- The symptoms must resolve within four days of onset of menses and not recur until after day 12 of the cycle.
- The symptoms must be present in at least two cycles during prospective recording.
- The symptoms must adversely affect social or work-related activities.

What is the SM-IV-TR criteria for PMDD?

I. In most menstrual cycles in the past year, at least five of these symptoms (including at least one of the symptoms in category A) were present for most of the time 1 week before menses, began to remit within a few days after the onset of the follicular phase (menses), and were absent in the week after menses.

A. Primary symptoms

1. Markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
2. Marked anxiety, tension
3. Marked affective lability (i.e., feeling suddenly sad or tearful)
4. Persistent and marked anger or irritability or increased interpersonal conflicts

B. Other symptoms

1. Decreased interest in usual activities such as friends and hobbies
2. Subjective sense of difficulty in concentrating
3. Lethargy, easy fatigability, or marked lack of energy
4. Marked change in appetite, overeating, or specific food cravings
5. Hypersomnia or insomnia
6. A subjective sense of being overwhelmed or out of control
7. Other physical symptoms (e.g., breast tenderness, bloating, weight gain, headache, joint or muscle pain)

II. The symptoms markedly interfere with work, school, usual activities, or relationships with others.

III. Symptoms are not merely an exacerbation of another disorder, such as major depressive disorder, panic disorder, dysthymic disorder, or a personality disorder (although it may be superimposed on any of these disorders).

IV. Criteria I, II, and III are confirmed by prospective daily ratings for at least two consecutive symptomatic menstrual cycles.

What are the treatment/management options for PMS?

- Treatment for symptomatology should be done. Ovulation suppression is definitive treatment (OCSs, GnRH analogues).

- SSRI (Fluoxetine): It is the most effective agent in medical treatment methods.
- Exercise and diet.
- Calcium, magnesium, vitamin E, and B6.
- NSAIDs.
- Spironolactone (for edema).
- Bromocriptine (for mastalgia).
- Anxiolytics: Alprozolam and buspirone.

What is the definition of chronic pelvic pain, what is the incidence?

- Pain in the lower abdomen and pelvis that persists in the same region for more than 6 months, causing functional loss or requiring treatment.
- Incidence is 12–20%.
- Gynecological causes are the most common cause of chronic pelvic pain.

What is the classification of chronic pelvic pain?

- Gynecological (noncyclic): endometriosis (most common), pelvic adhesions (most common), pelvic congestion syndrome, salpingo oophoritis, ovarian remnant syndrome, ovarian tumors, pelvic relaxation, adenomyosis
- Gastrointestinal: irritable bowel syndrome (the most common non-gynecological cause), ulcerative colitis, crohn's disease (inflammatory bowel disease), diverticulitis, carcinoma, infection, recurrent partial bowel obstruction, hernia, abdominal angina
- Genitourinary: interstitial cystitis/painful bladder syndrome, renal stones, bladder foreign bodies, urethral diverticulum
- Neurological: femoral neuropathy, neuroma
- Musculoskeletal: myofascial syndrome, fibromyalgia
- Psychosocial

Describe the management of chronic pelvic pain.

- In patients with chronic pelvic pain, a multidisciplinary approach is required and the underlying cause should be treated.
- Laparoscopic evaluation should be performed in patients who do not respond to NSAIDs.
- If pathology is detected during laparoscopy, surgical management (endometrial focus cauterization, adhesiolysis) could be performed at the same time.
- Laparoscopic uterine nerve ablation (LUNA) or presacral neurectomy could be performed during laparoscopy.
- In some cases, hysterectomy could be performed for pain relief.

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Chapter 32
Abnormal Uterine Bleeding (AUB)

Describe the main features of the normal menstrual cycle

- Frequency varies between 21 and 35 days
- Regularity (variation of menstrual cycle length, measured over 12 months): ±2 to 20 days
- Average normal bleeding amount: 5–80 mL
- An average of 5 days of episodes are defined as normal menstrual cycles

What is the definition of AUB?

- AUB is a symptom
- It is called menstrual bleedings that are not within normal limits. Such as:
  - Amenorrhea: No bleeding for 90 days
  - With irregular intervals: More than 20 days over 12 months
  - Normal Duration: 4.5–8 days
  - Heavy menstrual bleeding: Over 80 mL total blood loss, each cycle
  - Intermenstrual bleeding: Bleeding occurring between otherwise normal menstrual periods

What is the definition of acute and chronic AUB?

- Chronic AUB: In the last 6 months most of the time there is abnormality in terms of frequency, regularity, duration, and volume.
- Acute AUB: It is an excessive bleeding episode that is thought to require urgent intervention in order to prevent more bleeding by the clinician.

Describe AUB classification according to FIGO

- Structural (PALM acronym): polyp, adenomyosis, leiomyoma, malignancy, and hyperplasia
- Non-structural (COEIN acronym): coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, not otherwise classified

Acknowledgments The author would like to thank Dr. İ. İlker Arıkan, Dr. Müge Harma and Dr. Mehmet İ. Harma who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_32

How would you evaluate a patient with AUB?

- Anamnesis, initial history: It is questioned whether the bleeding is caused by uterine origin or not. Definition of the menstrual history, contraceptive methods, systemic illnesses, pregnancy test, complete blood count (CBC), cervical cancer screening results, history of coagulopathy, infectious causes, hormonal causes (thyroid, hyperprolactinemia, PCOS)
- Physical examination: Confirmation of bleeding from the uterus, speculum examination (if nonvirgo). Rectal examination (rectal bleeding?). Abdominal and vaginal examination; bimanual examination.
- Imaging: The first step is of imaging begins with ultrasound examination (transvaginal/suprapubic). In case of suspicious image of the uterine cavity (for submucosal fibroid, suspicion, and separation of endometrial polyps) Saline infusion sonography (SIS) is the preferred method.
- Sampling: Pipelle, Karman cannula, endometrial biopsy with sharp curette, therapeutic curettage could be applied, pathological examination is requested (more than 45 years of age in patients with AUK although the endometrial double wall thickness increase under the age of 45 considered to be estrogenized (>14 mm) reproductive period patients also receive endometrial biopsy).
- If there is no suspicion of focal lesion or a diagnosis (may be observed by SIS) biopsy, then hysteroscopy would be the preferred method to evaluate the uterine cavity.
- MRI is the most effective imaging modality for locating fibroids but since it is expensive, generally this modality would be reserved for complicated procedures.

What is the nomenclature of leiomyomas according to their location in the uterus?

- Submucous (FIGO type 0, 1, 2): Completely within the endometrial cavity and/or extend into myometrium.
- Intramural (FIGO type 3, 4, 5): They are located within the uterine wall (myometrium).
- Subserosal (FIGO type 6, 7): They are located on the serosal (outer) surface of the uterus extend beyond the uterus, could be pedunculated, intraligamentary (i.e., broad ligament), parasitic as well.
- Cervical (FIGO type 8)

Describe the management of leiomyomas in AUB

- Medical and surgical treatment can be applied.
- Follow-up of fibroids in patients with asymptomatic conditions, annual pelvic exams would be advised.
- Medical treatment (especially for heavy menstrual bleeding and improvement in anemia):
  - Oral contraceptives
  - Progestational agents
  - Levonorgestrel-releasing intrauterine system (LNG-IUD)

  - Gonadotropin-releasing hormone agonists (most effective medical therapy for uterine fibroids)
  - GnRH antagonists (rapid onset without initial flare-up that observed with GnRH agonists), selective estrogen receptor modulators (SERMs; Raloxifene)
  - Progesterone receptor modulators [Ulipristal acetate (monitor liver function tests), Mifepristone (antiprogestin—RU 486)]
  - Aromatase inhibitors
  - Antifibrinolytics (tranexamic acid)
  - Nonsteroidal anti-inflammatory drugs (NSAIDs; naproxene)
  - Androgenic steroids (danazol and gestrinone)

- Surgery:

  - Hysterectomy (in case of bleeding not responding to other therapies, completed fertility; fibroids are the most common indication for hysterectomy)
  - Myomectomy (patients with not completed fertility, wish to retain their uterus)
  - Endometrial ablation (completed fertility, wish to retain their uterus; not to be effective in intramural and subserosal fibroids)
  - Myolysis (i.e., radiofrequency ablation)
  - Uterine artery occlusion (alternative to uterine artery embolization)
  - Uterine artery embolization (interventional radiology)
  - Magnetic resonance guided focused ultrasound (MRgFUS) (noninvasive thermoablative technique).

What is the "M" stands for in PALM-COEIN classification?

- AUB-M: Meaning malignancy and hyperplasia. When a premalignant hyperplastic or malignant process is defined in the study of women of reproductive age AUB, it should be classified as AUB-M and then subclassified according to WHO or FIGO system.
- Adenomatous hyperplasia (AH) → atypical AH → Endometrial cancer.
- Leiomyosarcoma (LMS).
- Estrogen-secreting tumors (such as granulosa cell tumors of the ovary; most common type of sex cord stromal tumor).

What are the causes of postmenopausal uterine bleeding?

- Vaginal, endometrial atrophy (due to hypoestrogenism)
- Endometrial polyps
- Postmenopausal hormone therapy
- Endometrial hyperplasia
- Malignancies: endometrium, granulosa cell tumors of the ovary, leiomyosarcoma, cervical cancer, choriocarcinoma
- Anticoagulant therapy
- Endometritis

Count the reasons for the AUB in adolescence period

- The most common bleeding disorders in adolescent girls who present with heavy menstrual bleeding are von Willebrand disease (vWD), platelet function defects,

thrombocytopenia, and clotting factor deficiencies. The source of vaginal bleeding is often uterus. The reason is often the immature hypothalamic–pituitary–ovary axis. Besides, pregnancy, bleeding problems (coagulopathies), PCOS, thyroid dysfunction (hypothyroidism), hypothalamic dysfunction (stress, exercise, low weight or obesity), IUD, and infection may also be the other reasons for AUB.

- In case of the source of the bleeding is not the uterus; ovarian, cervical, vaginal, vulvar, gastrointestinal tract, urinary system may also be the reason for bleeding.
- Heavy bleeding in the first two years of menstrual period in adolescents is usually caused by anovulatory cycles because of immature hypothalamic–pituitary–ovary axis.

Describe the clinical approach and evaluation of the adolescent who presented with abnormal vaginal bleeding

- Anamnesis is taken. (menstrual pattern, age at menarche, regularity, duration, frequency, volume; sexual history, married or not, contraception, systemic disease, drugs, family history of bleeding, presence of weight gain–loss, fatigue, etc.)
- Vital signs, whether hemodynamically stable or not, should be considered urgently.
- First of all it is necessary to know whether she is pregnant, pregnancy test is requested.
- Routine blood tests are requested (CBC, TSH, PRL, FSH, coagulation parameters, blood group, cross match) (if there are signs of hyperandrogenism: DHEAS, free testosterone)
- Physical examination; breast development (estrogenization), abdominal palpation, external genitalia (sexual maturity or sings of sexual abuse)
- Pelvic ultrasound; to evaluate uterine–ovarian–pelvic anatomy.
- After pathological reasons are excluded, and the irregular menses do not disturb and affect the daily life of the patient, observation could be suggested.

What are the common reasons for irregular uterine bleeding in adolescents?

- PCOS, hypothyroidism, hyperprolactinemia, hypothalamic dysfunction, pelvic infections.

What is the definition of heavy (excessive) menstrual bleeding in adolescents?

- Prolonged (>7 days) or increased volume (>80 mL/cycle).
- Excessive menstrual bleeding in adolescents is usually anovulatory with irregular menses. However, if excessive menstrual bleeding occurs with regular menses then it could be associated with bleeding disorders.

In which conditions would you consider bleeding disorders in adolescents?

- Adolescents with bleeding disorders usually come with excessive uterine bleeding starting in the first menstrual bleeding. Hematologic consultation is required.

- Von Willebrand disease (vWD), immune thrombocytopenia, platelet dysfunction, secondary thrombocytopenia could be the reasons for that situation. The most common of these is vWD.

What should be the laboratory evaluation when bleeding disorders are considered in the patient with excessive bleeding in adolescents?

- CBC (Hgb <12 g/dL), peripheral smear. Ferritin (<15 micrograms/L).
- Coagulation panel (aPTT/PTT, PT, fibrinogen.)
- For vWD: vWD antigen, ristocetin cofactor activity, Factor VIII activity (these factors should be considered before estrogen therapy, because E2 may increase vWFs to normal and make diagnosis difficult)

What are the reasons for intermenstrual bleeding?

- Contraceptives: oral contraceptives, IUD, depot medroxyprogesterone acetate
- Endometritis: Especially chlamydial endometritis
- Cervical lesions: polyps, ectropion, trauma.
- Foreign body: missed tampons
- Medications: antiepileptic drugs, anticoagulants.

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Chapter 33
Sexually Transmitted Infections and Genital Ulcers

What are the diagnosis, characteristics, and treatment of bacterial vaginosis (BV)?

- The most common vaginal infection in all ages of women.
- In spite of the abnormal number of bacteria in the vagina, the infection cannot be objectively documented (polymorphonuclear leukocyte deficiency).
- Normally, it is characterized by abnormal proliferation of anaerobes (Gardnerella vaginalis and Mycoplasma hominis) which constitute less than 1% of vaginal flora.
- Dirty gray discharge, fishy foul smell, yellow gel-like discharge.
- Lactobacilli null/less, clue cells.
- Vaginal alkalization by frequent sexual intercourse and vaginal shower is responsible for the development of BV.
- There is no place for culture in the diagnosis of BV. Nugent scoring system (with grams staining) is the gold standard for the diagnosis of BV, but not used since it takes time.

Treatment:

1. Metronidazole (oral or vaginal)
2. Clindamycin (oral or vaginal)

What are the Amsel criteria used in bacterial vaginosis?

1. There is a gray-white, watery, and sticky discharge to the vaginal wall.
2. Vaginal pH above 4.5.
3. Clue cells (>20%) and very few leukocytes are seen in gram staining.
4. Vaginal secretion 10% KOH solution is instilled fish smell (Whiff Test). This is due to the large amount of amines in the vagina. There is a particular fish odor following male ejaculation (having alkali media).

   At least three of the four criteria should be met.

What are the cells and structures that appear under the microscope named as "clue cell"?

- Bacteria that are attached to the vaginal epithelial cells are called as clue cells.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_33

Describe the diagnosis, characteristics, and treatment of trichomoniasis

- It is an sexually transmitted disease (STD) with a high risk of contamination. It is the most common nonviral STD worldwide. Flagellated protozoan parasite.
- Trichomonas vaginalis is the causative agent of trichomoniasis, a common cause of vaginitis. The flagella move the protozoan.
- In 60% of patients with trichomonias also accompanied by BV.
- Frequently asymptomatic (only 11–17% present with typical symptoms).
- Purulent, green-yellow, frothy, malodorous discharge.
- Postcoital bleeding.
- Vulvar pruritis.
- Vaginal pH >5.
- Vaginal erythema and strawberry appearance in the cervix (colpitis macularis: subepitelial petechial bleeding).
- The whiff test may be positive.
- Diagnosis: Motile trichomonads with flagella on wet mount, positive culture, positive nucleic acid amplification test (NAAT), or positive rapid antigen or nucleic acid probe test.
- Treatment:
  - Metronidazole (for pregnant women as well, oral) or Tinidazole (not to be used in pregnants); single 2 g oral dose.
  - Since it is an STD, spouse-treatment is absolutely necessary and also abstaining from intercourse for seven days to prevent reinfection is advised.

Describe the diagnosis, characteristics, and treatment of vulvovaginal candidiasis

- In 90% of the cases, the causative agent is Candida albicans.
- Other types of vulvovaginitis are C. Glabrata and C.tropicalis and are generally resistant to treatment.
- Pseudohyphae—Blastospores.
- Vaginal and vulvar itching are the main symptoms.
- The discharge is in the form of milk cut-white cheese.
- External dysuria.
- The whiff test is negative and the cervix is usually normal.
- The vaginal pH is normal (pH <4.5) (this feature distinguishes candidiasis from other vaginosis/vaginitis).
- Diagnosis: In the microscopic examination of the vaginal discharge, the diagnosis is made with the appearance of budding yeast and mycelium.
- Treatment:
  - Topical or oral azoles (fluconazole) are used (avoid in pregnancy).
  - Another alternative is topical nystatin.

What are the predisposing factors of vulvovaginal candidiasis?

- Use of oral contraceptives
- Systemic steroids
- Wide-spectrum antibiotics

- DM
- Synthetic underwear
- Pregnancy

How is wet mount prepared? Describe the proper sampling technique for direct microscopy

- A speculum is attached to the patient.
- The cotton-swap is wetted by gently rubbing it in the discharge (sample is taken).
- Calculate the pH of this sample.
- The swap is left in the tube that has already been prepared and contained 1–2 mL of saline (S.F.).
- Sample taken from the vagina must be examined within 15 min.
- After this swap is applied on the slide, it is examined under a microscope with a magnification of 10 then 40.
- Apply 2 drops on the slides with the same bar and add 10% KOH (potassium hydroxide) on it. After performing the Whiff (odor) test, a coverslip is closed and examined with a 10 magnification then 40.

What can be detected in microscopic examination of fresh preparation?

- Serum prepared with physiological saline
- Trichomonias vaginalis: protozoa with flagella can be seen
- Bacterial vaginosis: clue cells can be seen
- Which pathogenic agents can be detected in the preparation prepared with KOH?
- Candida: micelle and spores can be seen

How to do Gram stains?

- After the speculum is applied, the cervical external os is rubbed by a gauze (sponge) attached to the ring forceps.
- Thin swap is inserted into the cervical canal several times (at least 30 s).
- Smear a very thin layer onto the slide.
- Air-dry the culture and fix it or over a gentle flame, while moving the slide in a circular fashion to avoid localized overheating.
- C: Drop a few drops of CRYSTAL VIOLA on the slide, wait for 10–12 s and pour off the stain, and gently rinse the excess stain with distilled water.
- L: Drop a few drops of Lugol's solution on the slide, wait for 10–12 s and pour off the iodine solution, and rinse the slide with running water. Shake off the excess water from the surface.
- A: Drop a few drops of alcohol (decolorizer) on the slide, wait for 10–12 s, and rinse with distilled water.
- S: Drop a few drops of Safranin, wait for 10–12 s, and rinse with distilled water.
- Dry in the air or dry with an absorbent paper towel and dry without rubbing.
- Inspected by immersion under a microscope at 100 magnification.

What are the causes of vaginal discharge?

- Foreign body (toxic shock syndrome)
- Bacterial infections (G. vaginalis, N. gonorrhoeae, Chlamydia, Mycoplasma hominis, Ureaplasma urealyticum)

- Viral infections [Herpes virus (Herpes simplex/varicella/herpes zoster/cytomegalovirus), pox virus, papova virus]
- Candidiasis (Candida albicans)
- Trichomoniasis (Trichomonas vaginalis)
- Cervicitis (N. gonorrhoeae, Chlamydia trachomatis, Trichomonas vaginalis)
- Atrophic vaginitis
- Other causes: cervical mucorrhea or vaginal epithelial discharge/Enterobius vermicularis/Entamoeba histolytica/desquamative vaginitis/vaginal ulcers/vaginitis emphysematosa/nonspecific vaginitis.

What is the most common STD agent?
- HPV

What are the microorganisms that make endocervicitis?
- N. Gonorrhoeae and C. Trachomatis

What is the most common infectious agent that causes ectopic pregnancy, infertility, and abnormal uterine bleeding (AUB)?
- Chlamydia

What is Fitz-Hugh-Curtis syndrome, what is the causative agent?
- It is often referred to as perihepatitis (Glisson capsule) accompanied by frequently chlamydial seldom gonococcal salpingitis.
- In this case, adhesions occur between the liver capsule and the anterior abdominal wall.
- It shows itself by the right upper quadrant pain.

What is the most common cause of genital ulcer?
- HSV type II

Describe the clinical features of and treatment of genital herpes.
- Primary infection: It starts with fever, weakness, and painful inguinal lymphadenopathy (LAP). The sensation of burning and itching is dominant in the vulva and cervix 24 h before the typical vesicles develop.
- Firstly, multiple small vesicles develop on the erythematous surface. Then, with the rupture of the vesicles, very painful ulcers with superficial, indented protrusions occur.
- Treatment: Acyclovir (3 × 400 mg; 5 × 200 mg), famciclovir (3 × 250 mg), or valaciclovir (2 × 1000 mg) is used.

What is the gold standard method of diagnosing genital herpes?
- The culture of the material from the lesion (vesicular fluid) is the gold standard.
- If culture cannot be done, the presence of multinucleated giant cells with intranuclear eosinophilic inclusion bodies in cytological examination of the smear (Tzanck smear) is helpful in the diagnosis.
- The cytological presentation includes binucleated, syncytial multinucleated giant cells along with the ballooning of cytoplasm and cowdry type A intranuclear eosinophilic inclusions with partial or complete loss of chromatin.

Describe the etiology and the stages of syphilis

- Treponema pallidum, a spirochete.

1. Early syphilis: It is an infectious stage and divided into 2 periods.

   (a) Primary syphilis:

   – After the first contact (3–90 days, average 21 days), the lesion begins as a papule, mostly painless, then ulcer with a raised, indurated margin (chancre) develops.
   – Associated with mild to moderate inguinal LAP (often bilateral) in this period.
   – Chancre is contagious and heals spontaneously within three–6 weeks.
   – -Serological syphilis tests are negative in the early primary stage.

   (b) Secondary syphilis:

   – Systemic illness develops after 2–10 weeks the first lesions.
   – The generalized LAP during this period is typical of the development of an ulcerable papillary lesion (condyloma lata), and is very infectious and contagious.
   – Serological tests were positive in this period.
   – Rash is the most common characteristic finding of secondary syphilis.

2. Latent syphilis:

The diagnosis can be made only by serological tests at this stage which can last for 2 years.

   – Non-treponemal tests (VDRL, RPR) become negative while treponemal serological tests (remain reactive).

3. Late syphilis:

   – Years after the start of the gummatous period, which affects all organs and progresses slowly.
   – Granulomatous lesions called gumma in this period commonly cause organ involvement, mostly in the liver.
   – There is no bacilli and no transmission, hypersensitivity reaction.
   – It can occur all over the body but it is most commonly seen in the skin, bones, and joints (the palate).

What are the non-treponemal tests used to screen syphilis?

(a) Wasserman–Kolmer test
(b) Venereal disease research laboratory test (VDRL)
(c) Rapid plasma reagin (RPR)

What are the Treponemal Tests used to diagnose syphilis?

(a) The fluorescent treponemal antibody absorption (FTA-ABS): the first serological test to become positive after inoculation.

(b) Microhemagglutination assay for treponema pallidum antibodies (MHA-TP): test is rarely used any more
(c) Western blotting: definitive diagnosis.

What is the treatment of early and late syphilis?
- Early syphilis (primary, secondary, early latent); benzathine penicillin G i.m. (2.4 million U, single dose i.m.)
- Late syphilis (tertiary, late latent); benzathine penicillin G i.m. (2.4 million U, once a week for 3 weeks)

What is Jarisch–Herxheimer reaction?
- Formed within 24 h following treatment with spirochete (syphilis); an acute, self-limiting, febrile reaction. Fever; systemic symptoms such as headache, myalgia, rigor, diaphoresis, hypotension, and rash.

What are the types of congenital syphilis?
1. Infantile type
    - At birth or immediately after
    - Bloody, purulent rhinitis, septum perforation
    - Blisters on the base of the hand and foot
    - Saddle of the nose, osteochondritis in long bones (pseudoparalysis is called parrot pseudoplasty)
    - Hepatosplenomegaly, hepatitis (the most common cause of death)
    - Syphilitic pneumonia (pneumonia alba)
2. Late type
    - Occurs after 2 years of age.
    - Hutchinson triad:
        - Hutchinson teeth
        - Interstitial keratitis
        - Internal ear type deafness

What is the causative agent of chancroid (soft chancre—ulcus molle)?
- Haemophilus ducreyi, a gram-negative bacillus

What are the characteristics of chancroid?
- It infects the injured skin as penetrating and does not infect the intact skin.
- 2–5 days incubation.
- Men>>>Women.
- Initially erythematous, papular lesions are observed.
- Then develops a sensitive unilateral inguinal LAP (buboe) with vesicular, fragile, easily bleeding purulent, and very painful 1–3 ulcers (more frequently in men).
- If LAP is fluctuated, it should come to mind.

How is the diagnosis of chancroid made by?
- It can be cultured in chocolate agar. Gram stain of the material taken from the edge of the ulcer can be seen in the pattern of “school of fish” (railroad track).

What is the treatment of chancroid?

- Azithromycin, ceftriaxone, ciprofloxacin, erythromycin
- Azithromycin single dose 1 g oral or ceftriaxone 250 mg i.m. most commonly used regimes. They can be used the same way in pregnant women.

What should be done for lymph adenitis that fluctuates in the chancroid?

- They must be drained, usually drained by needle aspiration. Because if no drainage is done this time, they are ruptured to form fistula or secondary ulcers.

Chancre	Chancroid
Incubation period: 21–30 days	2–5 days
Single lesion (mostly)	Multiple lesions (mostly)
Erosion-ulceration is present	Ulceration
Hard-based, lymphocytic infiltration present	Soft-center (purulent reaction)
Non-purulent, erythematous, serous base	Dirty, purulent, irregular-based
Regular borders	Irregular borders
Noninflammatory, painless, bilateral and non-fistulant bilateral LAPs	Inflammatory, painful, singular, unilateral, and fistulant through single orifice (hole) LAPs are present in 30–60% of cases

What is the causative agent of lymphogranuloma venereum (LGV)?

- It is formed by L1,2,3 serotypes of Chlamydia trachomatis.

Describe the characteristics of LGV.

- In particular, they cause lymphoid tissue and systemic disease. Incubation time is 1–2 weeks.
- Vulvar is a disease that can lead to the development of carcinoma.
- As the skin between the growing painful inguinal lymph nodes appears dim, it is called the groove sign and it is pathognomonic.
- Diagnosis: fluorescent antibody testing is performed with NAAT (nucleic acid amplification test).

Lymphogranuloma occurs in 3 different stages 1–3 weeks after venereum is taken by sexual contact. What are those stages?

1. Vulvar ulceration (primary infection) (seen as a painless vulvar ulcer that heals spontaneously)
2. Secondary infection
   (a) Lymphatic period: Inguinal and / or femoral nodes. It may be painful, ruptured, characterized by groove-shaped.
   (b) Anorectal stage: Rectal stricture and fistula formation, proctocolitis.
3. Late LGV: It is characterized by a chronic inflammatory response and the destruction of tissue, which is followed by the formation of perirectal abscess, fistulas, strictures, and stenosis of rectum. Chronic progressive lymphangitis

leads to chronic edema and sclerosing fibrosis. This results in strictures and fistulas that can cause elephantiasis of the genitals, esthiomene (chronic ulcerative disease of vulva leading to disfiguring fibrosis and scarring), and frozen pelvis syndrome

Describe the treatment of lymphogranuloma venereum (LGV).
- Azithromycin 1 g for 3 weeks, once a week
- Doxycycline 2 × 100 mg; 21 days
- Erythromycin 4 × 500 mg

What is the cause of granuloma inguinale (donovanosis)?
- Klebsiella (Calymmatobacterium) granulomatis, a small encapsulated bacterium in gram-negative cocobasil structure

What are the features of the lesion of granuloma inguinale?
- It starts in the form of small nodules or papules in the vulva, then expands and turns into painless easily ulcers.
- In chronic cases, obstructive LAP (painless) may be seen, except for LAP.

How to diagnose granuloma inguinale, what are Donovan bodies?
- Gram-negative bipolar rods in macrophages are called Donovan bodies and are pathognomonic.

What is the treatment of granuloma inguinale?
- Azithromycin 1 g/week, treatment for at least 3 weeks until lesions disappear.
- Doxycycline: 2 × 100 mg
- Ciprofloxacin: 2 × 750 mg
- Erythromycin: 4 × 500 mg

What are the diseases that are not among sexually transmitted diseases but which can make genital ulcers?
- Behçet: painful ulcers without regular borders; aphthous ulcers of the mouth, uveitis
- Crohn: makes "knife-cut" sign
- There are other causes such as drug eruptions: Lipschütz ulcer

What is the causative agent of condyloma acuminata?
- Anogenital warts caused by HPV types 6 and 11.

What are the macroscopic features of condyloma acuminata lesions?
- Wet, moist areas, vulva, vagina, anus, multiple, soft, cauliflower appearance, painless lesions occur.

What is the typical cell and characteristic of condyloma acuminata lesions in smear?
- Koilocytes: squamous cells with halo around the eccentric nucleus

What are the treatment options of condyloma acuminate?
- Podophylline, topical 5-fluorouracil, imiquimod, trichloroacetic acid, cryotherapy, electrocautery, laser, and surgical excision are used

Which is the most effective in the treatment of condyloma acuminata?
- Electrocautery

Which reduces the risk of recurrence in the treatment of condyloma acuminata?
- Imiquimod cream

Is condyloma acuminata contraindication to normal spontaneous vaginal birth?
- If the birth canal is closed by condyloma acuminate, obstructing the vaginal canal; otherwise not a contraindication

What is the cause of Molluscum contagiosum?
- Pox viruses

What are the macroscopic features of Molluscum contagiosum lesions?
- They are pink colored, dome shaped papules with central umbilication with a 1–5 mm diameter center.

What are Molluscum bodies, how are they observed?
- Microscopic observation of the white waxy material in the papule confirms the diagnosis of molluscum bodies (intracytoplasmic eosinophilic inclusion bodies) stained with Wright or Giemsa in the cytoplasm.

What is the treatment of Molluscum contagiosum?
- White waxy material is emptied and iodine or ferric subsulfate (Monsel solution) is applied to the base.

What is the causative agent of gonorrhea, how is the treatment done?
- Neisseria gonorrhoeae
- 250 mg i.m. ceftriaxone, azithromycin 1 g single dose

What are the common features of gonorrhea?
- Most infected women are asymptomatic
- Purulent vaginal discharge
- Dysuria and frequent urination
- Cultivation of microorganisms
- Pelvic infection or disseminated infection
- Incubation period: between 2 and 7 days (average 3 days)
- Vulvovaginitis in children: in prepubertal girls

What are the common regions of N. gonorrhoeae in the female genital system? What are the symptoms?
- Cervix, cervicitis; mucosal infection; mucopurulent discharge, vaginal itching. Pain usually occurs when the upper genital system is involved. Intermenstrual bleedings can be observed.
- Early symptoms: most women are asymptomatic, vaginal discharge due to lower genital tract involvement, urinary complaints, and rectal discomfort.
- Flow: inflammation, pruritus, and burning of the vulva, vagina, cervix and urethra.

- Bartolinitis: unilateral.
- Anorectal inflammation: itching, pain, discharge, or bleeding.
- Pharyngitis.
- Common infection: polyarthralgia, tenosynovitis, dermatitis, or purulent arthritis/septicemia.
- Conjunctivitis: ophthalmia neonatorum.
- Urethritis in non-cervical (hysterectomized) women. Urgency.

Count the diagnostic criteria of chlamydia
- Mucopurulent cervicitis
- Salpingitis
- Urethral syndrome
- Nongonococcal urethritis in man
- Neonatal infections
- LGV
- Hypertrophic cervical inflammation

What diseases can chlamydia cause?
- LGV.
- Trachoma.
- Mucopurulent cervicitis, salpingitis, non-gonogococcal urethritis, proctitis, epididymitis, inclusion conjunctivitis (adult, newborn), new born pneumonia. An important part of cases are asymptomatic (70–80% in women, 20–30% in men).
- The risk of developing PID in women with cervical chlamydia infection is 5–10%. 15–20% of cases of acute salpingitis cause chlamydia.
- There are strong serological evidence of chlamydia in cases of ectopic pregnancy and infertility.

What are the characteristics of chlamydia?
- There are more than 4 million chlamydia cases per year.
- Obligated intracellular microorganisms. Cell wall is similar to gram-negative bacteria.
- Cultured only in tissue cultures.
- Only adheres to the columnar epithelium, no deep tissue invasion.
- If the eye, respiratory system, and genital system are involved, discharge, swelling, erythema and pain are localized in that region.
- Chronic inflammatory changes, fibrosis, tubal infertility, ectopic pregnancy.
- Chlamydia infection is 2–3 times higher in sexually active women under 20 years of age.
- Low socioeconomic class, and polygamy increase the risk of infection.
- The incidence is high among OCS users.

What are the clinical findings of chlamydia?
- Generally asymptomatic (80%)
- Cervical inflammation, mucopurulent discharge, hypertrophic cervical inflammation, not accompanied by salpingitis
- Accompanies with 50% gonorrhea
- Gram staining: GNID (−), 10 and more PML (+) at a magnification of 100

Where are the primary locations of pelvic inflammatory disease (PID)?

- Upper genital tract is bacterial infection (endometritis, salpingitis, oophoritis, pelviperitonitis)

What are the primary pathogens of pelvic inflammatory disease?

- Primary pathogens are N.gonorrhoeae and C.trachomatis

What are the ways of pelvic inflammatory disease?

1. Ascending (90%) (vaginal infarction, surgical interventions)
2. Direct spread from infected adjacent tissues (appendicitis, diverticulitis)
3. Hematogenous spread (tuberculosis from lung), enteral, respiratory pathogens

What are the symptoms of pelvic inflammatory disease?

- Abdominal pain is usually the main symptom in the bilateral sub-quadrant.
- The onset of pain may be with the menstruation or immediately after the menstruation.
- Abnormal uterine bleeding.
- Frequent urination.
- Vaginal discharge.

What are the physical examination findings of PID?

- Findings such as abdominal tenderness in palpation (asymmetrical in the lower quadrants, asymmetric), rebound, fever, decreased bowel sounds are usually detected in severe infection.
- Pain with acute cervical movement, uterine-adnexal sensitivity is common, but adnexal tenderness is not expected to show significant lateralization.
- Purulent endocervical and/or vaginal discharge is common.

What are the risk factors of PID?

- Vaginal shower
- Substance use
- Multiple partner
- Low socioeconomic status
- New sexual partner
- Previously experienced PID attacks
- Using a mechanical and chemical barrier contraceptive method

What are the complications of pelvic inflammatory disease?

- Recurrent infection, infertility, ectopic pregnancy, tuboovarian abscess, and chronic pelvic pain

What are the laboratory findings of pelvic inflammatory disease?

- Leukocytosis, increased sedimentation, increased CRP. But they are not specific and sensitive

What are the preferred imaging modalities for evaluating pelvic inflammatory disease?

- Pelvic ultrasound is preferred as the first step and it is also useful for detecting pathologies that may cause pain (such as ovarian cyst, ectopic pregnancy, degenerated fibroid).

- However, if the pathologies of gastrointestinal system such as Tubo-ovarian abscess (TOA) or appendicitis are suspected, abdominal CT is performed.

What is the treatment of pelvic inflammatory disease?
- Outpatient treatment:
- (Cefoxitin [second generation] or ceftriaxone [third generation]) + (doxycycline [tetracycline] or azithromycin [macrolide])
- Inpatient treatment:
- Regimen A: (cefoxitin or cefotetan [second generation cephalosporins]) + Doxycycline
- Regimen B: Clindamycin [linkosamide] + (Gentamicin [aminoglycoside] or Ceftriaxone)

Which patients can only be prescribed antibiotics in Tubo-ovarian abscess?
- Hemodynamically stable, non-rupture, <7 cm in size, adequate response to the antibiotic, should be in the premenopausal period

What can be offered to a patient who has not responded to antibiotic treatment in TOA but does not worsen the condition?
- Minimally invasive abscess drainage

When is surgery performed in TOA?
- In case of abscess rupture
- To rule out malignancy in a postmenopausal patient
- If there is no response to antibiotic treatment or if the patient deteriorates
- Suspicion of sepsis
- Mostly complete surgery (hysterectomy and bilateral Salpingo-oophorectomy) is preferred

What are the most common organs involved in genital tuberculosis (TB)?
- Almost always secondary to pulmonary involvement of tuberculosis. Tubal involvement is most common in genital tuberculosis. TB on genital organs most often occurs in the fallopian tube (90–100% of cases) and in the endometrium (50–80% of cases)

What are the genital symptoms that occur in genital tuberculosis?
- Infertility (caused by the involvement of the endometrium), menstrual disorders, and chronic pelvic pain

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Chapter 34
Endometriosis

What is the definition of endometriosis?
- It is a disorder in which endometrial glands and stroma are located outside the uterine cavity.

What is the most frequent localization of endometriosis lesion?
- The most common localizations: ovaries, anterior and posterior cul-de-sac (Douglas), posterior broad ligament, uterosacral ligaments, tuba uterina, sigmoid colon, appendix, round ligaments

What are the symptoms of endometriosis?
- Dysmenorrhea: 60–80%
- Non-menstrual pelvic pain (bilateral-unilateral): 30–50%
- Deep dyspareunia: 25–40%
- Infertility: 30–40%
- Menstrual irregularity: 10–20%
- Cyclic dysuria—hematuria: 1–2%
- Cyclic rectal bleeding: 1%

What is the reason of pain in patients with endometriosis?
- Because of compression of the nerves by lesions and infiltration of endometriosis.
- Pain cannot be observed even if there is widespread peritoneal involvement without nerve involvement.

Which hormone is the key hormone in pathogenesis of endometriosis?
- Endometriosis is an estrogen-dependent disease. Estradiol aggravates the inflammation and the symptoms associated with endometriosis. Also, estrogen receptor-β in endometriotic tissues are >100 times higher than those in endometrial tissue.

Acknowledgments The author would like to thank Dr. Müge Harma who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_34

What is the name of ovarian cystic lesions of endometriosis?
- Endometrioma

What are the risk factors of endometriosis?
- Nulliparity
- Caucasian and Asian women
- First degree relative (polygenic/multifactorial transition)
- Heavy menstrual bleeding
- Shorter menstrual cycles
- Alcohol, caffeine, red meat and trans-unsaturated fat consumption?, smoking: some studies postulate that antioestrogenic effect of smoking has a protective effect, but also some studies found that smoking has a strong effect on inflammatory mediators and further trigger inflammation associated with the disease, resulting in pro-inflammatory gene overexpression.
- Müllerian anomalies (obstruction of menstrual outflow)
- Early menarche, late menopause
- Lower BMI
- Low birth weight

What are the factors that reduce the risk of endometriosis?
- Using OCS
- Pregnancy (but tend to grow lesions in the first trimester), multiple births
- Lactation
- Late menarche
- Black and Hispanic women
- Aerobic activity at an early age?

What is the classical presentation of a patient with endometriosis?
- At reproductive age, with secondary dysmenorrhea, dyspareunia
- Infertility
- CA-125 ↑
- Rectovaginal examination of nodularity
- Pelvic mass (endometrioma)

What is the most common physical examination finding of endometriosis?
- Tenderness and nodularity in posterior vaginal fornix

What methods can be used for the diagnosis of endometriosis?
- Observation of endometrioma in imaging methods such as ultrasound, MRI, CT.
- L/S, histological confirmation.
- Biopsy: The observation of peritoneal endometriosis is often considered adequate for diagnosis. Positive histology is confirmed to confirm the diagnosis, but negative histology does not exclude the diagnosis.
- Fine needle aspiration biopsy: In cases of scar endometriosis.

What are the theories explaining pathogenesis of endometriosis?
- Transplantation theory (Sampson's retrograde menstruation theory)

- Metaplasia theory of the coelomic epithelium (Meyer)
- Metastasis theory (Halban)
- From Müller channel residues (embryonic rest theory)
- Induction theory

What are the differential diagnoses of endometriosis?
- Hemorrhagic corpus luteum
- Ovarian abscess
- Interstitial cystitis
- Irritable bowel syndrome
- Pelvic inflammatory disease (PID)
- Ovarian neoplasm
- Ectopic pregnancy
- Appendicitis

What is the tumor marker that may increase in endometriosis?
- Ca-125

What is the gold standard for diagnosis in endometriosis?
- Laparoscopy

What are the stages of endometriosis according to American Society for Reproductive Medicine (ASRM) classification system?
- Stage I: Isolated implant, no adhesion
- Stage II: Superficial implants (<5 cm in aggregate) on the peritoneum/ovaries
- Stage III: Superficial and deep multiple implants. Adnexial adhesions may be prominent
- Stage IV: Multiple implants, large endometrioma, widespread adhesion, nodularity (Douglas)

What are the drawbacks of ASRM classification system in endometriosis?
- Staging is based on personal observations during L/S.
- Scores between stages are very variable.
- Endometriomas and deeply infiltrating endometriosis (DIE) are difficult to identify and not well documented.
- Extrapelvic lesions are ignored.
- Surgical difficulties are not considered.
- Not correlated with infertility.
- Does not give information about the prognosis of pregnancy.

How could we group the lesions of endometriosis according to the location?
1. Peritoneal
2. Ovaries (Endometrioma)
3. Deeply infiltrating endometriosis (DIE): Subperitoneal invasion depth > 5mm
4. Non-pelvis: Intestinal tract, ureter, pulmonary, umbilical

What gives dark chocolate color in endometrioma?
- Hemosiderin (hemosiderin-laden macrophages)

The effects of endometriosis on pregnancy?
- Preterm birth, preeclampsia, C/S risk increases. According to resent research in 2019, it was found that women with a history of endometriosis were at greater risk of pregnancy loss, GDM, hypertensive disorders of pregnancy (inflammation and abnormal placentation-preeclampsia) have been hypothesized to contribute, preterm birth, and low birth weight.
- Also, increased risk of abortus, ectopic pregnancy, placenta previa, antepartum hemorrhage, postpartum hemorrhage, low birth weight

Which cancers are associated with endometriosis?
- Clear cell ovarian cancer
- Endometrioid ovarian cancer
- Low-grade serous epithelial ovarian cancer, seromucinous borderline tumor
- Adenosarcomas
- Melanoma

Which tumor suppressor gene is the most common in ovarian neoplasms that associated with endometriosis?
- ARID1A tumor suppressor gene

How can endometriosis cause infertility?
- Especially because of inflammatory process (in mild and advanced stages of endometriosis)
- Decrease in functional ovarian tissue (ovarian reserve)
- Reduced fertilization potential of oocytes
- Defective folliculogenesis, fertilization
- Low quality embryos
- Implantation disorder (increased IL-6 in follicle fluid)
- Oxidative stress
- Luteal phase defect
- Changes in peritoneal fluid (increased numbers of macrophages, cytokines, etc.)
- Implantation disorder
- Increased IgG, IgA and lymphocytes in endometrium
- Reduction in integrin and L-selectin levels
- Increased sperm phagocytic activity of macrophages
- Pelvic adhesions

What are the treatment options of endometriosis?
- Observation in asymptomatic patients with mild pain
- Medical treatment
- Surgery
- Combined therapy

What are the medical treatment options in endometriosis?
- Nonsteroidal anti-inflammatory drugs (NSAIDs) (especially to treat dysmenorrhea), OCS (low dose estrogen with dienogest; endometriosis-related pain), anti-

progestin, progestins, dienogest, danazol, GnRH analogues-antagonists, aromatase inhibitors

What is the therapeutic mechanism of OCS in endometriosis?
- They suppress ovarian function, decrease estrogen level, and reduce disease activity and pain.

When would you prefer progestogens in endometriosis?
- I would prefer progestogens (medroxyprogesterone acetate, norethisterone acetate,
- levonorgestrel, and nomegestrol acetate, dienogest) in women with severe deep dyspareunia and when deep infiltrating endometriotic lesions are observed.

Why don't we prefer danazol as a first line treatment for endometriosis, which is a medical treatment option?
- Danazol, a derivative of 17 alpha-ethinyltestosterone, is not often preferred for its androgenic side effects, which includes acne, muscle cramps, edema, weight gain, intermenstrual spotting, and voice deepening.

Which medical treatment reduces the Ca-125 levels in endometriosis?
- Danazol

When should surgery option for endometrioma be considered?
- Severe pelvic pain
- Fast growing (neoplasm?)
- Suspicious sonographic findings (may cause cancer, 1%)
- Difficulty in reaching the follicles (in oocyte pick up, especially)
- Risk of rupture in large endometriomas (especially >6–7 cm)
- Increased IVF success/spontaneous pregnancy rate? (ACOG states: asymptomatic endometriomas do not require intervention for infertility)

What is the definition of adenomyosis?
- It is a disorder in which endometrial glands and stroma are located within the myometrium.

What is the reason for diffusely enlarged uterus that observed in adenomyosis?
- Endometrial glands and stroma within the myometrium induce hypertrophy and hyperplasia of the surrounding myometrium, causing globular enlargement of the uterus

What are the medical therapeutic options in patients with adenomyosis?
- Suppressive hormonal treatment with high dose progestins, oral contraceptives, levonorgestrel-IUDs, GnRH agonists, aromatase inhibitors, selective estrogen receptor modulator (SERMs), and selective progesterone receptor modulator (SPRM's) are able to reduce symptoms by reduction of adenomyosis.

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Chapter 35
Benign Diseases of Uterus

Which structures develop from the mesonephric duct (Wolffian duct) and the paramesonephric duct (Mullerian duct)?

- The male internal genital system develops from the mesonephric duct: Ductus deferens, epididymis, seminal vesicles, vas deferens, and ejaculatory duct.
- Female internal genital system develops from the paramesonephric duct: Tuba uterina, uterus, cervix, and the upper two-third of the vagina. (Lower one-third of the vagina is derived from sinovaginal bulb derived from urogenital sinus.)

Which factors determine the sexual embryonic differentiation?

- In female and male fetuses, the urogenital and the external genitalia are similar up to the ninth week. Androgens responsible for the male differentiation of the urogenital sinus and the external genitalia. Also it is important to remind the necessity of the 5a-reductase to produce active metabolite, dihydrotestosterone (T→DHT).
- Androgens (testosterone) released from fetal Leydig cells, antimüllerian hormone (AMH, also named müllerian-inhibiting substance, or müllerian-inhibiting factor, a glycoprotein) released from fetal Sertoli cells. The absence of AMH results in the development-differentiation of the paramesonephric ducts into the uterine tubes, uterus, and the upper two-third of the vagina.

Which hormones initiate the development of female internal genitalia in embryological period?

- In the absence of testes, female internal genital organs develop from the paramesonephric duct without any further stimuli (namely absence of testosterone is enough) and there is involution of the mesonephric ducts due to the absence of male androgens and Y chromosome.
- The cranial parts of the paramesonephric duct do not fuse in order to constitute tuba uterina, whereas the caudal vertical parts are fused to constitute the uterus, cervix, and two-third of the vagina.
- Since there is no androgen, the mesonephric duct regresses.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_35

Which structures are remnants of the mesonephric tubules?
- Epoophoron (organ of Rosenmüller or the parovarium, paraovarian cysts), at broad ligament
- Paroophoron, adjacent to the uterus
- Gartner canal's cysts, at ovarian hilus and paravaginally

Which structures are remnants of the paramesonephric duct?
- Hydatid cysts of Morgagni, at the end of the fallopian tube

Which organs would not develop a consequence of developmental failure of the paramesonephric ducts?
- The cervix, uterus, and upper 2/3 of vagina would not develop, which is a condition known as Mayer–Rokitansky–Küster–Hauser syndrome (MRKH).

Fusion anomalies develop with the failure of fusion in paramesonephric ducts and which system anomalies may accompany these anomalies?
- The incidence of urinary tract anomalies increases in fusion anomalies, but resorption anomalies (uterine septa) does not increase. Therefore, in the presence of fusion anomalies, intravenous pyelography (IVP) should be recommended.
- They also commonly develop skeletal abnormalities, particularly vertebrae. Those patients may also have hearing loss or heart defects.

What symptoms-complaints would you expect to see in utero-vaginal malformations?
- Infertility, pregnancy losses (or habitual abortus), dyspareunia, dysmenorrhea, amenorrhea, preterm deliveries, preterm premature rupture of membranes, small for gestational age, and cesarean section (CS) due to malpresentation.

What are the uterine anomalies in order of frequency of diagnosis (prevalence)?
1. Septate uterus: 34%
2. Bicornuate uterus: 26%
3. Didelphys uterus: 11%
4. Arcuate uterus: 7%
5. Unicornuate uterus: 5%
6. Uterine hypoplasia/aplasia: 4%

What is the most specific and sensitive imaging modality in the diagnosis of müllerian anomalies?
- Pelvic MRI. Also according to recent researches 3D Ultrasound (US) is a very accurate method for the diagnosis of congenital uterine anomalies when compared to hysteroscopy with laparoscopy.

Which congenital uterine anomaly has the best pregnancy outcome even not surgically managed?
- Didelphys uterus has the best outcome, no need to interfere (except progesterone supplementation in order to prevent premature delivery)

Which congenital uterine anomaly has the best reproductive outcome after surgical treatment?

- Septate uterus

What is leiomyoma, in general, count its properties.

- They are the most common benign gynecologic tumors in the reproductive years, with an incidence of 70%. It is a benign uterus tumor composed of smooth muscle fibroid pseudocapsule (which is formed by the compressed adjacent myometrium), and fibrous elements.
- The most common cause of laparotomy and hysterectomy in women.

What are the risk factors for leiomyomas?

- Age: incidence increases with age, reaches a peak at 50 years.
- Early menarche
- Family history: risk in case of first degree relative by 2.5
- Ethnicity: African-American
- Obesity
- Diet: red meat-rich diet increases the incidence. Vitamin D deficiency could also be a risk factor.
- Polycystic ovary syndrome.
- Chromosomal changes, point mutations: Mediator complex subunit 12 (MED12), is the most frequently mutated gene in uterine leiomyomas, with a frequency of 50%–85%

What are the preventive factors for leiomyomas?

- Exercise, multiparity (three or more delivery) decreasing the risk up to 5-fold, smoking (conflicting data, also subsequent studies showed an increased risk of myoma with smoking), oral contraceptives, and postmenopausal period reduce the incidence

What is the nomenclature of leiomyomas according to their location in the uterus?

- Submucous (FIGO type 0, 1, 2): Completely within the endometrial cavity and/or extend into myometrium
- Intramural (FIGO type 3, 4, 5): They are located within the uterine wall (myometrium)
- Subserosal (FIGO type 6, 7): They are located on the serosal (outer) surface of the uterus, extend beyond the uterus, could be pedunculated, intraligamentary (i.e., broad ligament), parasitic as well, abdominal wall fibroids.
- Cervical (FIGO type 8)

What is the most common neoplasia encountered at the round ligament?

- Fibroids

What are the common features of submucosal fibroids?

- It is usually found beneath the endometrial lining of the uterus. As it grows, it can fill the endometrial cavity and enlarge the uterus. Abnormal uterine bleeding, infertility, habitual abortion are more common in submucosal myomas.

What are the general features of subserosal fibroids?

- They originate from the myometrium at the serosal surface of the uterus. Sometimes it extends into the abdominal cavity, as it grows, it becomes a myoma that is connected with a stalk (pedunculated myoma). Rarely, this myoma adheres to the abdominal wall, omentum, mesocolon, where it finds another blood supply, and then the stalk is degenerated, which is called parasitic myoma, really rare. Also parasitic fibroids are hypothesized to arise as a result of accidental seeding during morcellation of uterine fibroids for removal during surgery.

What are the anatomical structures that complicate the surgical removal of intraligamentous fibroids?

- Surgery is difficult because of its proximity to the ureter and iliac vessels also may lead to concealed hematoma formation.

Which fibroids are associated with hydronephrosis?

- Cervical myoma that enlarge toward the parametrium and may constrict ureters causing hydroureters and hydronephrosis.

What is the main reason for degenerative changes to occur in fibroids? Which types of degenerative changes could occur in fibroids?

- Degenerative changes are considered to result from excessive growth that outmatches the blood supply or mechanical compression of the feeder arteries.
- Degenerative or secondary changes are detectable in approximately 65% of uterine leiomyomas.

1. Hyalen degeneration: most common (63%)
2. Myxomatous changes (13%)
3. Calcification (8%)
4. Mucoid changes (6%)
5. Cystic degeneration (4%)
6. Red degeneration (3%) (especially in pregnancy)
7. Fatty changes (3%)
8. Malignant (sarcomatous) degeneration: least observed

How is the usual clinical presentation of fibroids?

- They are mostly asymptomatic, generally coincidentally diagnosed.
- The most common complaint and reason for surgery of fibroid is abnormal uterine bleeding (AUB).
- Pain is the most frequent sign of uterine leiomyoma degeneration and presented clinically as dyspareunia, dysmenorrhea, pressure symptoms, and discomfort.
- Pressure symptoms: such as frequent urination, nocturia, or urgency, and may be tenesmus.
- Submucosal myoma: infertility may be the reason for admission to clinic.
- Subserosal myomas usually do not present with symptoms unless they grow in huge size.
- Thrombophlebitis may be associated with pelvic congestion.
- Polycythemia and hypertension can be seen in very large (giant) fibroids.

- Submucosal myoma may cause distortion in the uterine cavity and causes fertility by disrupting endometrial implantation.
- The most common complication of myomas is iron deficiency anemia due to AUB.

Can myoma uteri be the cause of acute abdomen?

- Acute abdomen develops rarely as a result of torsion or infarction of a subserosal myoma with a stalk (pedunculated fibroid); the acute abdomen may require emergency operation.
- Myoma degeneration may be the cause of pelvic pain and can be removed, described as dyspareunia or pelvic compression.

How could you diagnose fibroids?

- Clinically significant subserosal and intramural myomas can usually be diagnosed by bimanual pelvic examination; enlarged, irregularly shaped, firm, and nontender uterus.
- Transvaginal sonography (US) is the most preferred and least costly technique and used for differentiating myomas from other pelvic conditions.
- Submucous myomas often require saline-infusion sonography (SIS) (in order to differential diagnosis with polyps), hysteroscopy, or MRI for definitive diagnosis.
- In case of fast growing fibroids, dynamic MR is requested in order to make differential diagnosis with sarcoma.
- Definitive diagnosis of myomas is made by postoperative pathological examination.

Describe the management of leiomyomas.

- Medical and surgical treatment can be applied.
- Observation/follow-up can be performed in non-symptomatic conditions.
- In asymptomatic women, treatment should be decided in according to the fertility demand of the patient.
- Asymptomatic women without fertility desire could be followed up without surgery. Pregnancy could be allowed in untreated women having fibroids without a distortion in the cavity.
- Medical treatment (especially for heavy menstrual bleeding and improvement in anemia):
  - Oral contraceptives
  - Progestational agents
  - Levonorgestrel-releasing intrauterine system (LNG-IUD)
  - Gonadotropin-releasing hormone (GnRH) agonists (most effective medical therapy for uterine fibroids)
  - GnRH antagonists (rapid onset without initial flare-up that observed with GnRH agonists), selective estrogen receptor modulators (SERMs; raloxifene)
  - Progesterone receptor modulators [ulipristal acetate (monitor liver function tests), mifepristone (antiprogestin—RU 486)]

  - Aromatase inhibitors (not to use alone, cause ovarial cysts)
  - Antifibrinolytics (tranexamic acid)
  - Nonsteroidal anti-inflammatory drugs (NSAIDs; naproxene)
  - Androgenic steroids (danazol and gestrinone)
- Surgery:
  - Hysterectomy (in case of bleeding not responding to other therapies, completed fertility, and fibroids are the most common indications for hysterectomy)
  - Myomectomy (patients with not completed fertility, wish to retain their uterus)
  - Endometrial ablation (completed fertility, wish to retain their uterus; not to be effective in intramural and subserosal fibroids)
  - Myolysis (i.e., radiofrequency ablation)
  - Uterine artery occlusion (alternative to uterine artery embolization)
  - Uterine artery embolization (interventional radiology)
  - Magnetic resonance guided focused ultrasound (MRgFUS) (noninvasive thermoablative technique)

What are the indications for surgical treatment of fibroids?

1. Abnormal uterine bleedings that do not respond to medical treatment
2. Severe dysmenorrhea, dyspareunia, or severe pelvic pain, discomfort.
3. Acute abdomen caused by torsion of myoma, degenerative myomas
4. Uterine fibroids that protruded through the external orifice of the cervix into the vagina
5. Hydronephrosis (cervical myoma)
6. Infertility due to myoma (distortion of the uterine cavity)
7. Recurrent pregnancy losses (distortion of the uterine cavity, hinders implantation)
8. Rapid increase in uterine size during premenopausal period
9. Any increase in uterine size during postmenopausal period

How does myoma uteri in pregnancy affect the course of myoma and pregnancy?

- 30% of the myomas grow during pregnancy and the growth is highest within the first 10 weeks and after 4 weeks of delivery, the fibroids tend to shrink.
- Myoma degeneration is seen in 5% of pregnancy and the most common type of degeneration during pregnancy is red degeneration and mimics acute abdomen. The most appropriate treatment is resting and non-narcotic analgesic (ibuprofen).
- Vaginal delivery is preferred as long as it does not narrow the birth canal, but pay attention to postpartum hemorrhages!

What is the main hormonal cause of endometrial hyperplasia?

- Endometrial hyperplasia most often is caused by excess estrogen without progesterone

Describe clinical importance of endometrial hyperplasia and its relationship with cancer.

- The glandular epithelium of the endometrium proliferates (resulting in a greater gland-to-stroma ratio) and undergoes various stages to malignant degeneration. Malignant transformation may occur if the state of unopposed estrogen continues for a long period of time (type 1 endometrial cancer).

What are the risk factors for endometrial hyperplasia?

1. Anovulatory cycles (the most common cause; absence of ovulation and a luteal phase, so absence of progesterone as well)
2. Endogenous estrogen producing tumors (granulosa cell tumor, thecoma, or theca cell tumor)
3. Early menarche (menarche before the age of 12)
4. Use of exogenous estrogen without progesterone
5. Cirrhosis (estrogen degradation decreases and serum estrogen level increases)
6. Postmenopausal women on tamoxifen treatment

What is the most common symptom of endometrial hyperplasia?

- Heavy menstrual bleeding (AUB)

How could you make definitive diagnosis of endometrial hyperplasia?

- Endometrial biopsy is required for definitive diagnosis. Endometrial biopsy should be taken if the endometrial thickness is above 14 mm in women of reproductive age and 5 mm or above in postmenopausal women. On the other hand; according to latest committee opinion of ACOG on "The Role of Transvaginal Ultrasonography in Evaluating the Endometrium of Women With Postmenopausal Bleeding": An endometrial measurement greater than 4 mm that is incidentally discovered in a postmenopausal patient without bleeding need not routinely trigger evaluation

What is the classification and prognosis of endometrial hyperplasias?

- The 2014 WHO endometrial hyperplasia classification system has only two categories:
  - Hyperplasia without atypia (non-neoplastic)
  - Atypical hyperplasia (endometrial intraepithelial neoplasm-EIN)
- The 1994 WHO classification of endometrial hyperplasia had four categories:

	1994 WHO classification	Regression	Progression to cancer
1	Simple hyperplasia without atypia	80%	1%
2	Complex hyperplasia without atypia	70–75%	3%
3	Simple atypical hyperplasia	70–75%	8%
4	Complex atypical hyperplasia	50%	29%

What is the treatment of endometrial hyperplasia?

- Progesterone is used in the treatment. LNG-IUD (Mirena®) is more preferred and recommended recently.

- In cases of complex atypical hyperplasia, if there is no expectation of fertility, hysterectomy is recommended and hysterectomy should be performed in postmenopausal atypia hyperplasia, intraoperative frozen pathology should be studied because 40% of patients with endometrial biopsy results with complex atypical hyperplasia resulted as endometrial cancer.

What are the features of acute endometritis?

- Inflammation of the endometrium. Acute endometritis is characterized by the presence of microabscesses or neutrophils within the endometrial glands (but in chronic endometritis characterized by plasma cells within the endometrial stroma).
- The uterus is tender.
- There are foul-smelling vaginal discharge, high fever (but in C. sordellii infection absence of fever is one of its clinical features), and leukocytosis.
- The pathogens could be anaerobic organisms, group B streptococci, chlamydia, mycoplasma, and gonococci.
- Treatment is hospitalization and antimicrobial therapy (doxycycline 2 × 100 mg oral for 5 days or metronidazole 2 × 500 mg for 5 days oral).
- There is no indication for curettage in the treatment of endometritis unless there is retention of placenta; incomplete abortion.

What are the characteristics of chronic endometritis?

- Pathologically, plasma cells are seen in the endometrial stroma.
- Idiopathic endometritis is the most common cause of chronic endometritis.
- Women usually present with abnormal uterine bleeding, consisting of intermenstrual bleeding, spotting, postcoital bleeding, menorrhagia, or amenorrhea.
- Often encountered in postmenopausal women.
- Hysteroscopic view: hyperemia, mucosal edema, micropolyps.
- It occurs in the non-spilled basal layers of the endometrium.
- Treatment: Doxycycline 2 × 100 mg oral for 10–14 days.
- Endometritis → Endometrial nutrition deficiency → atrophy → postmenopausal bleeding.
- In case of continuous bleeding, hysterectomy may be recommended.

Describe the properties of endometrial polyps.

- It is formed by the hyperplastic development of the gland and stroma of the endometrium and may include smooth muscle cells.
- They are attached to the endometrium with a pedicle, their borders are regular (in endometrial cancer, the borders are irregular).
- Single or multiple.
- It can extend to the cervix or vagina.
- Microscopic view is similar to normal endometrium, it has estrogen and progesterone receptors.
- They are usually asymptomatic.

- Polyps are more prevalent in patients with Lynch, Cowden syndrome, obesity, receiving hormone replacement therapy, tamoxifen treatment. LNG-IUD (Mirena®) could be used as a preventive measure.
- The most common symptom is irregular bleeding (AUB-P), intermenstrual bleeding, postmenopausal hemorrhage (PMB), and bleeding during the coitus.
- Except hyperplasic types, polyps are not premalignant (at least 95% benign), but caution should be taken in patients taking tamoxifen because the rate of malignant transformation is more frequent in those patients (about 10%).
- Its treatment (usually above 1 cm) is removal of the polyp (generally with hysteroscopy).
- The relationship between endometrial polyps and spontaneous abortion and negative pregnancy outcomes was not proven in the trials.
- Diagnosis could be done by: direct observation of the polyp protruding through the endocervical canal, US, SIS, hysteroscopy.

In which cases should polypectomy be planned in an asymptomatic woman?

- Polyp > 1–1.5 cm
- Multiple polyps
- Protruded through the cervix
- Infertility

Describe Asherman's syndrome; what are the symptoms, diagnosis, and treatment?

- It is the presence of adhesions (fibrous bands) between the endometrial linings of the opposite sites of the uterus (intrauterine) due to aggressive or multiple curettage or due to infections.
- It may also occur due to tuberculosis.
- The uterine cavity is partially or completely closed (could be observed by hysterosalpingography -HSG or hysteroscopy).
- **Symptoms:**
- Secondary amenorrhea
- Infertility
- Hypomenorrhoea
- Diagnosis: Thorough Anamnesis then SIS or HSG or hysteroscopy.
- **Treatment:**
- Hysteroscopic adhesiolysis and intrauterine Foley's catheter balloon for prevention of intrauterine adhesions (10 days) or IUD is applied after the procedure. High dose estrogen is given. However, after adhesiolysis, approximately 30% of adhesions have a risk of recurrence. Follow-up could be done by ultrasound 3 weeks after hysteroscopic adhesiolysis. After 2–3 months, the cavity can be evaluated again with hysteroscopy. If significant adhesions are observed again, they are re-operated.
- Pregnancy rates after adhesiolysis; 61% in patients with mild adhesion, 53% in patients with moderate adhesions, and 25% in patients with severe adhesions.

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Chapter 36
Benign Diseases of Ovary and Tuba

What are the functional cysts of the ovary?

1. Follicular cyst (the most common functional ovarian cyst)
2. Corpus luteum cyst (most commonly ruptured and causing hemoperitoneum)
3. Theca-lutein cyst (hyperreactio luteinalis) (rarest functional ovarian cyst)

- They are the most common cysts, often asymptomatic.
- Torsion or rupture may result in acute abdomen.
- Smoking increases, oral contraceptive decreases the formation of functional cysts.

What are the main features of follicular cyst?

- It is the most common functional ovarian cyst.
- These cysts can reach 8 cm in diameter and often disappear spontaneously between 4–8 weeks.

What are the features of the corpus luteum cyst?

- They are unilateral and 3–11 cm in size.
- They usually regress spontaneously within 1–2 months.
- They may rupture in the 20–26 days of the menstrual cycle and cause intraabdominal hemorrhage.
- It can be clinically confused with ruptured ectopic pregnancy as it usually causes amenorrhea or menstrual delay, check β-hCG value.
- It is the most frequently ruptured cyst causing hemoperitoneum.
- Bleeding, rupture, or torsion of this cyst is the common cause of gynecological acute abdomen.
- The corpus luteum, which normally continues to function after ovulation by the LH hormone, will regress after a while if no hCG stimulation occurs.

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https://doi.org/10.1007/978-3-030-29669-8_36

- When regressed, the corpus becomes albicans and progesterone synthesis progressively decreases and menstrual bleeding begins (progesterone withdrawal bleeding).

How does Halban syndrome occur, and manifest itself clinically?

- The persistence of the corpus luteum without pregnancy is called Halban syndrome.
- Progesterone release from the corpus luteum continues.
- It manifests itself in the clinic with progesterone breakthrough hemorrhage and adnexal mass formation occurs after menstrual delay.
- This situation is most often confused with ectopic pregnancy.
- Differential diagnosis is made with hCG test.

What are the features of Theca-lutein cyst?

- They are the rarest form of functional cysts.
- They are usually bilateral and occur mostly during pregnancy (especially in molar and multiple pregnancy, because of high hCG).
- These cysts are usually large in size (30 cm) and multicystic.
- Since high hCG is a risk factor, it is associated with molar pregnancy, multiple pregnancies, diabetes, Rh isoimmunization, ovulation induction with clomiphene citrate, hMG or FSH, and the use of GnRH analogues.
- They can spontaneously regress.

What are the causes of pelvic masses in different age groups of women?

- Infantile period:
  - Functional cyst
  - Germ cell tumor
- Prepubertal period:
  - Functional cyst
  - Germ cell tumor
- Adolescent period:
  - Functional cyst
  - Pregnancy
  - Dermoid / other germ cell tumor
- Reproductive period
  - Functional cyst
  - Pregnancy
  - Fibroids
- Perimenopausal period
  - Fibroids
  - Epithelial ovarian tumors
  - Functional ovarian cyst

- Postmenopausal period
  - Ovarian tumor (benign / malignant)
  - Functional cyst
  - Metastases from other organs

How would you make a decision on an ovarian mass as benign from the appearance on ultrasonography?

- Diameter <8 cm
- Unilocular cyst
- Smooth surface
- No ascites
- Unilateral
- Mobile
- Thin-walled
- No additional abdominal organ pathologies
- No neovascularization
- Doppler values are normal
- No internal echogenicity and thick septation

What are the malignant appearance criteria of the ovarian mass on ultrasonography?

- Diameter> 8–10 cm
- Multilocular—solid mass
- Irregular surface
- Ascites
- Bilateral
- Fixation (adhering to surrounding tissues)
- Thick-walled
- Additional abdominal organ pathologies
- Neovascularization
- Doppler changes
- Internal echogenicity and thick septation

Describe the symptoms, diagnosis, and management of ovarian cysts in the prepubertal age group.

- The most common clinical presentation is abdominal pain.
- Ultrasonography is the most commonly used method in diagnosis.
- MRI (especially in detection of mullerian anomalies).
- Tumor markers are used (hCG, AFP, LDH, HE4, etc.).
- Unilocular cysts are almost always benign.
- Usually regresses in 3–6 months.
- Cyst aspiration is not recommended, since high recurrence rates.

Describe the symptoms, diagnosis, and management of ovarian cysts in adolescences and reproductive age groups.

- It is recommended to follow simple cysts smaller than 8–10 cm.

- After follow-up, oral contraceptives could be given in order to prevent new functional cysts.
- Surgery is planned if there is persistence or growth in size.
- Surgery is planned for masses over 8–10 cm or for suspected malignancies.

Describe the symptoms, diagnosis, and management of ovarian cysts in the postmenopausal age group.

- Asymptomatic cysts less than 8 cm, uniloculated, simple cystic appearance, and if tumor markers are within normal limits (CA-125 <35 IU/mL), the probability of malignancy is very low and these cysts can be monitored without surgery.

What is the features and clinic of ovarian torsion and how would you manage it?

- Twisting of the ovary on its vascular pedicle, causing venous congestion and then to the arterial blood supply becoming compromised, resulting in tissue necrosis.
- The most important risk factor is ovarian mass.
- Generally, the most common cause of torsion is functional ovarian cysts.
- The most common neoplastic torsion is mature cystic teratoma, since bilaterality is a common feature of dermoids, do not forget to examine the opposite over if there is dermoid cyst, even in cases of emergency unilateral torsion, so that future torsion cases can be prevented.
- Symptoms are sudden onset abdominal pain, nausea, and vomiting and acute abdominal symptoms are present.
- Doppler ultrasound is the most successful method in the preliminary diagnosis (whirlpool appearance; enlarged ovary, an echogenic mass).
- The definitive diagnosis is made during surgery (generally laparoscopy) since direct observation is needed.
- Laparoscopic procedure is preferred.
- Ovary and fallopian tube (namely adnexa) are often rotated together.
- Laparoscopically, first the torsion is detorsed and released and followed for minutes to visualize color changes or not (from purple to pink gain). Also ovary could be incised to observe its viability, ratio of ischemia, or necrosis. Cystectomy is performed.
- Oophorectomy may be considered if there are signs of peritonitis during follow-up.

What is the clinic of tubo-ovarian abscess and how do you manage it?

- Tubo-ovarian abscess (TOA) is the last step of PID.
- It often develops as a result of late or inadequate treatment.
- On examination, a semisolid mass is detected.
- Diagnosis should be supported by ultrasound.
- In case of TOA, the patient is hospitalized and given empirical antibiotic treatment.
- If there is no response to medical treatment, surgical drainage is required.

- Rupture requires immediate laparotomy because it causes acute peritonitis, emergency.
- If left untreated, it may cause sepsis and exitus.

Describe the hydrosalpinx and its management
- This chronic swelling in the fallopian tube, due to blockage, is usually one of the long-term results of PID.
- It is swollen, thin-walled, elongated tuba, pale, and translucent in appearance.
- May cause infertility and pelvic pain.
- Treatment varies depending on the desire for fertility and the symptoms.
- Salpingectomy could be performed in the patient who does not want fertility.
- Infertile and IVF patients with hydrosalpinx; Salpingectomy is recommended before IVF, since ectopic pregnancy rates are increased.

What is the most common benign tumor of the tuba?
- Fallopian tube tumors are rare.
- The most common benign tumor is mesothelioma.

What is the prevalence of adnexal masses in pregnancy?
- The prevalence of adnexal masses in pregnancy is estimated to be around 0.19–8.8%

What is the most important predictors for persistence of adnexal masses in pregnancy?
- The best predictors for persistence of adnexal masses in pregnancy are complex appearance on sonography and size of the mass (>5 cm).

What are the common complications of adnexal masses in pregnancy?
- Torsion, rupture, malignancy, abortion, preterm delivery, and bleeding.

When would you consider surgery in diagnosis of adnexal masses in pregnancy?
- In case of acute abdomen, strong suspicion of malignancy, surgical intervention is considered. If not urgent, surgery should be delayed until the second trimester.

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Chapter 37
Approach to Amenorrhea

What is the definition of amenorrhea, primary and secondary amenorrhea?

- Amenorrhea is the situation that the woman cannot see spontaneously menstruation in the reproductive age, namely absence of menses.
- Primary amenorrhea: absence of menarche until the age of 16, whose secondary sex characters developed, and until the age of 14 in those secondary sex characters not yet developed.
- Secondary amenorrhea: cessation of menses at least 3 cycles, 3 months in a woman who previously had regular menstruations, 6 months if she had irregular menstruations.

What are the most common etiologies of the primary amenorrhea?

1. Gonadal dysgenesis (i.e., Turner syndrome): 43%
2. Müllerian agenesis: 15%
3. Constitutional delay: 14%
4. Isolated gonadotropin-releasing hormone (GnRH) deficiency: 5%
5. Transverse vaginal septum: 3%
6. Weight loss/anorexia nervosa: 2%
7. Hypopituitarism: 2%
8. Imperforate hymen, complete androgen insensitivity syndrome, hyperprolactinemia, pituitary tumors, congenital adrenal hyperplasia, hypothyroidism, central nervous system defects, craniopharyngioma, and Cushing's disease: <1%

What are the most common and primary causes of secondary amenorrhea?

- The most common cause of secondary amenorrhea is pregnancy, never to forget!
- Other reasons:

    1. Chronic anovulation: 28%
    2. Hypothalamic suppression: 10%
    3. Anorexia / weight loss: 10%
    4. Prolactinomas: 7.5%

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https://doi.org/10.1007/978-3-030-29669-8_37

5. Asherman syndrome: 7%
6. Hypothyroidism: 1%

What is the classification amenorrhea according to FSH values?

- Hypergonadotropic hypogonadism: FSH = >30 mIU/mL
- Hypogonadotropic hypogonadism: FSH = 5–30 mIU/mL
- Normogonadotropic hypogonadism: FSH = <5 mIU/mL

What are the common etiologies of hypergonadotropic amenorrhea?

1. Gonadal dysgenesis (most common)
   (a) Turner syndrome (most common)
   (b) 46, XX pure gonadal dysgenesis
   (c) 46, XY pure gonadal dysgenesis (Swyer syndrome)
2. Partial deletion of X chromosome
3. Mosaic structure in sex chromosomes (45X / 46XX most common)
4. Fragile X syndrome
5. Gonadotropin receptor mutations
   (a) LH receptor mutation
   (b) FSH receptor mutation
6. Resistant ovarian syndrome (Savage syndrome)
7. Autoimmune oophoritis (Blizzard syndrome)
8. Galactosemia
9. Enzyme defects
   (a) 17a-Hydroxylase and 17-20 desmolase deficiency
   (b) Aromatase deficiency
   (c) Congenital lipoid adrenal hyperplasia
10. Radiation and chemotherapy
11. Infections
12. Complete androgen insensitivity (testicular feminization)

What are the common etiologies of hypogonadotropic amenorrhea?

1. Physiological (constitutional) delay (most frequent)
2. Kallmann syndrome
3. Central nervous system tumors (the most common: craniopharyngioma)
4. Pituitary lesions
   (a) Empty sella syndrome
   (b) Sheehan syndrome (pituitary apoplexy)
   (c) Infections (tuberculosis, sarcoidosis)
   (d) Schuller–Christian disease
   (e) Diabetic vasculitis
   (f) Sickle cell anemia
   (g) Pituitary adenomas and pituitary hypoplasia

5. Disruption of hypothalamic GnRH release
   (a) Anorexia nervosa, bulumia, malnutrition
   (b) Stress, extreme exercise
   (c) Hyperprolactinaemia
   (d) Hypothyroidism
   (e) PCOS
   (f) Cushing's syndrome, obesity
6. GnRH receptor mutation
7. FSH deficiency
8. 5α reductase enzyme deficiency

What are the common etiologies of normogonadotropic amenorrhea?

1. Müllerian anomalies
   (a) Imperfore hymen
   (b) Transverse vaginal septa
   (c) Absence of cervix or vagina
   (d) Mayer–Rokitansky–Küster–Hauser (RKMH) syndrome
2. Asherman syndrome
3. Absence of endometrium

What is the most common cause of primary amenorrhea and hypergonadotropic hypogonadism?

- Gonadal dysgenesis (Turner)

Which hypogonadism should be performed in the presence of karyotype analysis?

- Hypergonadotropic hypogonadism

When chromosome analysis is performed, and Y chromosome (SRY) is detected, why should the gonads be removed from the patient?

- Due to the malignant transformation risk (the most common: dysgerminoma) of the gonads immediately should be operated, except testicular feminization (gonadectomy performed after puberty)

Describe testicular feminization (complete androgen insensitivity syndrome-CAIS).

- The incidence is 1/20,000 births.
- The karyotype 46 is XY.
- Since there is androgen receptor defect, there is androgen unresponsiveness (resistance).
- Serum testosterone levels are very high.
- There is no uterus.
- Female phenotype with normal breast development.
- Testes present, as inguinal or labial masses.

- There are defects in the gene encoding the androgen receptor in the long arm of the X chromosome, recessively inherited from maternal X chromosome.
- Internal genitals have not developed (Empty)
- External genitals are female in nature, but there is a blind vagina from the urogenital sinus because only the lower one-third part of the vagina develops.
- Secondary sex character development is asynchronous; breast development with peripheral aromatization of androgens. There is no pubic and axillary hair due to androgen receptor defect.
- They have long arm, big hand, and foot, and they are tall.
- Because the pituitary androgen receptors are defective, androgens cannot form negative feed-back on LH and LH increases.
- The testosterone level is also at the normal male level.
- Gonadectomy should be performed when the pubertal development is complete.

What is the most common CNS tumor leading to primary amenorrhea?
- Craniopharyngioma

Describe Sheehan's syndrome.
- Pituitary necrosis due to hypovolemic shock caused by postpartum hemorrhage.
- Postpartum amenorrhea develops and usually the first finding is the absence of lactation.

What is the type of amenorrhea, which is often caused by anatomical anomalies?
- Normogonadotropic amenorrhea

Describe Rokitansky–Küster–Mayer–Hauser (Mullerian agenesis) syndrome.
- FSH levels are at the normal range between 5 and 30 mIU/mL. No need to perform karyotype analysis (46, XX; normal).
- Ovaries are present and ovarian functions are normal. However, the upper part of the vagina, tuba, and uterus are variably developed and present like a thin band.

Describe additional extragenital organ anomalies in Rokitansky–Küster–Mayer–Hauser Syndrome
- Mostly exhibit urologic anomalies: 40% of patients had double collecting duct, 15% had pelvic or horseshoe kidney, and renal agenesis
- 5–12% had skeletal anomalies (spine, costas, and extremities).
- Also may exhibit, heart, hand, hearing, palatial defect, and inguinal or femoral hernias.

What are the features of Asherman syndrome?
- Intrauterine adhesions are developed after harsh endometrial curettage, cesarean, myomectomy, and metroplasty operations due to the result of damage to the basal endometrium. These adhesions lead to secondary amenorrhea, menstrual irregularities, and infertility.
- Although amenorrhea is the most prominent symptom, pregnancy losses, dysmenorrhea, and hypomenorrhea are also encountered.

How would you evaluate a patient with amenorrhea? Explain the steps.

- History taking; primary or secondary amenorrhea.
- Measurement of the β-hCG, ruling out the pregnancy should be the first step.
- After ruling out the pregnancy then level of the FSH should be measured (premature ovarian failure? in case of secondary amenorrhea; in case of primary amenorrhea categorize the patient according to FSH levels that mentioned above).
- Also, TSH and PRL levels should be obtained. Pelvic ultrasound, uterus, and ovaries are examined.
- Algorithmically, patients with and without uterus are divided into two.
- Karyotype analysis and serum total testosterone levels are requested from patients without uterus.
- No uterus and karyotype: 46 XX is RKMH.
- No uterus and karyotype: 46, XY is androgen insensitivity syndrome, 5 alpha-reductase deficiency are possible preliminary diagnoses.
- In patients with uterus, according to FSH: high FSH and normal-low FSH.
- In patients with high FSH: if there are 17 alpha-hydroxylase deficiency findings (hypertension, no secondary sex characters or minimal hair), CYP17 analysis is performed.
- In case of 17 alpha-hydroxylase deficiency symptoms are not observed then karyotype analysis is performed.
- 46, XX: primary ovarian insufficiency (POI).
- 46, XY: gonadal dysgenesis (Swyer syndrome).
- 45, X: Turner.
- If uterus is present and FSH level is not high, it is divided into two categories according to breast development.
- Tanner stage 2 and above: presence of hematoma or similar defects are scanned by ultrasound. Imperforate hymen, transverse vaginal septum may exhibit those symptoms.
- If there is no finding detected by ultrasound; endocrinologic disorders such as hyperprolactinemia, abnormal TSH, PCOS could be the cause.
- Uterus is present but breast development is not sufficient (less than Tanner stage 2); FSH and LH are evaluated.
  - If the level of FSH and LH is low, structural delay, congenital GnRH deficiency could be the cause. Pituitary MRI would be a good option to evaluate intracranial reasons.
  - If the level of FSH is normal, but LH is low; functional hypothalamic amenorrhea may be the reason due to systemic diseases (i.e., Celiac, type 1 DM). Again pituitary MRI would be the option here.

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Chapter 38
Menopause-Osteoporosis

What is the definition of menopause and osteoporosis?

- The transition from normal cycles to menopause is a perimenopausal period (climacteric period) (40–50 years old) (old term, now more menopausal transition is used, takes 4–7 years).
- Menopause: Permanent cessation of menstrual cycle following loss of ovarian function (no menstruation during 12 months).

What are the risk factors for early menopause?

- History of hysterectomy
- Ovarian cyst or pelvic surgery
- Smoking (polycyclic aromatic hydrocarbons)
- Nulliparity
- Chemotherapeutics
- Radiotherapy
- Vegetarian nutrition
- Low socioeconomic level
- Low level of education

What are the hormonal changes in the perimenopausal transition period?

- As a result of a decrease in ovarian function, inhibin released from granulosa cells decreases.
- As a result of the reduction of the inhibition of FSH, FSH starts to rise firstly.
- High FSH indicates that ovarian reserve decrease.
- However, patients may have menstrual periods and become pregnant.
- There may be anovulation and follicular phase change with decreased ovarian quality.
- In this case, oligomenorrhea and polymenorrhea can be seen clinically.

Acknowledgments The author would like to thank Dr. Büşra Aynalı who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_38

- However, it should be noted that ovulation may occur and unintended pregnancies may occur.
- Therefore, without observing FSH >20 ng/dL, LH >30 ng/dL, contraception should not be forgotten.

Describe hormonal changes in the menopausal period
- After termination of ovarian follicular activity, serum FSH and LH levels are increased.
- Menopause is a natural hypergonodotropic hypogonadism.
- The increase in FSH value was significantly higher than LH, because LH was shorter in half-life, and Inhibin has no negative feedback effect on LH.
- The level of postmenopausal estradiol is very low.
- The main estrogen in this period is Estron.
- The origin of the Estron is the transformation of the peripheral androstenodion with the aromatase enzyme.

What can unopposed Estrogen cause in postmenopausal women?
- Endometrial hyperplasia, polyp increases the risk of endometrial cancer; causes a decrease in the rate of osteoporosis.

What are the primary steroids secreted from the ovaries after menopause?
- Androstenedione and testosterone

What is the cause and treatment of vasomotor symptoms (flushing) in menopausal period?
- It is a condition that occurs as a result of estrogen withdrawal; estrogen deficiency is not a cause, especially at nights.
- Dysfunction of the central thermoregulatory region in the hypothalamus is thought to be the cause. It is the most common cause of estrogen replacement initiation.
- Although the cause is not known exactly, central estrogen deficiency-fluctuation may be responsible.
- **Treatment:** Estrogen, progesterone, Venlafaxine, Selective Serotonin Reuptake Inhibitor (SSRI), Serotonin–norepinephrine reuptake inhibitors (SNRI), veraliprid (dopamine antagonist), clonidine (α2 rec agonist), vitamin E, bellergal.

What are the risk factors for vasomotor symptoms?
- Surgical menopause
- Smoking
- BMI (underweight? obese?)
- Race (Afro-American women has more tendency to experience vasomotor symptoms> Caucasian> Asian)
- Early menopause, low estradiol level, sedentary life, selective estrogen receptor modulator (SERM)

What kind of changes and increased risks do you expect to see in menopausal period?
- Atrophic vaginitis, endometrial, myometrial atrophy occurs and the uterus becomes smaller.

- Osteoporosis.
- Changes in mood occur (tension, irritability, depression).
- Increased cardiovascular disease (CVD) risk: In menopause, serum LDL level increases due to decreased estrogen and increased androgens. And serum HDL level decreases. After age of 60, the lipid profile becomes worse than males.
- With age; fibrinogen, plasminogen activator inhibitor-1 (PAI-1), and factor VII increase.
- Hypercoagulability.
- Hyperpigmentation of the skin, wrinkles and itching depends on depressed collagen content, decreased sebaceous gland, decreased elasticity, impaired blood flow, and epidermal changes.
- Buccal epithelium (mouth-to-cheek) is atrophied due to estrogen deficiency, leading to reduced saliva and sensation. Bad taste in the mouth, increase in dental caries.

What is the definition of Osteoporosis?
- Reduced bone mass and reduced bone resistance and increased bone fracture risk

How would you diagnose osteoporosis?
- The diagnosis is made by bone mineral density (BMD): T <−2.5 (central DXA machine).

What are the risk factors for osteoporosis?
- Increased Age
- White and yellow race
- Petite and thin women
- Early menopause
- History of fractures
- Family history
- Inadequate calcium and vitamin D intake
- Smoking, alcohol, sedentary life
- Low body weight
- Hyperthyroidism
- Hyperparathyroidism
- Heparin, anticonvulsants, thyroxine, SSRI, proton pump inhibitors (PPI), Steroid use, aromatase inhibitors usage
- Type 1 DM
- Hyperprolactinemia
- Chronic renal failure

Which type of bone loss is more common in type 1 osteoporosis?
- Trabecular bone loss, vertebra. Estrogen deficiency is the main causative factor here.

Which type of bone loss is more common in type 2 osteoporosis?
- Trabecular and cortical bone loss. Senile osteoporosis. Estrogen deficiency+increasing age.

What are the options for osteoporosis treatment?

- Calcium and vitamin D
- Hormone Replacement Therapy (HRT)
- Estrogen agonist and antagonists (SERM)
- Bisphosphonates: Alendronate, risedronate, clodronate, zoledronate, and ibandronate
- Calcitonin
- Strontium
- Tibolone
- Teriparatide (Forteo)

What are the indications of hormone replacement therapy (HRT)?

1. Vasomotor symptoms
2. Urinary system atrophy
3. Genital system atrophy
4. Osteoporosis treatment

In which conditions estrogen like HRT should not be used?

1. Undiagnosed uterine bleeding
2. Have undergone known or suspected breast cancer
3. Known or suspected estrogen-dependent neoplasms
4. Active or passed DVT, pulmonary embolism
5. Active or past arterial thromboembolic diseases (stroke or MI)
6. Liver diseases or liver function disorders
7. Hypersensitivity to estrogen
8. Known or suspected pregnancy
9. Triglyceride (TG) level >500 mg/dL
10. Neuro-ophthalmologic vascular disease

What are the complications of HRT?

1. Endometrium cancer
2. Breast cancer; more than 5 years, especially in combined HRT areas
3. Myocardial infarction (MI)
4. Stroke
5. Venous Thromboembolism (VTE)
6. Alzheimer's, dementia and negative effect on cognitive functions
7. Cholelithiasis
8. Increases TG level (in oral form) (does not increase TG level in transdermal form)

What are the positive effects of HRT?

- Protective against colorectal cancer
- No effect against cervical cancer
- Reduces insulin resistance (Since, estrogen decreases insulin resistance)
- Protective against rheumatoid arthritis
- Positive effect on glaucoma and cataract
- Positive effect on age-related hearing loss

What are the conditions in which transdermal estrogen treatment should be preferred as HRT?

- Patients at high risk of VTE
- Patients with hypertriglyceridemia
- Obese patients with metabolic syndrome
- Patients with hypertension, smokers. Patients with urinary incontinence (it is important to know that oral HRT has negative impact on urinary incontinence although local HRT has positive therapeutic effect). In vaginal atrophy.

What are the conditions in which progesterone should be added to estrogen therapy in hysterectomized patients?

1. Patients operated for endometrial cancer
2. Endometriosis
3. Endometrioid tumor history in ovaries
4. Supracervical hysterectomy
5. Also in cases with endometrial ablation we prefer to add progesterone.

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Chapter 39
Polycystic Ovary Syndrome (PCOS)

What are the diagnostic criteria of polycystic ovary syndrome (PCOS) in reproductive aged woman, Rotterdam criteria?

- Two out of three:
  - Irregular menses, oligomenorrhea, anovulation
  - Clinical or biochemical signs of hyperandrogenism (acne, hirsutism, male pattern hair loss)
  - Polycystic ovaries on ultrasound: Presence of 12 or more follicles in each ovary measuring 2 to 9 mm in diameter and/or increased ovarian volume

What are the symptoms of PCOS in reproductive aged woman?

- Hirsutism: Ferriman Gallwey scoring, to assess the degree of hirsutism → measure serum androgens (serum total testosterone, sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), 17-hydroxyprogesterone)
- Acne: Persisting and poor response to treatment. Too many (more than 10 in one area)
- Menstrual abnormality, oligomenorrhea (due to anovulation, typically begin in the teenage years) → measure TSH, hCG, FSH, prolactin to investigate other causes of menstrual irregularity; LH (not necessary since LH/FSH ratio is not a criterion for the diagnosis)
- Obesity, acanthosis nigricans (insulin resistance)

Which endocrinopathy leads to the disorder of tyrosine kinase system in PCOS?

- Insulin resistance

What are the situations that can accompany in case of long-term PCOS?

- Type II diabetes and gestational diabetes
- Low HDL and high triglyceride levels
- Sleep apnea

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https://doi.org/10.1007/978-3-030-29669-8_39

- Nonalcoholic fatty liver (steatohepatitis)
- Metabolic syndrome
- Cardiovascular diseases
- Atherosclerosis
- Infertility: PCOS is the most common cause of infertility in women
- Endometrial cancer: Due to estrogen dominance and insufficient progesterone (anovulation)

What is the differential diagnosis of PCOS?
- Hyperprolactinemia: Leading the menstrual period, mild hyperandrogenism.
- Congenital adrenal hyperplasia: In the early follicular phase, if the morning serum 17-hydroxyprogesterone is >200 ng/dL, the high-dose ACTH stimulation test (250 μg) is performed and the diagnosis is confirmed if 17-hydroxyprogesterone is <1000 ng/dL.
- Ovarian and adrenal tumors
  - Serum testosterone concentrations are usually >150 ng/dL.
  - In adrenal tumors >800 μg/dL.
  - Low serum LH concentrations.
- Medication history of the patient: Danazol, OCS (androgenic OCS).
- Cushing's syndrome.

What are the goals of PCOS treatment?
- Alleviate hyperandrogenic symptoms (hirsutism, acne, male type hair loss)
- Decrease the risk of underlying metabolic abnormalities and type II DM and cardiovascular diseases
- Prevent the endometrial hyperplasia and carcinoma due to chronic anovulation

What are the pregnancy complications of PCOS patients, especially if women are obese?
- GDM
- Preterm delivery
- Preeclampsia

What is the treatment of PCOS?
- Lifestyle changes, diet, exercise to improve insulin resistance and hyperandrogenism especially in obese and overweight women.
- Combined estrogen-progestin oral contraceptives (COCs; ethinyl estradiol 20 μg, norethindrone acetate) in a patient who does not pursue pregnancy; aware of increased risk of venous thromboembolism especially in obese women.
- Ovulation induction in a patient who pursues pregnancy; first line is clomiphene citrate (CC) which is a selective estrogen receptor modulator; also aromatase inhibitor (letrozole) is another drug of choice for ovulation induction in women with PCOS.
- Antiantrogens (spironolactone, finasteride, dutasteride, cyproterone acetate, flutamide) are added in suboptimal cosmetic response to COCs after 6 months of usage.

- GnRH agonists; to suppress ovarian androgen production.
- Metformin.
- Thiazolidinedione, but not preferred because of concern about cardiovascular adverse effects.

Which progestins are usually chosen in the treatment of PCOS and what is the reason?

- Norethindrone
- Norethindrone acetate
- Desogestrel
- Cyproterone acetate
- Drospirenone
- Since they have lower androgenicity

What are the diagnostic criteria for polycystic ovary syndrome in the adolescent girl?

- Being at least 2 years postmenarche, hyperandrogenism (clinical and/or biochemical), and irregular menses are the required diagnostic criteria for PCOS in adolescents

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Chapter 40
Pediatric and Adolescent Gynecology

What is the meaning of puberty and characterized by what kind of changes?

- Puberty is the period of transition between childhood and adulthood, characterized by the development of secondary sexual characteristics, gonadal maturation, and attainment of reproductive capacity.

Which gynecological problems / complaints could patients come with in childhood and adolescence period?

- Vulvar inflammation
- Vaginal discharge
- Genital injury (trauma): A sharp object, mostly after falling, sometimes after rape, tearing, ecchymosis, hematoma
- Vaginal bleeding

What are the features and characteristics of vulvovaginitis in the pediatric period?

- The most common complaint in the pediatric period (90%)
- Because of poor perineal hygiene
- After birth—pre and postpubertal period, physiological leukorrhea due to estrogen effect, does not require treatment
- Nonspecific
  - Poor perineal hygiene or foreign body—polymicrobial
- Secondary
  - As a result of urinary tract infections
- Specific
  - Transmitted by sexual contact: N. Gonorhea, G. Vaginalis, etc.

Acknowledgments The author would like to thank Dr. Adile Y. Akdemir, Dr. Aykut Barut and Dr. Ülkü Özmen who contributed to this chapter.

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https://doi.org/10.1007/978-3-030-29669-8_40

- Specific infection: Upper vagina and cervix
- Nonspecific infection: Lower vagina and vulva, 90% of them improves with perineal hygiene, foreign object

Describe the causes of vaginal bleeding in the prepubertal and neonatal period

- First 10 days of newborn
  - Withdrawal of maternal estrogens
  - No examination and treatment is required if it does not exceed 10 days
- Prepubertal period
  - Trauma, foreign body, precocious puberty

Which structures are important in physical genital examination of a newborn girl?

- Structure of external genital organs
- Hymen opening (Imperforate?)

What is the condition of GnRH in prepubertal period?

- GnRH is under central inhibition

How is the development of prepubertal genital organs from newborn baby to the puberty?

- Newborn
  - Vagina and uterus length is totally 4 cm
  - Cervix is 3 times larger than the uterine corpus
  - Vaginal pH is acidic
  - Ovaries are located in the abdominal cavity
- 1 month–7 years
  - Vagina is 5 cm
  - Vaginal pH is alkali
  - Cervix is two times larger than the uterine corpus
  - Ovaries are located in the pelvis
- 7–10 years
  - Vagina is 6 cm
  - Length of cervix is equal to the uterine corpus
  - Ovaries are located in normal location in pelvis
- 10–13 years
  - Vaginal size increases
  - Uterine corpus is two times larger than the cervix
  - Ectropion
  - Vaginal fornix are formed

Which neoplasms and anomalies can be observed in girls of mothers as a result of estrogen use during pregnancy?

- Clear cell vagina adenocarcinoma
- Cervical anomalies
- Uterine anomalies
- Vaginal adenosis

What are the clinical features of sarcoma botryoid (embryonal rhabdomyosarcoma)?

- It presents with vaginal bleeding.
- It is the most common soft tissue sarcoma in childhood and young adulthood and constitutes 4–6% of all malignancies in this age group.
- Originated from the cervix or vagina.
- Develops fast and protrudes from the vaginal introitus.
- Look similar to grapes.
- Easily bleeding by touch.

What are the clinical features of ovarian tumors in adolescence and childhood?

- They are rare.
- They show endocrine activity.
- Germ cell (65%) → precocious puberty.
- Stroma (15%) → precocious puberty.
- Epithelium (20%).

What are the features of congenital adrenal hyperplasia (CAH)?

- Autosomal recessive disorder
- Hyperandrogenism
- Subdivisions of CAH are:
  - 11-β hydroxylase deficiency
  - 17 α-hydroxylase deficiency
  - 21-hydroxylase deficiency (75–90%)
  - 3-β-hydroxysteroid dehydrogenase deficiency
  - Congenital lipoid adrenal hyperplasia
  - p450 oxidoreductase deficiency
- Deficient cortisol production
- High ACTH values
- 17-hydroxyprogesterone (17-OHP) test is used to screen for CAH
- Two-third aldosterone synthesis is impaired
- Therefore, hyponatremia and hyperkalemia are observed.
- If untreated: death in the first week after birth
- Amenorrhea-cycle irregularities
- Treatment—Cortisone

What are the effects of maternal synthetic progesterone use on the fetus and the newborn?
- Masculinizing effect
- Hypertrophic clitoris
- Labial fusion

What is the definition of puberty?
- Transition from childhood to adulthood
- Maturation of reproductive organs
- Lasts about 4.5 years
- 2 years earlier in girls than boys

What are the steps of puberty?
1. Development of secondary sex characters (telarche, pubarche)
   (a) Telarche—breast development
   (b) Pubarche (adrenarche)—axillary and pubic hair
   (c) Menarche—first menstrual bleeding
2. Acceleration of growth
3. Bone maturation
4. Relative change of body shape

What are the determinants of pubertal development?
- Genetic factor
- Regional factors
- Climate
- General health and nutritional status
- Psychological factors

What kind of changes occur in pubarche?
- Pubic hair appears 6–12 months after telarche
- Axillary hair appears after 1 year
- Adrenal and ovarian hormones, testosterone, and estrogen increases
- Sweat glands develop
- Adult sweat odor

Describe the menarche
- First menstruation
- Occurring after maximum growth peak
- Ovulatory cycles begin after 1–2 years

Describe precocious puberty
1. If secondary sex characters appear : <8 years
2. If adrenarche starts : <9 years
3. If menarche starts : <10 years
4. <1%
5. Girls>Boys (5 times)
6. First longer than coevals, then becomes shorter than their peers (short stature in precocious puberty due to premature closure of growth plates in long bones)

7. 75% idiopathic
    - Isosexual
        - Puberty findings Genetic + gonads compatible with
    - Heterosexual
        - Puberty findings are incompatible with genetics + gonads

Describe precocious puberty according to gonadal activation

1. Precocious pseudo puberty (peripheral)
    - No relationship with gonadotropin stimulation
    - Because of abnormal steroid secretion or end organ sensitivity
2. Real precocious puberty (central)
    - Effect of steroid secretion hypothalamo-pituitary hormones

What are the features and causes of central precocious puberty?

1. Structural (idiopathic) (90%)
2. Hypothalamus tumors: Hamartoma, astrocytoma, ependymoma, glioma, neuroblastoma
3. Other CNS lesions: Abscess, encephalitis, granuloma, head trauma, hydrocephalus, meningitis, optic glioma, vascular malformations
    - Reproductive function is not affected, no early menopause
    - Single unwanted effect is short stature

What is the treatment central precocious puberty?

- GnRH agonists

What are the types of pseudo precocious puberty (peripheral).

1. Adrenal
    - Premature adrenarche
    - CAH
    - Tumors: Virilizing tumors, very rare
2. Ovary
    - Follicular cysts
    - McCune–Albright syndrome: Agent unknown, bone lesions, café au lait spots on skin, early puberty, autonomous secretion of sex steroids, other endocrinopathy (Cushing, hyperthyroidism, etc.)
    - Tumors: Granulosa and theca cell tumors (estrogen-secreting ovarian tumors)
3. Use of exogenous hormones
4. Other (hepatoma, hypothyroidism)
   Hypothyroidism: Rare, early puberty, ovarian cyst, galactorrhea, high estrogen, prolactin, and gonadotropins

What are the diagnostic steps of precocious puberty?

- First rule out: CNS, ovary, or adrenal lesions
- Anamnesis and physical examination
- Tanner classification of breast development
- Brain CT or MRI
- Pelvic USG or CT
- Determination of bone age (right hand radiography)
- HCG, TSH, LH, FSH, and steroid hormone levels are checked

What is the treatment of precocious puberty?

- Brain Tumor → surgery ± RT (but benign hypothalamic hamartomas are often left in situ, and follow-up periodically)
- Idiopathic central → GnRH analogues (up to 10 years)
- Peripheral → suppress steroid supply, block hormone

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Chapter 41
Infertility

What is the definition of infertility?
- Failure to conceive despite regular sexual intercourse without contraception at least for 1 year

What is the incidence of infertility in reproductive age group?
- 10–15% of the reproductive age group

What is the difference between primary and secondary infertility?
- Primary infertility: Couples who have not become pregnant after at least 1 year having regular sexual intercourse without using birth control methods
- Secondary infertility: A history of at least one pregnancy

What is the meaning of Fecundability?
- Fecundability is the probability of achieving a pregnancy within one menstrual cycle.

What is the meaning of Fecundity?
- Fecundity is the probability that a couple will conceive leading to a live birth in any given menstrual cycle.

What are the reasons for the increase in the demand for infertility services in recent years?
- Postponing marriage and child expectation at an advanced age.
- Artificial reproductive techniques (ART) are improved.
- Public awareness.
- Increased rate of tubal dysfunction as a result of increased sexually transmitted diseases.

Acknowledgments The author would like to thank Dr. Eray Çalışkan who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_41

What are the changes in oocyte count, fertility rates, and spontaneous abortion rates in females from fetal life to advanced ages?

- The total germ cell number peaks at 20 weeks. Approximately 6–7 million oogonia in female fetus at 20th gestational week. Primordial follicle formation, a single layer of pregranulosa cells surrounds each oocyte and continues until just after birth.
- 300,000–400,000 oocytes at birth.
- Approximately 200,000 follicles remaining in the ovary at the puberty.
- In reproductive life, 400–500 oocytes are ovulated and others are destined to atresia.
- Follicle loss increases with advanced age.
- Fecundity decreases.
- ART success decreases with age.
- The live birth rate per embryo transfer is 41% for <35 age, 35% for 35–37 age, 25% for 38–40 age, 14% for 41–42 age, 6% for 43 age, 3% for >44 age.
- Spontaneous abortion rate in natural cycles is 7–15% under 30 years of age. 8–21% for 30–34 age; 17–28% for 35–39 and 32–52% for >40 age.
- Results are similar in ART cycles; the abortion rate for <35 age is <20%, 30% for 40 years, and >60% for > 44 age.

What is the percentage of male/female ratio among infertile couples?

- 30–40% male
- 40–50% women
- 10–15% non-identified

What are the causes of infertility?

- In couples
  - Male factor 35%
  - Tubal/pelvic 35%
  - Ovulatory dysfunction 15%
  - Idiopathic 10%
  - Other 5%
- In women
  - Tubal/pelvic 40%
  - Ovulatory dysfunction 40%
  - Idiopathic 10%
  - Other 10%

Which couples should consult the clinic for ovarian reserve?

- After 35 years old all infertile women
- People with unexplained infertility
- Having a family history of premature ovarian failure (POF)
- Smokers
- Poor response to exogenous gonadotropin treatment
- Ovulatory dysfunction
- Endometriosis

- Multiple fibroids
- History of previous pelvic inflammatory disease (PID), pelvic surgery, ectopic pregnancy

What is the basic anamnesis of the patient with female factor evaluation of infertility?

- Gravida, parity, previous pregnancy history (secondary infertility)
- Menstrual order/disorder, presence and severity of dysmenorrhea (such as endometriosis)
- Frequency of sexual intercourse, history of sexual dysfunction
- The duration of infertility, previous treatments and outcomes
- Previous history of surgery, PID, and sexually transmitted diseases
- Profession
- Smoking, alcohol, and drug use
- Thyroid diseases and systemic symptoms, galactorrhea, hirsutism
- Having a family history of premature ovarian failure (POF)

What should be considered in female factor evaluation and physical examination?

- Secondary sex characters
- Signs of androgen excess
- Presence of galactorrhea
- Thyroid enlargement, nodule
- Pelvic tenderness, mass, uterine size evaluation (bimanual examination, ultrasound)
- Cervical or vaginal anomaly, vaginal discharge, chlamydia
- Nodularity in Douglas

What are the ovarian reserve tests (ORT)?

- Basal follicle stimulating hormone (FSH) levels measured on day 3 of the menstrual cycle is the most widely used ORT to assess the ovarian response to stimulation (threshold is 25 IU/L).
- Anti-Mullerian hormone (AMH) is a hormone that is produced by granulosa cells of preantral (primary and secondary) and small antral follicles. AMH levels correlate with basal antral follicle count (AFC) (threshold is 0.2–1.26 ng/mL). It is important to note that AMH cannot be used as a marker to predict pregnancy.
- Women with a low day 3 inhibin B concentration (<45 pg/mL) have a poor response to superovulation for IVF and are less likely to conceive a clinical pregnancy.
- Basal estradiol (E2) > 70pg/mL indicates poor prognosis, an elevated basal E2 level may mask abnormal FSH levels.
- Clomiphene citrate challenge test (CCCT) is a dynamic test. On the 3rd day of the menstrual cycle, clomiphene citrate (CC) oral 2 × 50 mg/day (5–9) is given. Poor prognosis on day 3 FSH or day 10 FSH > 10 IU/L.
- Exogenous FSH ovarian reserve test is a dynamic test. On the 3rd day of the menstrual cycle, basal FSH and estradiol levels are measured and 300 IU FSH administered. The serum estradiol concentration is checked 24 h later.

- Number of antral follicles is checked by transvaginal ultrasonography in the early follicular phase. A count of 8–10 is considered as a predictor of a normal response.
- The ovarian volume which is measured by transvaginal ultrasonography remains unchanged till the perimenopausal period and does not add to the predictive value of antral follicle counting. Also ovarian Doppler flow during ovarian stimulation does not add to the predictive value of antral follicle counting.
- GnRH-agonist stimulation test involves the assessment of serum estradiol on day 2 of the cycle followed by the subcutaneous administration of GnRHa 100 μg. A change in estradiol levels is noted by repeating the test 24 h later on the 3rd day of the menstrual cycle. A rise in estradiol is considered to be indicative of good ovarian reserve.

What are the useful methods for determining ovulation?

- The absolute proof of ovulation is the formation of pregnancy.
- Disappearance or sudden decrease in follicle size detected by transvaginal ultrasonography. Detection of LH in urine.
- Basal body temperature (BBT) rises throughout the luteal phase, due to thermogenic effect of progesterone. In late luteal phase, when the corpus luteum regresses and serum progesterone level decreases, the BBT returns to the lower range within 1–2 days before, or just at, the onset of menstrual bleeding. The biphasic pattern of BBT retrospectively suggests ovulation.
- Mid-luteal progesterone measurement >3 ng/mL to detect ovulation.

Which blood tests are checked in patients with suspected ovulatory dysfunction?

- Amenorrhea: PRL, TSH, progestin challenge
- Perimenopause: FSH, E2
- Galactorrhea: TSH and PRL
- PCOS, acne, hirsutism, alopecia, male type hair loss: testosterone, dehydroepiandrosterone sulfate (DHEAS)
- Congenital Adrenal Hyperplasia (CAH): 17-OH progesterone
- Signs of hypothyroidism such as slowing of the metabolism, weight gaining, fatigue: TSH

Why and how to perform uterine factor examination in infertility examination?

- To examine the uterine cavity
- First transvaginal ultrasound is applied. In case of submucosal fibroids or endometrial polyps are suspected, then uterine cavity should be evaluated by saline infusion sonography (SIS).
- After SIS, if submucosal fibroids and polyps are observed then uterine cavity is reevaluated by hysteroscopy to see and treat. It is a definitive method.
- Also by hysterosalpingography (HSG) uterine cavity could be evaluated, and tubal patency could be checked as well.

What is the role of the uterine septum in infertility?
- Uterine anomalies 4.3% in general population, 3.5% in infertile patients, 13% recurrent pregnancy loss.
- Uterine septum is the worst obstetric outcome associated with recurrent pregnancy loss and obstetric complications.
- Most common congenital uterine anomalies (35%).
- The most common cause of obstetric complications.
- The relationship between primary infertility and septum has not been fully elucidated, but high pregnancy rates have been reported in infertile patients after hysteroscopic metroplasty.

What is the role of the fibroids in infertility?
- Whether fibroids reduce fertility is controversial.
- Possible mechanisms: Cornual occlusion. Dysfunctional uterine contraction prevents sperm or ovum transport. Embryo implantation is reduced as a result of reduced regional blood supply.
- Submucous fibroids: hysteroscopic myomectomy
- Intramural fibroids: controversial
- Subserous fibroids: follow-up

What is the role of endometrial polyps in infertility?
- The effect on fertility is not known.
- Hysteroscopic polypectomy, in case of >1 cm and in symptomatic polyps

What is the role of tubal factor in infertility?
- The most common cause of infertility in infertile couples (35%).
- History of PID, septic abortion, ruptured appendicitis, tubal surgery, ectopic pregnancy, tubal damage.
- PID is the major cause of tubal factor infertility.

What is the role of PID on tubal infertility?
- The incidence of tubal infertility after a PID episode is 10–12%, 23–35% after the second, and 54–75% after the third.
- Most patients with tubal disease do not have a history of pelvic infection, but quiescent ascending infection is the most common cause.

Which imaging methods are used to investigate tubal factor in infertility?
- HSG
- Laparoscopy and hysteroscopy
- Transvaginal hydrolaparoscopy

What is the role of HSG in the evaluation of tubal factor in infertility?
- 65% sensitivity and 83% specificity for testing tubal patency.
- 38% chance of tubal obstruction if HSG is abnormal.
- If HSG is normal, the probability of tubal openness is 94%.
- Normal HSG is more reliable.

What is the role of laparoscopy (L/S) in the evaluation of tubal factor in infertility?
- Gold standard to show tubal patency. See and treat.
- HSG shows the uterine cavity and the tubal patency, as for L/S shows intra-abdominal adhesions, endometriosis, and ovarian pathologies, as well.

What is the role of the male factor in infertility?
- It constitutes 35% of the causes of infertility.

What is the basic anamnesis of the patient with male factor evaluation of infertility?
- Anamnesis of previous fertility, presence of chronic disease, previous urogenital infection and surgery, alcohol, drug use, libido, coitus frequency, toxic substance or radiation exposure.

What is the basic physical examination of the patient with male factor evaluation of infertility?
- Physical examination: Varicocele, urethral mean, vas deferens, secondary sex characters

What are the components of male infertility etiology?
- The cause is unidentified → 31%
- Varicocele → 15.6%
- Hypogonadism → 9%
- Subclinical infertility → 8%
- Undescended testis → 7.8%
- Erectile dysfunction → 6%
- Immunological → 4.5%
- Systemic diseases → 3.1%
- Obstructive pathologies → 1.7%
- Other causes → 13%

What are the recommendations prior to semen analysis?
- After 2–3 days of abstinence.
- Ejaculate material is put into a clean container.
- Inspection within 1 h of collection.
- Abnormal test results should be repeated after 3 weeks.

What is the meaning of aspermia?
- Complete lack of semen with ejaculation

What is the meaning of azoospermia?
- No sperm in the semen

What is the meaning of oligospermia?
- <15 million/mL of sperm count in ejaculate

What is the meaning of severe oligospermia?
- <5 million/mL of sperm count in ejaculate

What is the meaning of asthenospermia?

- Low sperm motility: If there is no motile sperm, a sperm viability test should be performed.

What is the meaning of teratospermia?

- Sperm morphology in the ejaculate is called abnormal.

What are the treatment recommendations for unexplained infertility in <35-year-old patients and older 35-year-old patients?

- <35 years: follow-up without treatment for 6–12 months up to 24 months as well in 20–25-year-old patients
- >35 years: gonadotropin + IVF

What are the criteria to apply IVF?

- Oligoasthenospermia-azoospermia not responding to hormonal treatment.
- Bilateral complete tubal obstruction, primary ciliary dyskinesia.
- Severe pelvic adhesion is detected and cannot conceive 1 year after tubal surgery.
- Advanced stage endometriosis.
- Unexplained infertility.

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Chapter 42
Ovulation Induction

What are the factors that may lead to a diminished ovarian reserve?

- Increased age
- History of ovarian surgery
- Severe endometriosis
- Obesity
- Smoking
- Adhesion, frozen pelvis, previous pelvic infections
- Premature ovarian failure
- Poor response to Assisted Reproductive Technology (ART) before

What is the definition of ovulation induction?

- Ovulation induction is applied to stimulate ovarian follicular growth and ovulation with the help of various agents.

Describe the characteristics and main features of clomiphene citrate (CC).

- First synthesized in 1956.
- Clinical use began in 1960.
- The use of CC as an ovulation induction agent started in 1967.
- Nonsteroidal triphenylethylene derivative distantly related to diethylstilbestrol.
- Selective estrogen receptor modulator (SERM).
- Competitive inhibitors of estrogen binding to estrogen receptors (ERs) and have mixed agonist and antagonist activity, depending upon the target tissue (similar to tamoxifen and raloxifene).
- Orally taken.
- Half-life is 5–7 days.
- It is the most commonly used ovulation induction agent.
- Stimulates circulating follicle-stimulating hormone (FSH) by antagonizing estrogen in infertile patients so follicle development is stimulated.

Acknowledgments The author would like to thank Dr. Ülkü Özmen who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_42

- Highly effective in anovulatory patients.
- Ovulatory ovarian dysfunction, unexplained infertility, minimal and mild endometriosis, and luteal phase deficiency.
- The response is not good in patients with a Body Mass index (BMI) greater than 30.
- CC increases the sensitivity of the pituitary to GnRH.
- CC increases GnRH pulse frequency in normo-ovulatory women.
- CC increases GnRH pulse frequency and amplitude in anovulatory women.
- CC increases pulse frequency of GnRH by blocking the negative feedback effect of circulating endogenous estradiol, thereby increasing the FSH and LH.
- Maximum recommended treatment time is 6 months.
- Antiestrogen effect in uterus, cervix, and vagina (disadvantage).

In which group of patients clomiphene citrate is the first choice of agent in ovulation induction?
- In unexplained infertility
- Young patients
- Normogonadotropic, oligoovulation, or anovulation

What are the ovulation and pregnancy rates of clomiphene citrate?
- Although there is an ovulation rate of 75–80%, pregnancy rates are around 20–40% with 6 months treatment.

Describe clomiphene citrate treatment scheme.
- 50–250 mg monthly dose.
- 4–6 months treatment.
- 80% ovulation is obtained.
- 60–75% pregnancy in young couples.
- Generally started with an initial dose of 50 mg/day on the fifth day of the menstrual cycle (to be used for five days).

What are the side effects of clomiphene citrate?
- Hot flashes
- Abdominal distention and pain
- Nausea vomiting
- Breast discomfort
- Mood swings, depression, and headaches
- Visual disturbances
- Ovarian hyper stimulation syndrome (OHSS)
- Multiple pregnancies
- Iatrogenic luteal phase defect (antiestrogenic effects on the endometrium)

What are the advantages of clomiphene citrate?
- Cheap
- Ease of use (oral)
- Ease of follow-up
- Lower OHSS rate

What are the gonadotropins used in ovulation induction?

- FSH, especially in patients with PCOS.
  - rFSH (recombinant)
  - uFSH (LH less than 1IU)
- HMG (LH + FSH) can be used in other infertile patients except PCOS.

How would you apply gonadotropins in ovulation induction?

- FSH 100–150 IU/day or HMG.
- Gonadotropins begin on 2nd–5th days of menstruation. 5–7 days later patient is reevaluated.
- Follicle >10 mm → Same dose of gonadotropin.
- Follicle <10 mm → The dose is increased by one ampoule.
- Follicles are expected to grow 1–2 mm per day.
- 18 mm follicle in USG; E2 is 600–1500 pg/mL → HCG.
- >10 follicles over 5 mm or >5 follicles over 14 mm; E2 > 2000 pg/mL → cancel HCG.
- 76–95% ovulation.
- High risk of multifollicular development, multiple pregnancy, OHSS.

What are the characteristics of chronic low-dose gonadotropins used in ovulation induction?

- Applied to prevent multifollicular development.
- Starts with 50–75 IU.
- Patient is reevaluated after 5–7 days.
- Increase the dose until E2 level increase and 10 mm follicle is seen by ultrasound.
- FSH dose should be increased if the patient is obese.
- Reduced OHSS ratios.
- Good response, especially in patients with PCOS.
- 70% unifollicular development.

What are the characteristics of stepdown protocol of gonadotropins used in ovulation induction?

- Treatment is started with 100–150 IU and continued with this dose until follicle is developed.
- When 14 mm follicle is obtained (by transvaginal ultrasound), the dose is reduced and continued with reduced dose.
- Results are similar to chronic low-dose gonadotropins.
- Primary aim is to reduce OHSS ratios.

What are the features of GnRH analogues used in ovulation induction?

- To prevent uncontrolled early LH peak and follicular atresia, especially in patients with PCOS.
- Endogenous FSH and LH are suppressed.
- Long dose scheme of the GnRH analogue is used for controlled ovarian stimulation in IVF programs.

How would you describe clomiphene citrate resistance in ovulation induction?
- No response to treatment after at least three cycles.
- No response with 150 mg/day.
- Endometrial thickness is less than 6 mm at the time of ovulation.

What is the role of bromocriptine in ovulation induction?
- High prolactin levels impair the pulsatile effect of GnRH.
- In order to treat hyperprolactinemic patients.
- Treatment should be continued until ovulation or pregnancy is achieved.

What is the role and the dose of dexamethasone in ovulation induction?
- In order to treat hyperandrogenemic cases
- 0.5 mg daily dose at night

What is the role and the dose of metformin in ovulation induction?
- Especially in PCOS patients
- In insulin resistance
- In order to assist ovulation induction
- 2 × 500 or 850 mg daily oral (before meals, may cause gastointestinal disturbances)

What is the role of letrozole in ovulation induction?
- Letrozole is an Aromatase inhibitor.
- In patients with poor response to ovulation induction by CC
- Can be used in order to reduce the dose of gonadotropins
- Start with a dose of 2.5 mg and continue for 5 days (between 3 and 8 days of the cycle) → Day 13 hCG.

What are the indications of aromatase inhibitors?
- Breast cancer
- Endometrial cancer
- Endometriosis
- Ovulation induction
- Non-IVF (±IUI): PCOS, ovulatory empirical
- IVF

How is the combination of letrozole and gonadotropins used in ovulation induction?
- Letrozole 2.5 mg dose is started for 5 days (between 3 and 8 days of the cycle), FSH 150 IU/day is applied between 7 and 13 days of the cycle → Day 13 hCG.

What are the side effects of letrozole?
- Headache.
- Fatigue.
- Nausea.
- Vomiting.
- Rarely hot flashes.

- Letrozole has been shown to be safe for osteoporosis.

Is there any relation between clomiphene citrate (CC) and teratogenicity?
- Clomiphene citrate has been reported not to increase congenital anomalies.
- Food & Drug Administration (FDA) considered (CC) as category X.
- Intrauterine growth retardation is more frequent in pregnancies with CC.

Is there any relation between letrozole and teratogenicity?
- Teratogenic effect of aromatase inhibitors has been shown in animal studies.
- Letrozole increased fetal anomalies, fetal death, hydrops, lack of bone ossification in pregnant rats and rabbits.
- However, in ovulation induction studies with letrozole:
- *Ectopic pregnancy*
- *Abortion*
- *Cancellation of the cycle*
- *Anomaly ratios* were not different from CC and gonadotropins.

How is the response to ovulation induction monitored?
- Folliculometry with transvaginal ultrasound.
- E2 levels should be checked before hCG administration.
- Endometrial thickness measurement.
- Determination of the LH peak.

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Chapter 43
Artificial Reproductive Techniques (ART)

What are the indications of artificial reproductive techniques (ART)?
- Tubal factor
- Severe male factor
- Severe endometriosis
- Unexplained infertility
- Age >35 years
- No pregnancy after 1 year of conventional ovulation induction treatment

What are the aims of the ART?
- Achievement of oocyte from ovary with an artificial method.

What are the methods of the ART?
- In vitro fertilization: Oocytes achieved from ovary and these oocytes and sperm put same media. After fertilization, embryo transfer is achieved.
- Gamet intrafallopian transfer (GIFT): Oocyte and sperm are placed in the fallopian tube.
- Zygote intrafallopian transfer (ZIFT): Zygote is placed in the fallopian tube.
- Tubal embryo transfer.
- Peritoneal oocyte and sperm transfer.

Which artificial reproductive techniques are used in male infertility?
- Techniques of sperm achievement
  - Injection of one sperm to oocyte—Intracytoplasmic sperm injection (ICSI)
  - Testicular sperm extraction (TESE)
  - Microsurgical epididymal sperm aspiration (MESA)
  - Sperm aspiration from testis

Acknowledgments The author would like to thank Dr. Ülkü Özmen who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_43

Which screening tests are made before ART?
- Hormone profile
- HSG
- Sperm test
- Ultrasonography
- HIV1 and HIV2
- Hepatitis B and hepatitis C
- Chlamydia, syphilis, gonorrhea, CMV, and rubella

What are the treatment alternatives of artificial reproductive techniques?
- Spontaneous cycles (6% success)
- GnRH analogues
- GnRH antagonists
- Human menopausal gonadotropin (HMG)
- FSH
- Clomiphene citrate
- Metformin
- Aromatase inhibitors—letrozole, anastrozole

How to determine treatment options of patients requiring ART?
- Treatment is determined according to women age, and ovarian reserve.
- GnRH analogues + FSH are preferred in young women.
- Low-dose GnRH analogues + high-dose FSH ± combined oral contraceptives are preferred in advanced ages.
- GnRH analogues + FSH (or HMG) + letrozole preferred in patients with poor ovarian reserve.
- GnRH antagonist + low-dose FSH are used in PCOS.
- GnRH analogues + FSH (Luteal long protocols) are preferred in endometriosis.

How would you follow up a patient when ART is applied?
- Aim is controlled hyperstimulation.
- For each follicle (>14 mm), estradiol level of at least 200 pg/mL is preferred.
- Endometrial thickness in ultrasonography should be 7–12 mm; endometrial lining in ultrasonography should be triple line.
- Oocyte pick-up (OPU) is made 34–39 h after hCG injection.
- Embryo transfer is made 3–5 days later.
- Generally progesterone is given after embryo transfer.

What is the basic technique of oocyte pick-up (OPU)?
- Mild anesthesia and sedation is preferred.
- Optimal monitoring is made.
- Generally pick-up needle is inserted into an ovary once and oocytes are aspirated.

Describe the process of oocyte culture.
- Oocytes are examined under a microscope.
- Separated from the sheath (cumulus) around the oocyte after the egg collection.
- After 4–6 h, the sperm is injected into the egg or leave to fertilization.

- Sperm is separated by swim-up method (If IVF is done, 50,000–100,000 sperms are left per oocyte).

Describe the fertilization process.
- Matured oocytes are fertilized at 65–80%.
- Roughly 6% polyspermia-type 3 pronucleus cells are consisted.
- If fertilization problem is present or if sperm count is too low, ICSI should be referred.
- Surplus embryos are frozen.

Describe the embryo transfer process:
- Generally 8-cell embryos after 72–80 h are transferred.
- Or, if the quality embryo is high, embryo is transferred to the blastocyst stage after 5 days.
- Depending on the age of the woman, the number of embryos may increase. Normally good quality 1–2 embryos are given.
- Luteal phase support is needed.
- After the transfer, hCG is measured on day 10–11.
- Five weeks after last menstrual period, fetal heart activity is expected.

What are the pregnancy associated results of ART?
- Abortion rate 20%.
- It is stated that there may be minimal increase in congenital malformation because of increased multiple pregnancy.
- Ectopic pregnancy is seen 3%.
- Risk of multiple pregnancy 35%.
- After three unsuccessful cycles, success rate is significantly decreased.

Describe male factor in fertility in artificial reproductive techniques.
- Fertilization rate is low.
  - ICSI is recommended treatment.
  - All kinds of immature, immobile sperm can be used.
  - Morphological selection of sperm is recommended.

Describe genetic problems in male factor infertility
- Infertile men have chromosomal anomaly in 5–7%.
- There are high deletions in the Y chromosome in the presence of azoospermia.
- 7–10% Y deletion in oligospermia.
- 10% of sperms carry extra chromosomes.
- There is 0.84% sex chromosomal anomaly in ICSI pregnancies due to male infertility.
- Genetic screening should be made to azoospermic men.
- Klinefelter syndrome
  - LH β subunit mutation
- There may be congenital absence of vas deferens. It is seen 1–2% in infertile men.
- There may be cystic fibrosis mutation.

Describe oocyte donation.

- Forbidden in some countries. Oocyte donation is the process in which a fertile woman's several oocytes are aspirated, usually following ovarian stimulation, in order to be used in another patient (mostly infertile due to ovarian failure; Premature ovarian failure, Turner syndrome, Ovarian failure following chemotherapy or radiotherapy, IVF failure, genetic disorders).
- It may be used in patients with premature ovarian failure.
- Donor age 22–24 is preferred.
- Success rate is approximately 50%.

In which patients, preimplantation genetic diagnosis (PGD) is preferred?

- Cystic fibrosis
- Duchenne muscular dystrophy
- Sickle cell anemia
- Hemophilia
- Tay–Sachs disease
- Lesch–Nyhan syndrome
- Trisomy

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Chapter 44
Pelvic Relaxation

What does pelvic relaxation mean and define the main features of it.

- Herniation of the pelvic organs into or out of the vagina.
- Etiology is multifactorial but the main factor is the weakness of the pelvic floor support (especially pelvic diaphragm).
- The most common indication of the hysterectomies in women over 55 years is pelvic relaxation.

What are the etiological factors of pelvic relaxation?

- Pregnancy
- Vaginal delivery
- Increased age
- Menopause, hypoestrogenism, estrogen deficiency
- Chronical increasing of the intra-abdominal pressure; constipation, chronic obstructive pulmonary disease (constantly coughing)
- Pelvic floor traumas; recent operations and hysterectomy
- Connective tissue diseases (e.g., Ehlers–Danlos syndrome)
- Spina bifida

What are the anatomical structures that support the pelvic floor?

- Endopelvic fascia
- Cardinal and uterosacral ligament
- Pelvic diaphragm
  - M. levator ani (m. pubococcygeus, m. puborectalis, m. iliococcygeus)
  - M. coccygeus

Acknowledgments The author would like to thank Dr. Onur Numan who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_44

What does cystocele mean, and what are the etiological factors?
- The herniation of the bladder into the vagina from the retropubic area.
- Most commonly related to the defects on the pubocervical fascia, due to the traumas during the labor.
- The grade of the prolapse may increase because of the defects of pubocervical fascia because of hypoestrogenism after menopause.
- Any protrusion or bulge felt on the anterior or superior side vaginal orifice are the signs of the cystocele.

What are the complications of the cystocele?
- Residual urine related complications (cystitis, dysuria, urgency) secondary to the incomplete drainage of the bladder

What are the treatment options of cystocele?
(a) Medical and non-surgical

- Pessary
- Kegel exercises
- Local estrogen for postmenopausal women

(b) Surgery

- **Anterior colporrhaphy** is the most commonly used technique in the surgical treatment of cystocele. It is important to know that, In 2019, the US Food and Drug Administration (FDA) banned the sale and distribution of surgical mesh for use in transvaginal anterior compartment prolapse (ie, cystocele, rectocele) repair because they were unable to confirm that the probable benefits outweighed the probable risks.

What does rectocele mean, how is it physically examined?
- The herniation of the rectum to the lumen of the vagina from the posterior vaginal wall.
- Usually secondary to the traumatic deliveries.
- **Median episiotomy** increases the risk. Other risk factors are menopause and chronically increased intra-abdominal pressure.
- **Sense of vaginal pressure and rectal fullness** are the most common symptoms.

What are the treatment options of rectocele?
(a) Medical

- Fluid intake and use of laxatives

(b) Surgical

- Posterior colporrhaphy

What does enterocele mean, how is it physically examined?
- Protrusion of the small intestines and peritoneum into the vaginal canal.
- Hysterectomy is the most common reason.

- Common symptoms are: urinary incontinence, defecation disorders (tenesmus, constipation, diarrhea, fecal incontinence), pelvic pain, low back pain, dyspareunia.

What are the treatment options of enterocele?

(a) Medical

- Vaginal pessary
- Bacteriostatic and estrogen containing topical agents

(b) Surgical

- Enterocele could be repaired with transabdominal or vaginal approach. Enterocele pouch is obliterated with sacrouterine ligaments and endopelvic fascia by transabdominal approach (Moschcowitz technique).
- The vaginal approach gives the best results in enterocele which occurs after hysterectomy. Colpopexy, sacrospinous fixation, and high sacrouterine ligament suspension (Mc Call Culdoplasty) are mentioned in these kinds of techniques.

What does uterine prolapse mean, and what are the etiological factors?

- The apical supporters of the cardinal and uterosacral ligament weaken and the cervix and uterus descends towards or into the vagina.
- The risk is higher for the retroverted uterus.
- Procidentia is the complete prolapse of the uterus out of the vagina. Risk factors of pelvic organ prolapse are: Vaginal childbirth (strongest risk factor), episiotomy and operative vaginal delivery, age, increased intraabdominal pressure, increased body mass index (some studies do not find any relationship, though), repetitive heavy lifting, chronic constipation, cigarette smoking and chronic obstructive pulmonary disease, chronic coughing, connective tissues diseases (like Ehlers-Danlos and Marfan's syndrome) etc.

What are the surgical and non-surgical treatment options of uterine prolapse?

(a) **Non-surgical**

- Vaginal pessary

(b) **Surgical**

- The surgery in younger patients is recommended to perform after the fertility is completed.
- **Le Fort Operation**
  - In senile patients who cannot overcome a major surgery
  - Internal closure of the vagina
- **Manchester-Fothergill Operation**
  - Performed in younger patients

  - Cervical amputation, shortening of the cardinal ligaments, and anterior colporrhaphy

- Vaginal hysterectomy is performed in most of the cases.

What are the stages of pelvic organ prolapse quantification (POPQ) system?

- **Stage 0:** No prolapse.
- **Stage 1**: The most distal portion of the prolapse is more than 1 cm above the level of the hymen.
- **Stage 2:** The most distal portion of the prolapse is 1 cm or less proximal or distal to the hymenal plane.
- **Stage 3:** The most distal portion of the prolapse protrudes more than 1 cm below the hymen but protrudes no farther than 2 cm less than the total vaginal length.
- **Stage 4:** Complete vaginal eversion.

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Chapter 45
Urinary Incontinence

What are the main features of urinary incontinence?
- Incidence is 8–51%, according to different studies.
- Urinary incontinence is a manifestation of the pelvic floor disorders.
- More common in the geriatric population.

How do you define the stress urinary incontinence?
- The involuntary leakage of urine, in the cases of increased intra-abdominal pressure during physical exertion or upon coughing, sneezing, laughing, etc.

How would you define urge incontinence?
- The involuntary leakage of urine associated with a sudden, strong desire to void (urgency) although intra-abdominal pressure does not increase.

What is the definition of true incontinence?
- The urinary incontinence without the patient awareness of urge or stress and occurs in such cases like ectopia vesicae (bladder exstrophy), epispadias, and fistulas.

What is paradoxic (overflow) incontinence?
- The overflow incontinence is the leakage of urine at greater than normal bladder capacity due to chronic urinary retention and flask bladder.

How would you define the frequency?
- Urination more than 8 times in 24 h

What is nocturnal enuresis?
- The involuntary urinary incontinence which occurs while sleeping

How is the urinary incontinence classified? What are the incidences of them?
- True stress incontinence → 50%
- Urge incontinence → 30%

Acknowledgments The author would like to thank Dr. Onur Numan who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_45

- Mixed incontinence → 20%
- Overflow incontinence
- Complete incontinence
- Unclassified incontinence

Summarize the classification of urinary incontinence and the characteristics

	Stress incontinence	Urge incontinence	Overflow incontinence
Symptoms	Sense of pelvic compression	Urgency, nocturia	Sense of fullness, frequency
Loss	Fewer, as urinary incontinence	More	Fewer, as dripping
Time	Short, synchronous with the stress	Moderate	Continuous
Increasing factors	Coughing, sneezing, physical activity	May not occur	
Triggered by sound of running water	No	Yes	No
Position	Most often, while standing	May occur in any position	May occur in any position
Cause	Anatomic (cystocele, ureterocele)	Loss of bladder inhibition	

What are the intrinsic and extrinsic factors effect on urethral closure?

- Extrinsic factors (the factors that stabilize the urethrovesical angle) "M. levator ani" muscle group:
  - M. pubococcygeus
  - M. iliococcygeus
  - M. pubovaginalis
  - M. pubourethralis
  - M. puborectalis
  - Endopelvic fascia
- Intrinsic factors
  - Urethral muscles
  - Congestion of submucosal venous plexus
  - Epithelial fold of urethral lumen
  - Elasticity of urethra
  - Tone of urethra
  - Parasympathetic nervous system → voiding, cholinergic receptors
  - Sympathetic nervous system → bladder filling
  - Dominance of alpha adrenergic receptors on bladder neck and beta adrenergic receptors on trigon

What are the urodynamic tests to evaluate urinary incontinence?

- **Bladder filling tests** are used for evaluating the functional capacity of bladder.
- **Cystometric (Pressure/Volume tests)** is a cystometric compliance and pressure test that evaluates the bladder capacity and the gold standard test

for the diagnosis of the "true urinary incontinence" and determines the causes of urinary incontinences.
- **Urethral pressure profile** shows the sphincter integrity.
- **Q-tip test** evaluates the hypermobility of the bladder neck. A cotton-based thick is placed into the urethra and the patient is asked to cough and the movement of the thick is checked.
- **Bead chain** is placed in the bladder through urethra and then the urethrovesical angle is measured by the lateral X-ray.
- **Bonney-Marchetti test:** After showing the leakage of urine with straining while the patient is standing, the physician observes no incontinence while elevating the urethra with two fingers without applying pressure on urethra (like hammock).

What are the main features of stress urinary incontinence (SUI)?
- The common incontinence type in women
- Occurs in the cases where the intra-abdominal pressure increases
- Symptoms
  - The patients complain of involuntary leak of urine during coughing, sneezing, or physical activities such as sport activities and sudden changes of position.
  - The observation of loss of urine from the urethra with coughing, sneezing, or physical exertion.
  - The patients feel the incontinence and socially uncomfortable and hygienically feel poor.

What are the main features of genuine urinary incontinence?
- Stress incontinence shown by urodynamic tests
- Two of the most important reasons:
- Hypermobility of the bladder neck (85%)
  - The patients expected to benefit from surgical and conservative treatment
  - Menopause, hormonal changes, traumas during vaginal delivery, pelvic surgeries, etc.
- Intrinsic sphincter failure (15%)
  - Pelvic/incontinence surgery
  - Pelvic radiation history
  - Trauma
  - Neurogenic factors

What is the treatment of stress urinary incontinence?
- Kegel pelvic muscle exercises help patient to increase the control of the pubococcygeal muscle.
- If there is no contraindication, local estrogen creams should be chosen as a first step in postmenopausal patients with urogenital atrophy who suffer from urinary incontinence.
- **α-adrenergic drugs.**
  - The tone of urethra and bladder neck is under control of α-adrenergic system.

  - Imipramine.
  - Phenylpropanolamine (PPA).
  - Pseudoephedrine.
  - Ephedrine.
  - Norepinephrine.

- **Surgical:** Surgical procedures are described below as anterior colporrhaphy.
- **Anterior colporrhaphy.**
  - Although anterior colporrhaphy is done to repair the cystocele, it also supports the bladder neck and urethra by Kelly-Kennedy sutures and may help in treating the stress urinary incontinence.
  - It is the first procedure which had been performed for stress urinary incontinence ever but long-term cure rates of this procedure are lower (40%).
- **Retropubic suspension procedures.**
  - **Marshall-Marchetti-Krantz (MMK) procedure**: Periurethral fascia is attached to the posterior periosteum of symphysis pubis.
  - **Burch procedure**: Periurethral fascia is attached to the Cooper ligament.
  - **Turner-Warwick vagino-obturator procedure:** Periurethral fascia is attached to internal obturator muscle's fascia.
- **Sling procedures** are the most popular techniques especially intravaginal minimal invasive sling procedures (Tension-free Vaginal Tape—TVT, Intravaginal Sling—IVS, Trans-Obturator Tape—TOT) are usually preferred).
- **Periurethral injections.**
  - Collagen
  - Autologous fat
  - Silicon particle (Macroplastique™) injection
  - Hyaluronic acid

What are the main features of urge incontinence?

- The hyperactivity of detrusor muscle is the most common reason.
  - Detrusor hyperreflexia (neuropathic detrusor hyperreflexia)
  - Detrusor instability (idiopathic detrusor instability) (most common)
- The most common reason of the urinary incontinence in senile women (stress incontinence is the most common one in all age groups).

How is the urge incontinence diagnosed?

- Diagnosed with cystometry to evaluate bladder function.
- With strong involuntary detrusor contractions and micturition reflex cannot be inhibited.
- Urinary tract infections must be ruled out.

How is the urge incontinence treated?

- Anticholinergic drugs (propantheline bromide, hyoscyamine sulfate, oxybutynin chloride, dicyclomine hydrochloride).
- Surgery is not recommended.

What are the main features of overflow incontinence?

- Because of the excessive distention of bladder
- Bladder outlet obstructions
  - Stricture
  - Cystocele
  - Impacted fecaloid material
- Non-contractile bladder (hypoactive detrusor, atonic bladder)
  - Diabetes mellitus
  - Multiple sclerosis
  - Spinal cord injury
  - Drugs

What does "Detrusor sphincter dyssynergia (DSD)" mean, and in which patients is it seen?

- Detrusor sphincter dyssynergia (DSD) is the urodynamic description of bladder outlet obstruction from detrusor muscle contraction with concomitant involuntary urethral sphincter activation.
- Especially in patients with multiple sclerosis.
- Patient cannot start the micturition.
- A catheter has to be used.

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Chapter 46
Endometrial Carcinoma

What is the most common gynecologic malignancy in developed countries?
- Uterine cancer (endometrial cancer)

What is the most common gynecologic malignancy in developing countries?
- Cervical cancer (endometrial cancer is the second one)

What is the most common histologic site and type of uterine cancer?
- Adenocarcinoma of the endometrium

What is the main symptom of endometrial cancer?
- Abnormal uterine bleeding (75–90%)

What is the main risk factor for endometrioid endometrial carcinoma?
- Unopposed estrogen (estrogen excess, non-opposition by a progestin)

What are the risk factors for endometrial cancer?
- Increased estrogen exposure
- Advanced age
- Obesity, hypertension, diabetes mellitus
- Low parity, nulliparity
- Early menarche, late menopause
- Anovulatory infertility, polycystic ovary syndrome
- Dietary, animal sourced fat, alcohol
- Estrogen-secreting tumor (like granulosa cell tumor)
- Tamoxifen therapy (in postmenopausal women)
- Lynch syndrome (hereditary nonpolyposis colorectal cancer (HNPCC): germline mutation in one of the DNA mismatch repair genes—MSH2, MLH1, MSH6, PMS2, EPCAM)
- Cowden syndrome (mutation in the PTEN tumor suppressor gene)

Acknowledgments The author would like to thank Dr. Mehmet İ. Harma, Dr. Müge Harma, and Dr. Anıl Turhan Çakır who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_46

- Family history of endometrial, ovarian, breast, or colon cancer
- HRT

What are histologic categories of endometrial carcinomas?
- Type I tumors: 80%. Endometrioid histology. Estrogen-dependent, better prognosis,
- Type II tumors: 20%. Non-endometrioid histology; serous, clear cell, mucinous, squamous, transitional cell, mesonephric, and undifferentiated. High-grade, worse prognosis, usually not associated with estrogen excess, estrogen independent.

What are the protective factors against endometrial cancer?
- Use of combined oral contraceptives (by 30%)
- Advanced age at last birth
- Breastfeeding
- Increased physical activity
- Progesterone use
- Smoking (nevertheless, smoking has been associated with an increased risk of type II endometrial cancer)
- Increased parity
- Early menopause
- Suggestive protective factors: coffee, tea, aspirin?

What are the most important prognostic factors of endometrial cancer at diagnosis?
- Stage, grade, depth of invasive disease, Lymph-vascular space invasion (LVSI), and histological subtype.

How would you perform endometrial cancer screening?
- Routine screening for endometrial cancer in asymptomatic patients is not recommended.
- Ineffective screening: Pap smear
- In symptomatic women, endometrial thickness is measured by transvaginal ultrasound → Endometrial biopsy
- In case of Lynch syndrome, even in asymptomatic women, endometrial sampling and transvaginal ultrasound (every year beginning at age 30–35 years)

Which lymph nodes are most commonly involved pelvic lymph nodes in endometrial carcinoma?
- The external iliac lymph nodes are the most common, followed by the obturator and common iliac nodes

What are the causes of postmenopausal uterine bleeding?
- Vaginal, endometrial atrophy (due to hypoestrogenism)
- Endometrial polyps
- Postmenopausal hormone therapy
- Endometrial hyperplasia

- Malignancies: endometrium, granulosa cell tumors of the ovary, leiomyosarcoma, cervical cancer, choriocarcinoma
- Anticoagulant therapy
- Endometritis

Describe the preoperative evaluation of patient with endometrial cancer?
- Chest X-ray.
- Clinical and gynecological examination.
- Transvaginal ultrasound.
- Complete blood count (CBC), and liver and renal function profiles.
- Abdominal computed tomography (CT) scan is indicated for investigating extrapelvic disease.
- Dynamic contrast-enhanced magnetic resonance imaging (MRI) is the best tool to assess the cervical involvement.
- [18F] Fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT could be useful to detect distant metastases accurately.

What are the relative high risk factors for recurrence in early stage endometrial cancer?
- Histological subtype
- Grade III histology
- Myometrial invasion ≥50%
- Lymphovascular space invasion (LVSI)
- Lymph node metastases and tumor diameter >2 cm.

In which cases of endometrial cancer, pelvic lymph node dissection is needed?
- Histological type adenosquamosis, clear cell, papillary serous
- Grade III
- Grade II patients with tumor of greater than 2 cm
- Myometrial invasion >½
- Cervical stromal involvement

Explain the endometrial cancer staging.
- Endometrial cancer staging is performed surgically on the basis of the 2017 FIGO classification.
- Surgery: Total extrafascial hysterectomy and bilateral salpingo oophorectomy, pelvic and para-aortic lymph node dissection. Cytoreduction can be performed in the presence of metastases.
- Peritoneal washing cytology is taken during surgery, but does not affect staging; it affects prognosis.

Which factors determine the prognosis of endometrial cancer?
- Primary stage and histology of cancer (grade and histological subtype) determine prognosis. Patients generally have a better prognosis because they are usually diagnosed at an early stage.
- Other factors: African American, advanced age, positive peritoneal cytology, lower uterine segment involvement.

- Molecular prognostic factors: increase in p53, p16 expression (Type II Endometrial cancer) is a negative factor; the PTEN mutation (Type I Endometrial cancer) is favorable; microsatellite instability (MSI) is negative; the absence of estrogen and progesterone receptor (ER, PR) is associated with a negative prognosis (especially in the absence of PR), and mutation in the PI3K/AKT/mTOR pathway is associated with a negative prognosis. Lynch syndrome is a positive prognostic factor; however, MSI-H and ATR mutation is a negative prognostic factor.

What is the definition of low-risk endometrial cancer?

- Histologic grade I and II
- Stage 1A: Cancer limited to the endometrium; or invading less than one-half of the myometrium, with no lymphovascular space invasion (LVSI)
- Cancer that is not with a high-risk histologic type (e.g., clear cell, serous, or carcinosarcoma)

Explain the treatment of endometrial cancer.

- All women diagnosed with endometrial carcinoma (with endometrial sampling) should undergo surgical staging; however, if fertility is demanded in early stage cancers such as grade I, pregnancy can be tried with progestin treatment such as megestrol acetate, but it will be risky to try out this option except for young couples who have no children.
- After performing surgical staging, treatment is planned according to the result of the final pathology. Patients with type I, stage 1 A (i.e., invading less than half of the tumor myometrium) do not require additional treatment.
- In stage 1B, brachytherapy (internal radiotherapy) is recommended.
- In later stages, radiotherapy and chemotherapy (platinum-based chemotherapy) are applied.

How would you follow up a patient with endometrial cancer, after treatment?

- It is recommended to follow up the patient every 3–4 months with physical and gynecological examination for the first 2 years, and then with a 6-month interval until 5 years.

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Chapter 47
Ovarian and Tubal Cancer

Which cancer has the highest mortality of all gynecologic malignancies?
- Ovarian cancer

What are the risk factors of ovarian cancer?
- Age
- Family history
- BRCA-1 and -2 mutation
- Lynch syndrome (especially MLH1 and MSH2 carriers)
- RAD51C, RAD51D, BRIP1 mutation
- Infertility, nulliparity
- Late menopause, early menarche
- Smoking (mucinous?)
- Obesity
- Endometriosis
- Black tea?

What are the preventive factors for ovarian cancer?
- Multiparity, use of oral contraceptives (OCS) (duration ↑, risk ↓), hysterectomy, tubal ligation, salpingectomy, breastfeeding
- Effect of pregnancy: prevention of ovulation, high P4 level → apoptosis, exposure to fetal antigens, prevention of retrograde menstruation, pituitary gonadotropin release ↓
- OCS effect: prevention of ovulation/↓, pituitary gonadotropin release ↓, high P4 level → apoptosis, ovarian stromal activity ↓, menstruation ↓
- Long-term low-dose use of aspirin?

Acknowledgments The author would like to thank Dr. Mehmet İ. Harma, Dr. Müge Harma, and Dr. Tuba Zengin Aksel who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_47

Which biomarkers could be used in ovarian cancer?
- Cancer-Antigen 125 (Ca-125), human epididymis (HE4)
- TP53, Protein Z, glycodelin, MMP7, CYFRA21-1, CA72-4, CA15-3, and VTCN1

What are the symptoms of epithelial ovarian cancer (EOC)?
- Common complaints at admission to hospital:
  - Abdominal distention, abdominal pain, GIS complaints, nausea and vomiting, anorexia, early satiety.
  - Vaginal bleeding, dysuria, fatigue, fever, dyspnea, low back pain, weight loss.
  - 10% cases in the early stage are asymptomatic.
  - Symptoms are similar in early and advanced stages.

What are the Pelvic examination findings of ovarian masses?
- Benign: unilateral, cystic, mobile, smooth surface
- Malignant: bilateral, solid, fixed, irregular surface, ascites, nodule at Douglas

What are the proportions of subtypes of EOC?
- High-grade serous carcinoma (70–80%)
- Endometrioid carcinoma (10%)
- Clear cell carcinomas (10%)
- Mucinous carcinoma (3%)
- Low-grade serous carcinoma (<5%)

Classify the Germ Cell Ovarian Tumors.
- Germ cell tumors
  - Dysgerminoma
  - Endodermal sinus tumor
  - Embryonal carcinoma
  - Polyembryoma
  - Choriocarcinoma
  - Teratoma
- Mature. Mature cystic teratoma (dermoid cyst)
- The immature cystic teratoma
- Monodermal: struma ovarii, carcinoid
  - Mixed germ cells
- Germ cell + sex cord stromal tumors
  - Gonadoblastoma
  - Mixed types

What are the main features of dysgerminoma?
- Frequently observed in adolescents and young adults, most of them are caught at an early stage.
  - Most common bilaterality is observed in this type of ovarian tumor (20%), hCG and LDH secretion, hCG → precocious puberty

- One of the most common malign ovarian tumor in pregnancy.
- Seminoma is the male analogue of the dysgerminoma, lymphatic spread is common (the most common lymphatic spreading ovarian tumor), radiosensitive (single ovarian cancer that is responsive to radiation).

Which germ cell tumors are found in Schiller–Duval bodies?
- Endodermal sinus tumor (yolk sac tumor)

What is the most common complication of teratomas?
- The torsion

Which endocrine disorder is observed in the struma ovarii?
- Hyperthyroidism

Which ovarian tumor can cause menometrorrhagia, endometrial hyperplasia, precocious puberty, postmenopausal hemorrhage, and due to which specificity?
- Granulosa cell tumor and thecoma → secrete estrogen

Which ovarian tumor is microscopically observed in the Call–Exner body?
- Granulosa cell tumor

What are the components of Meigs syndrome?
- Ascites, pleural effusion, and benign ovarian tumor (ovarian fibroma, fibrothecoma, Brenner tumor, and occasionally granulosa cell tumor)

What is the most common subtype of Tubal cancer?
- Papillary adenocarcinoma

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Chapter 48
Cervical Preinvasive Lesions, Cervical and Vulvar Cancer

Describe the Transformation Zone (TZ), what is its clinical significance?
- It is the area between the first and the last squamocolumnar junction (SCJ). Squamous metaplasia occurs here.
- All dysplasias (and cancer) originate from here.

What are the risk factors of cervical cancer?
- Persistant and long term infection of Human Papilloma Virus (HPV) (The most important risk factor)
- Early onset of sexual intercourse
- Multiple sexual partners
- History of sexually transmitted infections
- Immunosuppression
- High parity (independently of sexual behavior)
- Smoking (associated with squamous cell cancer of the cervix, not associated with adenocarcinoma of the cervix, independent of sexual behavior)
- Low socioeconomic status
- Nutritional factors
- Long-term use of oral contraceptives (five or more years, stronger association for adenocarcinomas than squamous cell carcinoma)
- Genetic factors

What are the most common histologic types of cervical cancer?
- Squamous cell carcinoma (SCC) (69%) and adenocarcinoma (25%)

What are the histopathologic types of cervical cancer?
(a) Squamous cell carcinoma (SCC) (69%) and adenocarcinoma (25%)

- Large cell, keratinizing
- Large cell, non-keratinizing

Acknowledgments The author would like to thank Dr. Mehmet İ. Harma and Dr. Müge Harma who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_48

- Verrucous carcinoma
- Papillary squamous and transitional cell carcinoma
- Lymphoepithelioma-like carcinoma

(b) Adenocarcinoma

- Mucinous, endocervical variant
- Mucinous, intestinal type, signet ring variant
- Mucinous, adenoma malignum (minimal deviation variant)
- Mucinous, villoglandular adenocarcinoma (well differentiated)
- Endometrioid type
- Clear cell type
- Papillary serous type
- Mesonephric type

(c) Adenosquamous carcinoma
(d) Adenoid cystic carcinoma
(e) Neuroendocrine (carcinoid, small cell, large cell)
(f) Undifferentiated carcinoma
(g) Mixed epithelial and mesenchymal tumors

What are the early symptoms of cervical cancer?

- Postcoital bleeding (most frequent)
- Irregular vaginal bleeding
- Bloody and foul-smelling discharge (usually if large tumors with tissue destruction and necrosis)

What is the most common type of cervical cancer in women using oral contraceptives?

- Villoglandular papillary adenocarcinoma

What are the cervical cancer's routes of spread (metastasis)?

- Direct extension (uterine corpus, ovarium, vagina, parametria, peritoneal cavity, bladder, or rectum)
- Lymphatic (obturator lymph nodes, pelvic and para-aortic lymph nodes)
- Hematogenous spread (lungs, liver, and bone; the bowel, adrenal glands, spleen, and brain)

Describe the HPV vaccines.

- Bivalent vaccine (Cervarix®): against HPV 16, 18
- Quadrivalent vaccine (Gardasil®): against HPV 6, 11, 16, 18
- Nonavalent vaccine: against HPV 6, 11, 16, 18, 31, 33, 45, 52, 58.

What are the HPV vaccines' indication groups?

- Women aged 9–26 years, but the main target is girls and boys aged 11–12, preferably before first sexual activity. World Health Organization (WHO) recommends; a 2-dose schedule of the Human Papillomavirus (HPV) vaccine for

adolescents who get the first dose below 15 years of age. In a 2-dose series, the second dose should be given 6–12 months after the first dose (0, 6–12 month schedule); for people who gets the first dose ≥15 years of age: 3-dose HPV vaccine is recommended. The second dose should be given 1–2 months after the first dose, and the third dose should be given 6 months after the first dose (0, 1–2, 6 month schedule). Additionally in recent studies it is found that the protective effect of the HPV vaccine in 2-dose schedule is not inferior to 3-dose series between 15 and 18 years old adolescents.

Explain the cervical cancer screening protocol.

- HPV screening begins after the age of 30. It is repeated every 5 years. However, if a high-risk HPV type other than HPV 16 or 18 is detected, then the HPV test should be repeated 1 year later. If positive again (1 year later) → colposcopy.
- Pap smear (Cervical cytology) should be performed after 21 years of age and is repeated every 3 years.

What are the symptoms of vulvar cancer?

- Pruritus (itchy skin)
- Mass
- Pain
- Bleeding
- Ulceration
- Dysuria
- Vaginal discharge
- Mass in the groin

What is the most common histologic type of vulvar cancer?

- Squamous cell carcinoma (75%)

Which lymph node dissection is performed in vulvar cancer?

- Inguinal lymphadenectomy

What are the risk factors for vulvar cancer?

- Vulvar or cervical intraepithelial neoplasia (VIN, CIN)
- A prior history of cervical cancer
- Cigarette smoking
- Vulvar lichen sclerosis
- Immunosuppression
- Increasing age

What are the main factors affecting prognosis in vulvar cancer?

- Lymph node positivity
- Number of positive nodes
- Tumor ploidy
- Tumor size
- Surgical margin

Which patients with vulvar cancer would not require inguinal (groin) lymph node dissection?

- Patients with a primary vulvar cancer up to 20 mm in diameter with up to 1 mm of stromal invasion do not require inguinal node dissection.

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Chapter 49
Vaginal Preinvasive Lesions and Vaginal Cancer

Describe main features and characteristics of vaginal intraepithelial neoplasia (VaIN).

- Vaginal squamous epithelial cells have abnormal mitosis, abnormal maturation, and nucleus aneuploidy (irregular nuclear contours and chromatin clumping, nuclear enlargement).
- The lesion is limited to the vaginal epithelium and the basal membrane is intact.
- It is precancerous lesion.
- It is less common than cervical and vulvar intraepithelial lesions.
- The pathophysiology is not known clearly.
- For similar etiological reasons, it may be associated with cervical intraepithelial neoplasia (CIN) and vulvar intraepithelial neoplasia (VIN).
- The actual incidence is unknown (<1/100,000).
- It is between the ages of 43 and 60 years.
- Human papilloma virus (HPV) is the most important risk factor.

What are the risk factors of VaIN?

- The most important risk factor for lower genital tract neoplasia is the presence of HPV infection.
- HPV 16 and 18 are responsible for most lesions.
- Other risk factors:
  - Low education level and low family income
  - Advanced age
  - Vaginal condyloma or CIN history
  - Polygamy
  - Risky sexual intercourse
  - Cigarette
  - Pelvic radiotherapy

Acknowledgments The author would like to thank Dr. Mehmet Bülbül who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_49

  - Presence of immunosuppression such as human immunodeficiency virus (HIV) infection
  - Intrauterine diethylstilbestrol (DES) exposure

- 50–90% of patients with VaIN are associated with cervical or vulvar premalignant lesions/neoplasia.
- In patients with CIN III, 5% (1–7%) VaIN can be detected.
- Some high-grade VIN or VaIN lesions may be caused by high-grade or malignant cervical disease.

Describe the etiology of VaIN.

- Lesions that extend into the vagina in CIN and cannot be detected.
- Isolated lesions may develop de novo (multifocal lesions).
- The cervix, vagina, and vulva with similar histological structure are exposed to the same carcinogenic agents → Multicentric neoplasms (50% of women with VaIN have concurrent vulvar or cervical neoplasia).
- Coitus/tampons use → Erosion zones → Recovering metaplastic areas → Persisted HPV infection → Neoplasia
- Unlike cervix, the vagina epithelium is more stable and VaIN is rarer.
- In women with DES exposure, squamous metaplasia is more common. This explains the increased risk of VaIN.

Explain VaIN's clinic.

- It is usually asymptomatic.
- Postcoital and/or postmenopausal bleeding.
- There may be bloody vaginal discharge sometimes due to superimposed vaginal infections.
- In 50% of the patients, the lesion is multifocal.
- 90% of patients with VaIN have CIN (multicentric).
- If there are no identifiable cervical lesions or abnormal smear findings after hysterectomy, VaIN should be excluded.
- The most common location is vaginal 1/3 proximal posterior wall (57–83%).
- In 31% of patients, it is caused by the lower 1/3 part of the vagina.
- According to the VaIN epithelium involvement:

  - VaIN I (lower 1/3): between pillows, ovoid, puffy from the surface.
  - VaIN II (up to 2/3): Acetone white becomes prominent, thicker, and limited lesion.
  - VaIN III, CIS (carcinoma in situ) (almost or full layer): papillary structure, punctuations, and mosaic vascular structure.

Describe the diagnosis of VaIN.

- Vaginal touch is required to assess vaginal wall thickening and irregularity.
- Detailed colposcopic examination (acetic acid and lugol) and, if necessary, vaginal biopsy are performed.
- Partial closure of the speculum during biopsy facilitates the procedure.
- After topical estrogen treatment in the menopause, the lesions become more visible.

Describe the treatment of VaIN.

- Premalignant potential is lower than CIN.
- VaIN I often regresses spontaneously.
- There is no malignant potential. It is multifocal and has a tendency to recur after treatment. No treatment required.
- Treatment options:
  - Topical treatment (5-FU (fluorouracil), imiquimod): large or multifocal lesions
  - Ablation (laser, cryo/cautery): depth of invasion to the tissue should be considered.
  - Excision: (local excision, partial or total vaginectomy)
  - Radiotherapy: intracavitary, rarely used.
- History of unsuccessful treatment, multifocal disease, additional diseases of the patient, and sexual function is important in the choice of treatment.
- Ablative therapies are an option if the lesion is completely seen and invasion is excluded by biopsy.
- VaIN II → Ablative treatment (laser).
- VaIN III → 2–8% progress to invasive cancer or with 28% invasive cancer → Excision required.
- Follow-up after treatment
  - Smear + HPV test should be performed at 6 months/1 year intervals.
  - Colposcopy if anyone is abnormal.
  - Long-term follow-up is required.
- HPV vaccine, smoking cessation, treatment of other lesions may prevent the development of VaIN.

49.1 Vaginal Cancer

Describe the main features of the vaginal cancer.

- 80–90% of vaginal cancer is seen as metastasis of other cancers (cervix, endometrium, ovary, GIS, breast, GTN, colorectal, vulva, urinary system).
- Primary vaginal cancer is rarer and usually originates from the vaginal epithelium.
- 2% of all genital system cancers.
- In situ or invasive vaginal cancer is seen in approximately 1/100,000 ratio.
- It is usually seen in postmenopausal women (mean age 60 years).
- It is associated with HPV (HPV 16 and 18 are positive in 50% of patients).
- Other risk factors: low socioeconomic status, lifetime sexual partner, early coitus, smoking, chronic vaginal irritation, history of abnormal Pap smear, history of cervical cancer, history of radiotherapy (RT), intrauterine DES exposure.
- In 50% of cases, there is a cervical cancer.

- In women with CIN III, the risk of developing vaginal cancer increases by 6.8 times.

Describe the clinic for vaginal cancer.
- 1/5 of women are asymptomatic at the time of diagnosis.
- Vaginal discharge (watery, bloody, or smelly vaginal discharge).
- Painless vaginal bleeding.
- Findings related to adjacent organ involvement (polyuria, hematuria, tenesmus, melena, constipation).
- Vaginal mass from the hand.
- Five percent of the patients have pelvic pain due to their spread to the surrounding tissues.
- It usually spreads through the neighborhood by direct invasion. It can also spread through lymphatic and hematogenous routes.

What are the histological types of primary vaginal cancer?
- Squamous cell carcinoma (epidermoid type) (80–90%).
- Adenocarcinoma (9%),
- Melanoma (3–5%)
- Sarcoma (3%),
- Others (undifferentiated, small cell carcinoma, lymphoma, carcinoid) (2%),

What are the main features of the squamous cell carcinoma of the vagina?
- It is the most common type. HPV is related. It is seen around the age of 60 years.
- Lesions can be ulcerative, indurated, endophytic, or exophytic.
- Verrucous carcinoma is a rare squamous cell carcinoma variant with well-differentiated and low malignant potential.
- Locally aggressive, rarely metastasis.
- It can reach big sizes.
- It consists of large papillary leaves covered with histologically dense keratin.

What are the main features of the adenocarcinoma of the vagina?
- It is generally seen as a metastasis of colon, endometrium, ovarian, stomach, and pancreatic cancers.
- The primary adenocarcinoma is rare.
- Almost all cases of primary vaginal cancer under 20 years of age are adenocarcinoma.
- It may develop from vaginal adenosis, wolffian canal residues, periurethral gland, and endometriotic foci.
- Clear cell carcinoma is an adenocarcinoma that develops on the basis of vaginal adenosis in young women with intrauterine DES exposure.
- At diagnosis, 70% is stage I.
- It is usually caused by the front wall of the vagina.
- Intrauterine exposure for the first 12 weeks is the highest risk.
- Intrauterine DES exposure also increases the risk of invasive/in situ squamous cell cancer in the cervix (5.4 times).
- DES-associated vaginal cancer is seen at a mean age of 19 years (7–33 years).

- The first gynecological examination of women exposed to DES; cervical and vaginal cytology, palpation, and colposcopic evaluation should be performed.
- Clear cell carcinoma treatment with primary surgery and/or RT results is good.
- The prognosis of other adenocarcinomas is worse.

What are the main features of the sarcoma of the vagina?

- Primary sarcomas seen in the vagina: leiomyosarcomas, endometrial stromal sarcomas, malignant mixed Müllerian tumors, and rhabdomyosarcomas.
- The most common embryonal rhabdomyosarcoma (sarcoma botryoides) is seen (the most common malignant mesenchymal tumor of the vagina in childhood).
- There is a mass of grape-shaped nodules in the vagina.
- The mean age is 3 years, with poor prognosis.
- It is multimodal treated including surgery, chemotherapy, and RT.

What are the main features of the melanoma of the vagina?

- Vaginal melanomas are rare.
- It originates from mucosal melanocytes or atypical melanocytic hyperplasia.
- The average age is around 60 years (22–84 years).
- The most common symptoms are vaginal bleeding.
- It is more common in Caucasian women.
- It is most common in the vaginal 1/3 distal anterior wall.
- Lesions are usually in the form of non-pigmented blue-black or black-brown mass, plaque, or ulceration.
- Aggressive tumors.
- The 5-year survival rate is <20%.

How is vaginal cancer diagnosed?

- Squamous cell carcinoma is usually located 1/3 proximal, posterior wall of the vagina. During the pelvic examination, it is necessary to pay attention to the bottom of the speculum.
- Diagnostic evaluation:
  - Pelvic examination
  - Vaginal cytology
  - Colposcopy
  - Vaginal biopsy
- Pelvic examination should include a bimanual examination, palpation of the masses on the vaginal wall, palpation of the inguinal lymph node, and rectovaginal examination.
- Vaginal cytology.
- Vaginal colposcopy should be performed with acetic acid followed by Lugol dye.
- Vaginal biopsy can be performed under anesthesia if necessary.
- Imaging methods for staging: evaluation by thorax and skeletal radiography.

- Computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET-CT) can also be used if necessary.
- The diagnosis is made by vaginal biopsy.
- Other genital pathologies (menopausal vaginal atrophy, vaginal infection, and trauma) that cause vaginal bleeding in differential diagnosis should be excluded by pelvic examination.
- Benign causes (vaginal polyps, Gartner canal cyst, vaginal adenosis, and endometriosis) should be excluded in the presence of vaginal mass.

Describe ways of spreading vaginal cancer.
- Direct extension to pelvic soft tissue: vulva, cervix, bladder, rectum, other pelvic organs
- Lymphatic: from the upper 1/3 vagina to the pelvic/para-aortic lymph nodes, from the lower 1/3 vagina to the inguinal and femoral lymph nodes
- Hematogenous: lung, liver, and bone.

How is staging of vaginal cancer done?
- Clinical staging system is used (The International Federation of Gynecology and Obstetrics (FIGO)).
- Clinical staging:
  - Physical examination, cystoscopy, proctoscopy, chest and skeletal radiography are based on the findings.
  - Biopsy of the inguinal/femoral or other lymph nodes or the results of fine needle aspiration can be included in clinical staging.
- At the time of diagnosis, 26% of the patients were stage I, 37% were stage II, 24% were stage III, and 13% were stage IV.
- **Staging**
  - Stage 0 → In situ cancer, VaIN III.
  - Stage I → Cancer limited to the wall of the vagina.
  - Stage II → Cancer kept the vaginal tissue, but did not reach the pelvic wall.
  - Stage III → Cancer has reached the pelvic wall.
  - Stage IVA → The cancer was directly spread out of the true pelvis and/or kept the bladder/rectum mucosa (bullous edema does not do the stage IV).
  - Stage IVB → Cancer has spread to distant organs.

What are the important prognostic factors of the vaginal cancer?
- Tumor stage, location, and size are important prognostic factors.

What are the treatment options of the vaginal cancer?
- Treatment options: surgery, RT, and chemo-radiotherapy.
- In the choice of treatment: the stage of the tumor, negative surgical margin and the patient's sexual function is important.

In which situations surgical therapy of the vaginal cancer is chosen?
- In stage I, if the tumor is 1/3 in the vagina; Radical hysterectomy + upper vaginectomy (>1 cm surgical margin) + bilateral pelvic lymphadenectomy.

- If there is no uterus; radical upper vaginectomy + bilateral pelvic lymphadenectomy.
- Young patients who need radiotherapy; laparoscopic ovarian transposition + surgical staging + bulky lymph node resection should be performed.
- If there is a rectovaginal/vesicovaginal fistula in patients with stage IVA cancer; pelvic lymphadenectomy + pelvic exenteration.
- If there is a central recurrence after RT; pelvic exenteration (Evidence C).

In which situations radiotherapy is chosen?
- It is difficult to obtain negative surgical margins in large tumors.
- In addition to inguinal lymph node dissection, vulvovaginectomy is often required in middle/lower vaginal involvement. Therefore, surgery is not a good option.
- In stage I patients, RT is more effective if the tumor diameter is >2 cm or there is middle/lower vaginal involvement.
- Vaginal lower 2/3 part involvement; inguinal lymph nodes should be dissected or given RT (Evidence C).
- RT alone provides adequate treatment in early stage tumors.
- Adding brachytherapy to external RT increases survival from 3.6 years to 6.1 years.
- A total radiation dose of 70–75 Gy is recommended.
- Small superficial stage I tumor; intracavitary RT.
- Large and thick lesions; intracavitary and interstitial RT before external RT.

In which situations chemo-radiotherapy is chosen?
- In advanced vaginal cancers, surgery or RT has low chances of success.
- Success in stage II–IV patients: Chemoradiotherapy > RT > surgery (52% > 44% > 14%).
- Cisplatin/fluorouracil can be used simultaneously with radiotherapy.
- It is the primary treatment in patients with stage II–IV tumors.
- Recommended for tumors larger than 4 cm in diameter.

In which situations chemotherapy is chosen?
- It is an option in recurrent or advanced cases in which surgery or radiotherapy cannot be performed.
- Neoadjuvant chemotherapy and then radical surgery are a promising alternative. However, it has not been proven yet.
- If there is no treatment option, **palliative care** should be performed.

What are the complications of the vaginal cancer after treatment with surgery and radiotherapy?
- Complications occur in 10–15% of patients after treatment (rectovaginal or vesicovaginal fistulas, radiation cystitis or proctitis, rectal and vaginal stenosis and rarely vaginal necrosis).
- Surgery related urethra, bladder, and rectum injury.
- Vaginal dilators should be used to prevent vaginal stenosis after RT.

What is the ideal follow-up after treatment?

- In patients early stage/without additional treatment:
  - First 2 years; every 6 months
  - Then annually
- In advanced stage/additional treatment patients:
  - First 2 years; every 3 months
  - 3–5 years; every 6 months
  - Then annually
- History and physical/pelvic examination is performed.
- If recurrence is suspected, CT or PET may be taken.

What is the most important factor affecting the prognosis of the vaginal cancer?

- The most important factor affecting the prognosis is the stage of the disease at the time of diagnosis (tumor prevalence, size and depth of invasion).

What are the 5-year disease-free survival rates of the stages of the vaginal cancer?

- 5-year disease-free survival is 85% in Stage I, 78% in Stage II, and 58% in Stage III–IV.

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Chapter 50
Gestational Trophoblastic Diseases

What is the definition of gestational trophoblastic disease (GTD)?

- Benign and malignant neoplasms caused by abnormal proliferation of trophoblastic tissue

What is the incidence of GTD?

- The incidence of GTD after all types of pregnancy is 1/40,000.
- The incidence of GTD varies according to regions and countries.
- The incidence of GTD varies according to the type of previous pregnancy.
- Approximately 50% of GTD cases develop after molar pregnancy, 25% after miscarriage or ectopic pregnancy, and 25% after normal pregnancy.

What are the risk factors/epidemiology for GTD?

- Previous molar pregnancy: the most important risk factor (10×)
- Extremes of maternal age: ↑ Risk in the ≤15 and ≥45 ages
- Diet:
  - Dietary vitamin A and animal fat deficiency ↑ (for complete mole, but not for partial mole)
- Presence of maternal diabetes
- Oral Contraceptives (OCS): increase the risk of partial MH
- Increase in the parity
- Low serum folic acid and copper levels
- High vitamin B12 and zinc levels
- Genetics
- Geographical: more common in Asia
- Oxidative stress

Acknowledgments The author would like to thank Dr. Mehmet İ. Harma, Dr. Müge Harma, and Dr. Talip Karaçor who contributed to this chapter.

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_50

What is the classification of the benign GTDs?
- Hydatidiform mole
  - Complete (CHM)
  - Partial (PHM)
- Placental site nodule
- Exaggerated placental site

What is the classification of the malignant GTD/GTN?
- Choriocarcinoma
- Placental Site Trophoblastic Tumor (PSTT)
- Epithelioid Trophoblastic Tumor (ETT)
- Invasive Mol.

In which situations GTN is considered as a possible diagnosis?
- After complete or partial mole result of a uterine curettage:
  - If the hCG levels plateau or rise in three measurements.
  - If hCG is detected 6 months after evacuation.

What is the most commonly described appearance of CHM on ultrasound?
- The most prominent ultrasound feature of CHM during the first trimester is an enlarged uterus filled with a heterogeneous predominantly echogenic mass with several hypoechoic foci, resulting in the *snowstorm appearance*.

What are the main features of the CHM?
- The most common GTD.
- No fetus and placenta.
- Genetic structure diploid 46,XX chromosomes with both Xs from paternal origin
- Very little (10%) 46 XY.
- Empty ovum is formed as a result of fertilization of two different sperms or duplication of a paternal sperm that fertilizes the empty ovum.
- The entire genetic structure is of paternal origin.
- 46 YY chromosomal structure is not seen.
- Hydropic avascular degeneration and hyperplasia in trophoblasts.

What are the main features of the PHM?
- Placenta and fetal structures are found.
- Genetic structure 90% triploid (69 XXX, 69 XXY, 69 XYY).
- One haploid gene is of maternal origin, two haploid genes are of paternal origin.
- 10% is mosaic.
- Placenta and fetus which are present at partial moles are the most common triploid structure.

What is the risk of recurrence in molar pregnancy?
- After one molar pregnancy (1–1.9%)
- After two molar pregnancies (15–17.5%)

What are the main features of the Exaggerated Placental Site (EPS)?
- It is an extreme physiological response.
- It is not a real lesion.
- The distinction between normal placental region and EPS is difficult.
- The associated placenta is usually normal.
- Endometrial glands and stroma are normal.
- Mitotic activity is not observed.
- Cells have hyperchromatic, irregular shaped nuclei and eosinophilic cytoplasm.

What are the main features of the placental site nodule or plaque (PSN)?
- Non-neoplastic equivalent of ETT.
- Cells are small and monomorphic.
- Mitotic activation is rare or usually absent.
- 50% of PSNs are detected incidentally in curettage or hysterectomy specimens.
- Ectopic pregnancy can also be seen in the fallopian tube.

What are the main features of Placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT)?
- Placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT) are rare variants of gestational trophoblastic neoplasia. PSTT originates from the implantation site intermediate trophoblasts and ETT orginates from chorionic type extravillous trophoblasts. They may be diagnosed several months or even years after the pregnancy. Despite PSST having a benign course in most cases, in approximately 30% of the cases it might display aggressive behaviour. In PSTT or ETT cases, it is very difficult to make a definitive diagnosis before the operation. PSTT and ETT are relatively resistant to chemotherapy and patients with PSTT/ETT confined to the uterus may be cured with primary hysterectomy alone without adjuvant chemotherapy. Also local resection may be successful in carefully selected patients who wish to preserve fertility. Patients with high risk PSTT/ETT should be treated with a combination of surgery and chemotherapy.

What are the main features of the invasive mole hydatidiform?
- Always occurs after molar pregnancy.
- Hydropic villas invade myometrium, vascular spaces, and extrauterine areas.
- It can metastasize to lung and vagina like choriocarcinoma.
- It is difficult to detect by uterine curettage.
- Usually the diagnosis is confirmed in hysterectomy specimens.
- The presence of hydropic villi is an important criterion in distinguishing them from choriocarcinoma.

Which organs are vulnerable to GTN metastases, and what are their rates?
- Lungs (80%)
- Vagina (30%)
- Pelvic (20%)
- Liver (10%)
- Brain (10%)

What is the main approach and diagnostic methods in GTD?
- Anamnesis: about previous pregnancy
- Physical examination: uterus larger than normal, adnexal mass
- Symptoms: abnormal vaginal bleeding
- Laboratory: β-hCG, TSH
- Imaging:
  - Ultrasound: Uterine larger than normal, anechoic area in the cavity, increased blood flow, typical snow storm appearance, absence of fetal parts, cystic appearance of the placenta, and deformed gestational sac may indicate early molar pregnancy.
  - Lung X-ray: Hyper-echogenic foci in the lung, snowstorm image, pleural effusion.
  - CT: Intracranial lesions.

What is the most common presentation of a hydatidiform mole?
- Abnormal vaginal bleeding in pregnancy

What are the histopathological findings of the hydatidiform moles?
- **CHM**
  - The chorionic villi are diffuse hydropic, usually surrounded by atypical trophoblasts.
  - Does not contain fetal/embryonic tissue.
- **PHM**
  - Usually contains normal-looking chorionic villi and fetal tissue mixed with hydropic villi.
  - Hydropic changes are less pronounced, trophoblastic hyperplasia and atypia are focal and less pronounced.

What are the clinical findings in GTD?
- High β-hCG > 100,000 IU/mL compared to gestational week.
- Amenorrhea.
- Abnormal vaginal bleeding.
- Pelvic pain.
- Uterus size is larger than normal.

What are the results of pathologically hCG stimulation in GTD?
- Hyperthyroidism
- Theca-lutein cysts
- Hyperemesis
- Preeclampsia

What are the signs of metastasis in GTDs?
- Lung metastasis: dyspnea, chest pain, cough, hemoptysis
- Vaginal metastasis: vaginal bleeding, purulent vaginal discharge

- Central nervous system metastasis: headache, dizziness, nausea, speech, visual disturbances
- Liver metastasis: jaundice, epigastric pain, back pain

What are the FIGO Criteria for Diagnosis of Postmolar GTN?

- GTN may be diagnosed when the plateau of human chorionic gonadotropin hCG lasts for four measurements over a period of 3 weeks or longer; that is, days 1, 7, 14, 21.
- GTN may be diagnosed when there is a rise of hCG of three weekly consecutive measurements or longer, over at least a period of 2 weeks or more; days 1, 7, 14.
- GTN is diagnosed when the hCG level remains elevated for 6 months or more.
- GTN is diagnosed if there is a histologic diagnosis of choriocarcinoma.

Which classification is used in pretreatment prognostic classification in GTN patients?

- **International Federation of Gynecology and Obstetrics (FIGO)**
  - **Stage I**: Disease confined to the uterus
  - **Stage II:** GTN extends outside the uterus, but is limited to the genital structures (adnexa, vagina)
  - **Stage III:** GTN extends to the lungs, with or without genital tract involvement
  - **Stage IV:** All other metastatic sites

World Health Organization (WHO) Prognostic Scoring System

- Age
- Antecedent pregnancy
- Interval from last pregnancy
- Pretreatment serum hCG level
- Largest tumor (including uterine)
- Site of metastases
- Number of metastases
- Prior chemotherapy treatment

	Score			
Risk factor	0	1	2	4
Age (years)	<40	≥40	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Interval from last pregnancy (months)	4	4–6	7–12	>12
Pretreatment serum hCG (mIU/mL)	$<10^3$	10^3 to 10^4	10^4 to 10^5	$>10^5$
Largest tumor (including in uterus)	<3 cm	3–4 cm	≥5 cm	–
Site of metastases	Lung	Spleen, kidney	GI tract	Brain, liver
Number of metastases	–	1–4	5–8	>8
Prior failed chemotherapy	–	–	Single drug	≥2 drugs

Which scoring system is more predictive than the use of individual risk factors in GTD?

- Prognostic scoring system of the World Health Organization (WHO)

What is the risk score of GTN to be considered as low risk or high risk?

- A risk score of 6 and below is classified as low risk and above 6 is considered high risk

Describe non-metastatic GTD treatment.

– Vacuum evacuation/suction curettage/sharp curettage: first choice.
– Hysterectomy: if there is no desire for fertility, the risk of metastasis continues.
– Post-procedure hCG levels are monitored in series (weekly > 3 negative values > monthly > 12 months).
– 12 months contraception: OCS is preferred, attention to the risk of IUD perforation.
– Prophylactic chemotherapy is controversial.
– Single agent methotrexate or actinomycin D protocols.

Should anti-D immune globulin be given to patients with Rh (D) negative in GTDs?

– Must be done because Rh (D) factor is expressed on trophoblasts

How would you follow up a patient after treatment of GTN?

- hCG monitoring every month for at least 12 months

Indicate the necessity and method of contraception in GTD patients.

- It is recommended that they use reliable contraception throughout the entire hCG monitoring.
- A new pregnancy makes it difficult or impossible to interpret hCG results.
- Hormonal birth control or barrier methods can be used.
- Because of the risk of uterine subinvolution, invasive moles, or uterine perforation, IUD is not recommended unless hCG is normalized.

Describe the treatment in malignant GTN.

- Chemotherapy is the main treatment of GTN.
- Surgery: chemotherapy-resistant GTN (PSTT and ETT), in uncontrolled uterine bleeding. Neurosurgery is needed if there is bleeding into the brain or increased intracranial pressure. In patients with an isolated drug-resistant tumor, removal of isolated cranial or pulmonary nodules or hysterectomy can improve survival.
- Radiotherapy: in treatment of brain metastasis.

What are the options of chemotherapy in GTN treatment?

- Single agent: Methotrexate (MTX), Actinomycin D (Act D).
- Multiple agents: The most commonly used is EMA-CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine).
- Experimental agents: Paclitaxel, ifosfamide, 5- Fluoruracil (5-FU), Floxuridine, Capecitabine, Liposomal doxorubicin, Gemcitabin etc. Also as an additional information according to recent researches, some therapies against oxidative stress such as All *trans*-retinoic acid (ATRA) is also a promising agent, since

main pathology of GTN is regarded as oxidative stress, but currently ATRA it is not used in GTDs, it is just experimental in cell culture studies.

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Chapter 51
Approach to Breast Diseases

What would be the options of next step in management of the mentioned patient below?

- **A 64-year-old woman had routine screening mammogram. A cluster of micro calcifications in the left lower inner quadrant of her breast was found on mammography. Based on the spot compression magnification mammogram, calcifications were found to be suspicious and classified as BI-RADS 4.**

  – Stereotactic core needle biopsy
  – Wire localized excisional biopsy

What would be the options of next step in management of the mentioned patient below?

- **An asymmetric density in the subareoler zone of left breast was found in a 54-year-old postmenopausal woman on routine screening mammography. Sonographic imaging demonstrates 10 mm intraductal mass with ill-defined borders.**

  – Ultrasound guided core needle biopsy targeting papilloma
  – Wire localized excisional biopsy targeting papilloma
  – Seed localized excisional biopsy

What are the indications to excise a lesion diagnosed as intraductal papilloma by core needle biopsy?

- The presence of atypia associated with papilloma
- The presence of clinic-radiologic imaging discordance
- The association of atypical ductal hyperplasia with the papilloma

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The original version of this chapter was revised. The correction to this chapter can be found at https://doi.org/10.1007/978-3-030-29669-8_52

Author: Güldeniz Karadeniz Çakmak

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_51

- The association of atypical lobular hyperplasia with the papilloma
- The presence of symptoms due to papilloma

What are the breast imaging-reporting and data system (BI-RADS) categories of the lesions that should be observed/follow-up?
- BI-RADS 1
- BI-RADS 2
- BI-RADS 3

What are the breast imaging-reporting and data system (BI-RADS) categories of the lesions that should be biopsied?
- BI-RADS 4
- BI-RADS 5

Which imaging modalities are used for breast imaging-reporting and data system (BI-RADS) for classification?
- Breast ultrasound
- Mammography
- Breast MRI

What does provide the sensory innervation of the breast?
- The anterior and lateral cutaneous branches of the second to sixth intercostal nerves
- The supraclavicular branches of the cervical plexus

What does provide the sensory innervation of the nipple–areola complex?
- The deep division of the lateral cutaneous branches of the fourth intercostal nerve
- The third and fourth anterior cutaneous branches of intercostal nerve

What is Berg classification of axillary lymph nodes?
- There are three groups of axillary lymph nodes according to their position relative to the pectoralis minor muscle.
- Level I lymph nodes are located laterally to the lateral margin of the pectoralis minor muscle.
- Level II lymph nodes are located behind the muscle.
- Level III lymph nodes are located medially to the medial-superior margin of the muscle.

What are the stages of breast development?
- Prenatal stage
- Infant stage
- Peripubertal stage
- Adult stage (including pregnancy and lactation)
- Postmenopausal stage

What are the characteristic features of Poland's syndrome?
- Absence of costal cartilages and a portion of the third or third and fourth rib
- Absence of the nipple or breast with accompanying hypoplasia

- Absence of subcutaneous fat
- Absence of axillary hair
- Absence of the pectoralis minor muscle
- Absence of costosternal part of the pectoralis major muscle

What are the major risk factors associated with breast cancer?
- Female gender
- Increasing age
- Past history of breast cancer
- Past history of other high-risk pathology
- Previous radiation therapy
- Genetic mutations

What are the major modifiable lifestyle risk factors for breast cancer?
- Physical inactivity
- Obesity
- Alcohol consumption
- Exogenous hormone administration (oral contraceptives, hormone replacement therapy)

What are the high-penetrance hereditary breast cancer genes?
- BRCA1 and BRCA2
- TP53
- STK11
- PTEN
- CDH1

What are the criteria for designating women at high familial risk for breast cancer according to American Cancer Society?
- Women with a known mutation in *BRCA1* or *BRCA2* or their untested first-degree relatives
- Women with Li–Fraumeni syndrome
- Women with Cowden's syndrome
- Women with Bannayan–Riley–Ruvalcaba syndrome
- Woman with hereditary diffuse gastric cancer
- Woman with Peutz–Jeghers syndrome and their first-degree relatives
- Women having a lifetime risk equal to or greater than 20–25% according to BRCAPRO or other family history-based models

What are the criteria for breast cancer screening for high familial risk women?
- Mammography begins at the age of 25–30 years or 10 years before the age at diagnosis of a first-degree relative; nevertheless, the age at onset of screening should not be younger than 25.
- Mammography and MRI are complementary examinations; both should be performed.
- Ultrasound is performed if a patient cannot undergo magnetic resonance imaging.

What are the risk reducing strategies for breast cancer?
- Surveillance
- Chemoprevention
- Risk-reducing surgery of the breasts
- Risk-reducing surgery of ovaries and fallopian tubes

What are the US National Comprehensive Cancer Network's recommendations for surveillance for BRCA1 and BRCA2 mutation carriers?
- Giving information about "breast awareness" starting at the age of 18
- Clinical breast exam every 6–12 months from the age of 25
- Annual breast screening using MRI from age 25 to 29 years
- Annual breast MRI and mammography from 30 to 75 years
- After the age of 75 years, surveillance should be considered on an individual basis

What are the options of breast reconstruction after prophylactic mastectomy?
- Implant-based reconstruction
- Autologous reconstruction

What are the possible predictors of complications after breast reconstruction?
- Smoking
- High body mass index
- Preoperative irradiation

What are the techniques of autologous breast reconstruction?
- Latissimus dorsi flap
- Transverse rectus abdominis musculo (TRAM)-cutaneous flaps
- Superficial inferior epigastric abdominal (SIEA) perforator flaps
- Transverse myocutaneous gracilis (TMG) flaps
- Deep inferior epigastric perforator flaps

What are the factors included in National Cancer Institute's breast cancer risk assessment tool (Gail model)?
- Age
- First menstrual period age
- First live birth age
- First-degree relatives with breast cancer (include only mother, sisters, and daughters)
- Previous breast biopsy
- Race

What are the available current multigene assays in breast cancer?
- Oncotype DX Breast Recurrence Score Assay
- MammaPrint
- Prosigna (PAM50)
- EndoPredict

- Breast cancer index
- Insight Dx Mammostrat

What are high-risk breast lesions?
- Flat epithelial atypia
- Atypical ductal hyperplasia
- Atypical lobular hyperplasia
- Lobular carcinoma in situ
- Radial scar (RS)/complex sclerosing lesion
- Intraductal papilloma

What is the next step in management if a high-risk lesion is diagnosed on core breast biopsy specimen?
- Diagnostic surgical excision

Define ductal carcinoma in situ
- Ductal carcinoma in situ (DCIS) of the breast represents an intraductal lesion of the breast characterized by increased epithelial proliferation with cellular atypia not invading the basement membrane of the ductal lobular unit.

What is the common feature of DCIS on mammogram?
- DCIS often appears as microcalcifications or less commonly as a mass or area of architectural distortion.

What are the current treatment options routinely offered for DCIS?
- Surgery (lumpectomy/wide excision/segmental mastectomy or mastectomy)
- Radiation
- Endocrine therapy

What are the risk factors for recurrence for DCIS?
- Symptomatic presentation of DCIS
- Greater extent (size) of DCIS
- The presence of DCIS at the resection margin
- High grade
- Multifocality

What are the absolute contraindications for breast-conserving therapy to treat breast cancer?
- Radiation therapy during pregnancy
- Diffuse suspicious or malignant-appearing microcalcifications
- Widespread disease that cannot be incorporated by local excision of a single region or segment of breast tissue that achieves negative margins with a satisfactory cosmetic result
- Diffusely positive pathologic margins
- Homozygous (biallelic inactivation) for ATM mutation

What are the indications for mammography?
- Breast cancer screening
- Assessment of patients with clinical symptoms

- Image-guidance for biopsy
- Preoperative staging
- Preoperative localization
- Therapy monitoring and follow-up

What does determine the density of the breast in mammography?

- The proportion of fibroglandular tissue and fatty tissue determines the density of the breast.

What are the categories of breast density according to the breast imaging-reporting and data system (BI-RADS®) in mammography?

- Category A: Breasts are almost entirely fatty
- Category B: There are scattered areas of fibroglandular density
- Category C: The breasts are heterogeneously dense, which may obscure small masses
- Category D: The breasts are extremely dense, which lowers the sensitivity of mammography

What are abnormal findings on mammography?

- Masses (characterized by shape, margins, and density)
- Architectural distortions
- Asymmetries
- Microcalcifications (evaluated by their morphology and distribution)
- Skin and nipple changes (thickening, retraction)
- Chest wall invasion
- Axillary lymphadenopathy

What are the frequent features of benign microcalcifications in mammography?

- A cutaneous or vascular location
- A round shape or rim appearance
- Large coarse “popcorn- like” morphology
- A large rod-like shape and a peri-, intraductal punctate pattern
- Diffusely homogeneous punctate pattern
- Amorphous dystrophic calcification after trauma
- Milk-of-calcium sediment calcifications

What are the commonest imaging findings after surgery and radiation therapy for breast cancer?

- Scarring—deformity of the breast
- Distortion of the parenchymal pattern
- Skin thickening
- Radiation fibrosis
- Postsurgical fluid collections
- Fat necrosis
- Dystrophic calcifications
- Artificial material

What are the indications of breast ultrasonography?
- Adjunct to screening mammography in dense breast
- Characterization of abnormalities found in other modalities
- Evaluation of palpable masses and other breast-related symptoms
- Evaluation and characterization of palpable masses and other breast-related signs and/or symptoms
- Evaluation of suspected or apparent abnormalities detected on mammography
- Treatment planning for radiation therapy
- Axillary staging in women with breast cancer
- Evaluation of breast implants
- Guidance of interventional procedures in the breast and axilla
- Evaluation of young, pregnant, and breastfeeding patients with clinical symptoms

What are the indications of breast magnetic resonance imaging (MRI)?
- Screening modality for women with high lifetime risk of breast cancer
- Preoperative staging
- Pretreatment evaluation of local disease extent
- Monitoring of neoadjuvant systemic treatment
- Evaluation of residual disease after neoadjuvant systemic treatment
- Unequivocal findings from other imaging modalities
- With negative mammography and ultrasound, to detect an occult primary tumor in patients with metastatic involvement of axillary lymph nodes; assessment of breast implants

What are the techniques used for preoperative marking for breast masses?
- Wire guidance
- Carbon marking
- Radioactive agent guidance marking
- Clip placement
- Skin marking
- Ultrasound guidance

What are the potential physical and psychological hazards of mammographic screening?
- Radiation exposure
- Overtreatment
- Pain
- False-positive results
- False-negative results

What are the breast cancer screening modalities that have been assessed in population-based breast screening?
- Clinical breast examination
- Breast self-examination
- Mammography

What are the clinical symptoms and signs of breast cancer?
- Breast mass
- Skin retraction
- Nipple inversion
- Changes in the size and shape of the breast
- Discoloration of the skin
- Breast pain
- Skin edema
- Axillary nodal mass

Define locally advanced breast cancer (LABC)
- Any breast cancer that is >50 mm in greatest dimension or tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules), or metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases, or metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement with no distant metastases (T3–T4, or N2–3, no metastases: M0) is defined as LABC.

What are the main features of phyllodes tumor?
- A group of rare fibroepithelial lesions.
- They have different malignant potentials.
- They represent 0.3–0.5% of all breast tumors.
- The majority of them are diagnosed in the fourth and fifth decade of life although they can appear at almost any age.
- The majority present as benign-feeling lumps often thought to be fibroadenomas clinically or on imaging but may be larger or grow more rapidly.
- In most cases, a definitive diagnosis is established after core needle biopsy and in some cases surgical excision.

What are the non-epithelial malignancies of the breast?
- Angiosarcoma
- Osteogenic sarcoma
- Embryonal rhabdomyosarcoma
- Lymphoedema-associated lymphangiosarcoma
- Lymphoma
- Metastatic tumors

What are the most common organs that breast cancer metastasizes?
- Bone
- Lung
- Liver
- Brain

What are the methods of breast biopsy in use to diagnose breast cancer?
- Fine needle aspiration (FNA) biopsy
- Core biopsy (CB)
- Vacuum-assisted biopsy
- Punch biopsy
- İncisional biopsy
- Excisional biopsy

What are the elements of 8th ed. AJCC UICC-TNM clinical prognostic staging classification for breast cancer?
- Tumor size
- Lymph node status
- Distant metastasis
- Grade
- Human epidermal growth factor receptor 2 (HER2) status
- Estrogen receptor (ER) status
- Progesterone receptor (PR) status

What are molecular or intrinsic subtypes of breast cancer?
- Luminal A: ER+ and PR+, low grade, HER2−, non-proliferative 5
- Luminal B: ER+ and PR−, or PR low/high grade/proliferative, or HER2+
- HER2 + : HER2+, ER−
- Basal like–Triple negative: ER−, PR−, HER2-

Define sentinel lymph node for breast tumor
- A sentinel node is defined as the first lymph node that drains a breast tumor along a direct lymphatic pathway from the primary tumor.

What is oncoplastic breast surgery?
- Breast surgery to treat breast cancer focusing on optimizing both oncologic and esthetic outcomes, irrespective of the type(s) of surgery performed.

What is radical mastectomy (Halsted)?
- Removal of the totality of the glandular breast tissue, overlying skin, nipple-areola complex, pectoralis major and minor muscles and ipsilateral axillary lymph nodes

What is modified radical mastectomy?
- Removal of the totality of the glandular breast tissue, overlying skin, nipple-areola complex, and concurrent level I–II axillary lymph node dissection

What is skin-sparing mastectomy?
- Removal of the totality of the glandular breast tissue, removal of the nipple-areola complex, preservation of the skin envelope overlying the breast (followed by immediate reconstruction)

What is nipple-sparing mastectomy?
- Removal of the totality of the glandular breast tissue, preservation of nipple–areola complex and skin envelope (followed by immediate reconstruction)

What are indications for mastectomy in breast cancer management?
- Extensive, multicentric, invasive, or in situ disease not amenable to breast-conserving surgery
- Second ipsilateral in-breast event (recurrence or second primary cancer) following previous breast-conserving surgery and radiotherapy
- Patient choice (instead of breast-conserving surgery)
- Prophylactic (risk-reduction) surgery in patients with high family risk of breast cancer (i.e., BRCA or p53 mutation carriers, or non-carriers with >30% overall lifetime risk of breast cancer)
- Inflammatory breast cancer
- Previous mantle radiotherapy for Hodgkin's disease

What are the dissection borders when performing modified radical mastectomy?
- Dissection is carried out up to the level of the clavicle *superiorly*, down to the inframammarian fold and rectus sheath *inferiorly*, lateral to the sternum *medially* and up to the anterior border of the latissimus dorsi *laterally*.

What are the methods for impalpable tumor localization?
- Guidewire localization
- Radioguided occult lesion localization (Roll)
- Radioactive seed localization
- Intraoperative ultrasound localization
- Carbon dye injection localization
- Superparamagnetic iron oxide localization

What are the indications of oncoplastic surgery?
- Adverse tumor volume to breast volume ratio
- Adverse tumor location (supero-medial, central/sub-areolar, inferior)
- Multifocal and multicentric disease
- Macromastia
- Redo conservation surgery

What are the methods used for sentinel lymph node detection?
- A radioactive tracer
- A vital blue dye
- The combination of a radioactive tracer and a vital blue dye
- Super paramagnetic iron oxide

What are the indications for sentinel lymph node biopsy for axillary staging?
- All patients with invasive breast cancer with a clinically negative axilla at primary surgery
- For patients with DCIS and going to undergo mastectomy

What are the factors associated with an increased risk of postoperative complications after breast surgery?
- Age
- Obesity

- Smoking
- Excessive use of alcohol or recreational drugs
- Diabetes mellitus
- Chronic renal failure or chronic obstructive pulmonary disease
- Atherosclerosis and cardiovascular disease
- Autoimmune and connective tissue disorders
- Preoperative chemotherapy
- History of irradiation to the chest wall
- Previous surgical procedures on the breast

What are the indications for neoadjuvant chemotherapy for breast cancer?

- Inflammatory breast cancer
- Inoperable breast cancer
- To facilitate breast conservation surgery
- If the same systemic therapy would also be indicated in the adjuvant setting
- If adjuvant chemotherapy is likely to be advised and complex surgery is planned which may otherwise delay systemic therapy
- If adjuvant chemotherapy is likely to be advised and the results of gene testing are awaited which may affect subsequent treatment decisions

What are the indications for adjuvant radiation therapy after mastectomy for breast cancer?

- Tumor >5 cm
- Four or more positive axillary lymph nodes (post-mastectomy radiotherapy mandatory)
- One to three axillary lymph nodes (post-mastectomy radiotherapy is recommended)
- Positive surgical margins when further surgery is not possible
- Chest wall/skin infiltration (T4a, T4b, T4c)
- Inflammatory cancer (T4d)
- Pectoral muscle invasion

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Correction to: Approach to Breast Diseases

Correction to: G. Sel (eds.), *Practical Guide to Oral Exams in Obstetrics and Gynecology*, https://doi.org/10.1007/978-3-030-29669-8

In the initially published version of the book, the authorship in Chapter 51 Approach to Breast Diseases was incorrectly given.

Güldeniz Karadeniz Çakmak is the only author of this chapter.

The updated online version of this book can be found at https://doi.org/10.1007/978-3-030-29669-8_51

G. Sel, *Practical Guide to Oral Exams in Obstetrics and Gynecology*,
https://doi.org/10.1007/978-3-030-29669-8_52