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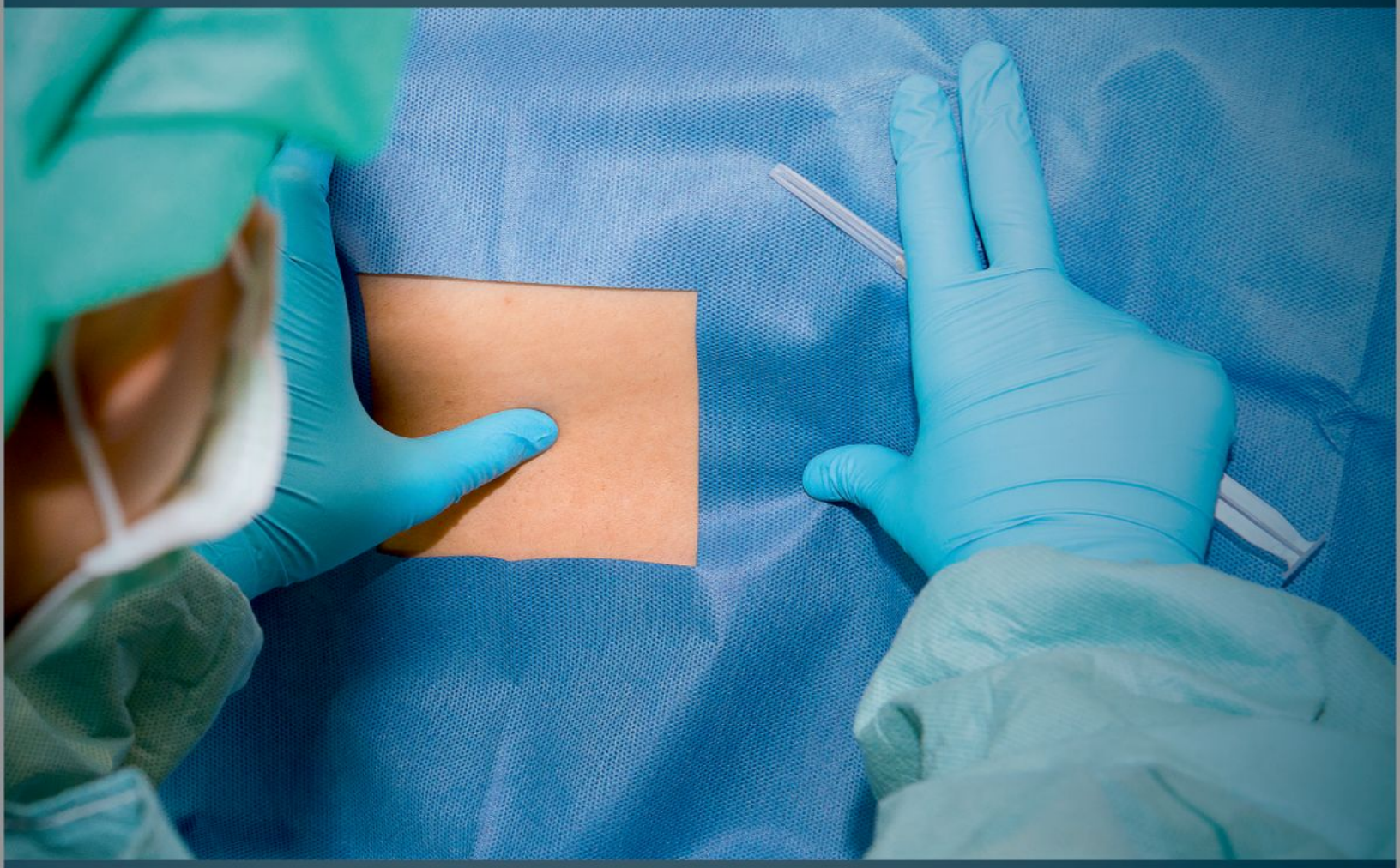

OBSTETRIC ANESTHESIA PRACTICE

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Obstetric Anesthesia Practice

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To my wife Dr. Kim Kaye and my children, Aaron and Rachel Kaye, for being the inspiration to work hard in my life;
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—Alan D. Kaye

To all my mentors for all their advice and for being there when I need them;
To my wife Dr. Zina Matlyuk and my children, Abigail and Isabelle, for their love and support;
To my patients who ultimately will be the beneficiaries of this book;
To my colleagues who inspire me every day.
—Richard D. Urman

Contents

Foreword
Preface
Contributors

1. Physiological Changes During Pregnancy
   Shairko Missouri, Trevor Miller, and Taylor Mueller
2. The Placenta: Anatomy, Physiology, Uteroplacental Blood Flow, and Drug Transfer
   Sandra N. Gonzalez, Easha Patel, and Christa L. Riley
3. Fetal Physiology and Antepartum Fetal Surveillance
   Agathe Streiff and Yelena Spitzer
4. Coexisting Disease and the Parturient: Part One—Cardiovascular, Respiratory, Renal, Gastrointestinal Systems
   Carole Zouki and Aladino De Ranieri
5. Coexisting Disease and the Parturient: Part Two—Hematologic, Neurologic, Musculoskeletal and Immune Systems
   Benjamin F. Aquino, Afshin Heidari, and Leila Haghi
6. Parturient Pre-Anesthesia Assessment and Evaluation
   Patrick McConville, Carrie Polin, and Justin Swengel
7. The High-Risk Obstetric Patient: Pregnancy-Induced Conditions
   Jacqueline Curbelo
8. Intrapartum Monitoring and Fetal Assessment
   Courtney Rhoades and Kristen Vanderhoef
9. Obstetric Management of Labor and Vaginal Delivery
   Marianne David, Geoffrey Ho, Daniel Fisher, Laura Roland, Everett Chu, and Michelle S. Burnette

10. Pharmacology and Non-anesthetic Drugs During Pregnancy and Lactation
Adam L. Wendling

11. Local Anesthetics
Michelle Eddins

12. Opioid Analgesia
Najmeh Izadpanah, Seung Lee, Kanchana Gattu, and Blake Watterworth

13. Neuraxial Anesthesia
Paulina Cardenas

14. Alternative Regional Anesthetic Techniques
Michelle S. Burnette, Laura Roland, Everett Chu, and Marianne David

15. Non-Opioid Analgesic Techniques for Labor and Vaginal Delivery
Anvinh Nguyen, Yi Deng, and Melissa A. Nikolaidis

16. Non-pharmacologic Labor Analgesia
Michael Marotta and David Gutman

17. Neuraxial Techniques and Medications for Cesarean Delivery
Elvera L. Baron and Daniel Katz

18. Airway Management
Joel Sirianni and Robert Mester

19. General Anesthesia for Cesarean Delivery
Lacey E. Straube

20. Obstetric Hemorrhage
Faiza A. Khan and Jill M. Mhyre

21. Cesarean Delivery: Postoperative Management
Thais Franklin dos Santos, Arina Ghosh, and Reine Zbeidy

22. Neonatal Assessment and Resuscitation
Fatoumata Kromah, Darshna Bhatt, Nayef Chahin, Miheret Yitayew, and Joseph Khoury

23. Postpartum Complications in Obstetric Anesthesia
Lucy Li, Jingping Wang, Alan D. Kaye, and Henry Liu

24. Trauma and Critical Care During Pregnancy
Gavin T. Best, Melissa A. Nikolaidis, and Yi Deng

25. Non-obstetric Surgery During Pregnancy

Arunthevaraja Karuppiah, Jessica Galey, and Shobana Bharadwaj

26. Anesthesia for Fetal Surgery

Beata Evans, Kevin Quinn, Rajanya S. Petersson, Timothy Wills, and Fatoumata Kromah

27. Anesthesia and Assisted Reproductive Techniques

Nora Martin, Fadi Farah, and Shamantha Reddy

28. Medicolegal Issues in Obstetric Anesthesia

Samuel Onyewu and Fatoumata Kromah

Index

Foreword

Obstetrics as a specialty continues to evolve. Here in the United States, preterm delivery rates are finally decreasing, while cesarean section rates have continued to increase in some locations. Recently, maternal mortality has become the major concern occupying the attention of physicians, hospitals, and beaurocrats. Despite all of these issues, one major change in the last forty-years, which has dramatically transformed the field of obstetrics, pain control.

Obstetric anesthesia as a specialty has been around for some time. The journey has gone from medication and specifically administered local anesthesia, such as pudendal blocks, to epidurals that remove the vast majority of pain during this otherwise painful process. As an obstetrician, it is quite common for my patients to think more highly of the anesthesiologists that they just met, than myself who has cared for them during the course of their pregnancy. Pain elimination has that effect on people.

Like most specialties, obstetrical anesthesia has evolved and become an art. Scientific evidence has shown us the best techniques, medications, and the best timing for their use. The current book by Kaye and Urman is a comprehensive evaluation of anesthesia's use in obstetrics. It includes all the current techniques and drugs.

As a health care provider, we are called to always practice our best. This includes keeping up with the latest techniques and information. This book provides the necessary foundation for the reader to accomplish this goal.

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Preface

The first edition of *Obstetrical Anesthesia* is intended to provide a timely update in the field of obstetrical anesthesia and continue the mission of providing a concise, up-to-date, evidence-based, and richly illustrated book for students, trainees, and practicing clinicians. The book comprehensively covers a robust list of topics focused to improve understanding in the field with emphasis on recent developments in clinical practices, technology, and procedures. We strived for a simple, accessible format that avoids encyclopedic language and lengthy discussions.

As the practice of obstetric anesthesia becomes increasingly recognized as a major subspecialty of anesthesia, there is a growing interest from current practitioners to evolve their neuraxial, regional, and general anesthesia techniques and understanding of the latest evidence. This book contains all the essential topics that are required for the practitioner to quickly assess the obstetric patient and stratify her risk; decide on the type of analgesic and anesthetic plan that is most appropriate for the patient, including its feasibility and safety; provide expert consultation to the other members of the obstetric team; manage anesthesia care and complications; and arrange for advanced care if needed. We placed particular emphasis on clear, detailed anatomic color drawings; latest techniques and images; an easy-to-read outline format when appropriate; and clinically relevant, practical aspects of obstetric anesthesia. The chapter contributors are national and international experts in the field, and the book's compact size makes it easy to carry around in the labor and delivery suite.

There is nothing as miraculous as watching a healthy baby be born into this world full of opportunity. We as clinicians must consistently strive to improve ourselves to deliver the best care for newborns and mothers each day. We hope you enjoy our book!

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1

Physiological Changes During Pregnancy

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The Cardiovascular System

A high-flow, low-resistance hyperdynamic circulation develops in pregnancy, at first driven by hormonally mediated peripheral vasodilation. This begins as early as 8 weeks of gestation. The heart rate steadily climbs before plateauing at 10–15 beats above baseline by 30-32 weeks gestation.[2] With the increase in heart rate, cardiac output also incrementally increases. Initially, the heart rate-mediated increases in cardiac output result in a slight decrease in mean arterial pressure (MAP) and widening pulse pressures. The decreased MAP activates renin-angiotensin autoregulation, resulting in improved salt and water retention and overall plasma volume expansion by up to 40–50%. The larger plasma volume increases preload, end-diastolic volumes, and thus stroke volume beginning around the middle of the first trimester. This is augmented by a 20% increase in blood volume.[4] The effects of peripheral vasodilation on systemic vascular resistance (SVR) and blood pressure (BP) are pronounced, resulting in an average decrease in SVR of 20% and decreased systolic and diastolic BP of 8% and 20%, respectively.[5] Despite the expansion in intravascular volume, the peripheral vasodilation and increased pulmonary vascular compliance cause the central venous pressure (CVP) and pulmonary capillary wedge pressures to remain relatively unchanged.[5] Additionally, the ejection fraction remains unchanged relative to baseline values.[6]

By 20 weeks of gestation, the enlarging uterus approaches the level of the umbilicus and begins compressing the inferior vena cava (IVC) and descending aorta in the supine position. The decrease in SVR also plateaus

in the middle of the second trimester. The rise in cardiac output continues, but in a nonlinear[1] trajectory.

Cardiac output (CO) reaches its peak in the early third trimester, with heart rate (HR) peaking at 16 beats per minute above baseline.[1] There is also an average of 40 gram increase in left ventricular mass above baseline in the early third trimester.

By 38–40 weeks, cardiac output decreases by 25–30% when turning from lateral to supine position due to aortocaval compression. Because there is no autoregulation of uteroplacental blood flow, this can compromise flow to the fetus resulting in uteroplacental insufficiency and fetal heart rate decelerations. Maternal compensation includes an increase in sympathetic tone and diversion of blood flow through collateral circulation to reach the right heart through the azygous veins and vertebral plexus system.[1,2,3]

Electrocardiographic (EKG) changes occur late in pregnancy around gestational weeks 37 due to the cephalad displacement of the diaphragm, causing left-sided rotation of the heart. There will be widening of the lower chest wall by 5–7 cm associated with the 4 cm displacement of the diaphragm. Consequently, normal Q waves on the inferior leads and T wave inversion are not unexpected on the EKG during late pregnancy.[8]

Labor and Delivery

Epidural veins and venous plexus are engorged and during uterine contraction there is autotransfusion of 500 ml from the uterine vasculature as the muscular wall contracts. Increases in cardiac workload and autotransfusion pose a danger for pregnant patients with limited cardiac reserve, due to the risk of ventricular failure or development of pulmonary edema.

During early labor, CO increases 15% above baseline, and during active labor it increases by 25%. It rises by 50% during maternal pushes in the second stage of labor. These increases are tempered to varying degrees by the epidural anesthetic. Notably the increase in cardiac output with uterine contractions persists. In addition, the fact that positioning the patient in left lateral position significantly increases CO during labor relative to supine suggests CO during labor is preload dependent.[1] At the time of delivery,

there is an 80% increase in CO as the uterus involutes following delivery of the fetus and placenta.

HR and BP return to baseline prepregnancy levels within 6–8 weeks[1] postdelivery. CO returns to normal over the course of a month. In as short as two weeks, there is a reduction in left ventricular size and contractility.[7]

Cardiovascular Parameters During Pregnancy

Parameters	Changes
Cardiac output	30–50% increase
Stroke volume	30% increase
Plasma volume	50% increase
Hear rate	15–25(bpm) increase
SVR	20% decrease
Systolic BP	slight decrease
Diastolic BP	20% decrease
CVP	unchanged
FVP	2–3 × increase

Pregnancy is a high-flow and low-resistance state.
SVR = systemic vascular resistance, BP = blood pressure, CVP = central venous pressure, FVP = femoral venous pressure

The Hematologic System

The pregnant patient prepares for hemorrhage during delivery through the development of physiologic anemia and a prothrombotic state. Overall there is an expanded plasma volume, mild neutrophilia, mild thrombocytopenia, increased procoagulant factors and decreased anticoagulants, and diminished fibrinolysis. There is an increase in plasma and red and white cell volumes during pregnancy. The increase in plasma volume is 40–50%, while the increase in red cell mass is only 15–20%.[9] The increase in red cell mass is 10–15% at 6–12 weeks and expands until 30–34 weeks before plateauing at near term.[9] This creates a physiologic anemia of pregnancy. The increase in red cell mass requires improved maternal stores of up to a two-fold increase in iron, a two-fold increase in B12, and a ten to twenty fold increase in folate.[15] This is driven by increased erythropoietin (EPO)

levels, which climb to 50% above baseline. Corresponding with red cell mass expansion is an increase in 2,3—DPG (Diphosphoglycerides) which facilitates offloading of O_2 to the fetus.[16] As mentioned in the cardiovascular section, the plasma expansion is thought to be driven by an initial hormonally mediated (atrial naturietic peptide, estrogen, progesterone, and nitric oxide) vasodilation and transiently dropping blood pressure, and causes RAAS activation and compensatory fluid and salt retention.[10]

Pregnancy is associated with a mild leukocytosis, with mean values ranging from 10,000–16,000 with reported upper levels of 29,000. The leukocytosis is primarily neutrophilic-predominant and begins to develop in the second to third month of pregnancy, plateauing in third trimester.[17]

A gestational thrombocytopenia is common in pregnancy, with typical levels remaining in the normal range: 150,000–450,000. Levels less than 100,000 should be investigated, and differential diagnosis includes idiopathic thrombocytopenic purpura (ITP), severe preeclampsia, sepsis with disseminated intravascular coagulation (DIC), HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelets count), Thrombotic Thrombocytopenia Purpura (TTP, antiphospholipid syndrome, and drug-induced thrombocytopenia.

Overall, the coagulation profile demonstrates an increase in procoagulant factors, a reduction in anticoagulant factors, and a reduced state of fibrinolysis. Factor I, VII, VIII, IX, X, XII, and fibrinogen levels are elevated during pregnancy. Von Willebrand factors increases two- to fourfold during pregnancy and returns to baseline postpartum.[18] Factors XIII and antithrombin (AT) are decreased. AT levels may be slightly increased or stable during pregnancy with a noticeable fall in level by 30% below baseline following delivery. This is likely mediated by consumption. AT levels return to baseline 72 hours postpartum.[19] Thrombopoietin, platelet production, and destruction are all increased with a gradual decline in platelet counts as pregnancy progresses.[11] Resistance to activated protein C reaches a plateau in the second and third trimester.[12] Free protein S decreases.[13] Fibrinolytic inhibitor levels, including thrombin activated fibrinolytic inhibitor and plasminogen activator inhibitor 1 and 2, increase, thus leading to decreased fibrinolysis.[20] Hence, pregnancy is a hypercoagulable state and should return to normal 12 weeks postpartum.

Over the course of 6-8 weeks following delivery, the plasma volume, white blood cell count, red blood cell count, platelets, and coagulation fibrinolytic system return to baseline.[21]

Respiratory Changes

Most patients who have underlying lung pathologies, except for pulmonary hypertension or chronic respiratory insufficiency due to parenchymal or neuromuscular disease, can tolerate normal pregnancy.[22] Minute ventilation increases during pregnancy, due to higher respiratory center sensitivity and drive, compensated respiratory alkalosis, and reduced functional residual capacity (FRC). Vital capacity and forced expiration are preserved.

Anatomical Changes

The costochondral ligaments of ribcage become more relaxed, allowing for widening of the subcostal angle by approximately 68° to 103°. This causes an expansion in the lower rib cage circumference[25] by around 5 cm to accommodate for the enlarged uterus later in pregnancy.[23] Similar elastochondral relaxation takes place in the pelvic ligaments at the sacroiliac joints and the pubis. Such relaxation is mediated by the hormone relaxin.[24] It takes a few months after delivery for those changes to get back to normal.

There is also 4 cm elevation of the diaphragm, which compromises the chest wall compliance by 35–40%,[26] which progressively worsens as the gravid uterus increases intraabdominal pressure. This will also lead to a reduction in the end expiratory volume (EEV).

Despite the elevated diaphragm, tidal volume (TV) is increased during pregnancy as a result of the widening in the ribcage and strong respiratory stimulation from an increase in progesterone[30] which attenuate tidal volume dependency on diaphragmatic excursion. The inspiratory capacity (IC) will increase. The inspiratory reserve volume (IRV) is reduced early in pregnancy due to an increased TV (Figure 1.1). IRV increases in the third trimester due to reduced FRC.[27,28]

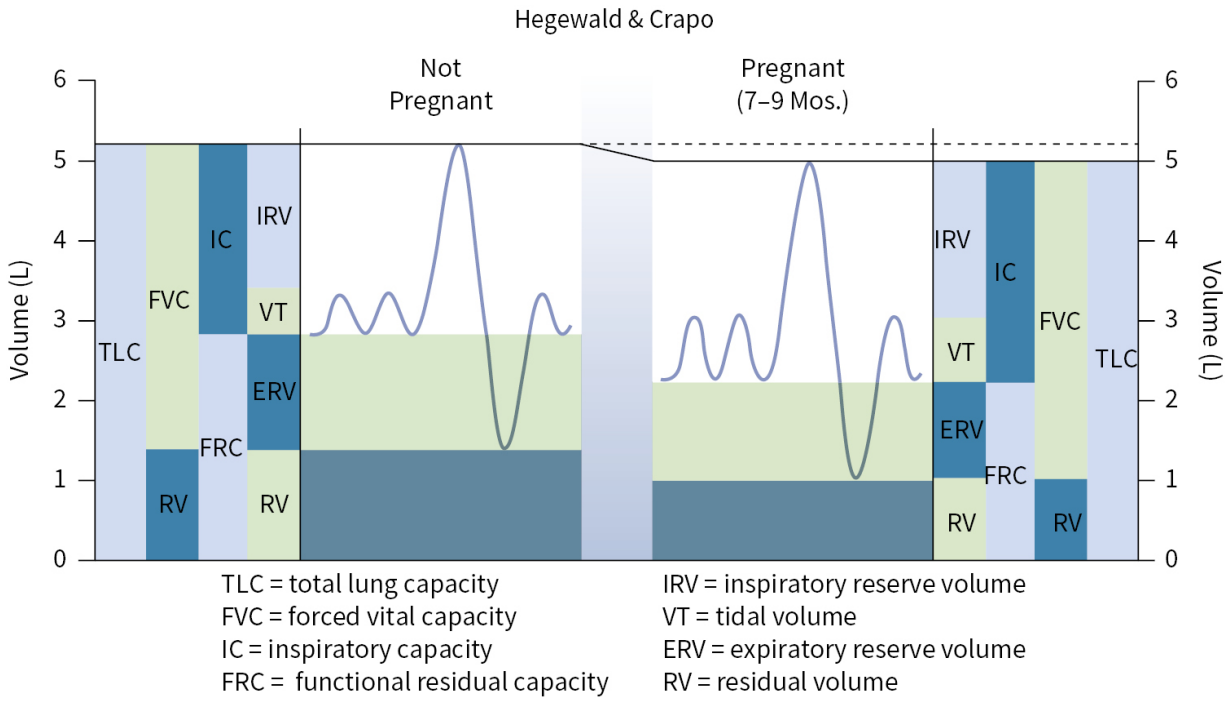

Figure 1.1 Changes in lung volumes with pregnancy. The most significant changes are reductions in FRC and its subcomponents ERV and RV, and increases in IC and VT.
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FRC will be reduced due to the reduction in chest wall compliance and this will be more noticeable at 12 weeks of gestation when the residual volume (RV) begins to decrease. This will maintain vital capacity (VC) at its normal pre-gravid level or cause a mild increase in VC.

The FRC will decline during the late stage of pregnancy with supine position and lead to closure of closing volume (CV) earlier in tidal volume, causing an increase in alveolar-arterial-gradient (PA-Pa).

Minute volume (MV) will increase by 30% during pregnancy even at rest due to the increase in TV.[30]

Lung compliance will not change during a healthy pregnancy.

The CO_2 chemo-sensitivity and respiratory drive start early in pregnancy and return to normal soon after delivery.[31]

Pulmonary function test (PFT) values remain almost the same during pregnancy. The forced expiratory volume in 1 second (FEV1), peak expiratory flow rate (PEFR), and FEV1 to forced vital capacity (FVC) ratio are all normal during pregnancy.[27,28]

The volume compliance curve will stay the same as during nonpregnant women and dead space will be decreased in pregnancy due to the increase cardiac output and an improved physiological shunt at the apices.

Carbon dioxide production increases by up to 300 ml/min due to high metabolic production. However, a state of respiratory alkalosis with $PaCO_2$ during pregnancy between 30–34 mm Hg is normal. Pregnancy increases TV and MV, creating respiratory compensation.[29] Respiratory alkalosis will stimulate renal excretion of bicarbonate (HCO_3) to keep HCO^3 at the 15–20 mEq/L[30] level.

The alkalosis state will increase 2,3 diphosphoglycerate synthesis which will shift oxygen dissociation curve to the right, favoring oxygen delivery and extraction to fetus through the placenta.[30]

The hypoxic ventilatory drive doubles during pregnancy, despite the blood and cerebrospinal fluid alkalosis that inhibit hypoxic ventilatory response. The sensitivity of the drive is attributed to both estrogen and progesterone.

Due to hyperpnea in pregnancy, the partial pressure of oxygen (PaO_2) is mildly elevated, with ranges of 100–105 mm Hg, enhancing the diffusion gradient of oxygen across the placenta.[32,33]

The diffusing capacity of carbon monoxide (D_{CO}) is either unchanged in pregnancy or slightly reduced. The diffusion will increase with high cardiac output and the pulmonary capillary recruitments; however, this increase in diffusion is offset by the hemodilution of pregnancy.[34] Normally there is increase in D_{CO} in supine position which will be absent during pregnancy as a result of reduction in venous return.

Summary of the Respiratory Changes During Pregnancy

Parameters	Changes
Minute volume	increased
Tidal volume	increased
Respiratory rate	unchanged
TLC	unchanged/reduced
VC	unchanged/increased
LC	unchanged
Chest wall compliance	reduced
Inspiratory capacity	mild increase
FRC	reduced
RV	mild
ERV	reduced
Thoracic diameter	increased 5–7 cm
Diaphragm	elevated 4 cm
FEV1	unchanged
FVC	unchanged
FEV1/FVC	unchanged
PH	7.44
PaO_2	107-105-103 mm Hg elevated 1st 2nd and 3rd trimesters consecutively
$PaCO_2$	30 mm Hg decreased
HCO_3^-	15–20 mEq/L decreased
D_{CO}	unchanged/mild reduction

TLC = total lung capacity, VC = vital capacity, LC = lung capacity, FRC = functional residual capacity, RV = residual volume, ERV = expiratory, residual volume, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, D_{CO} = diffusing capacity for carbon monoxide

High Altitude and Pregnancy

High altitude imposes certain changes and risk to pregnant women. D_{CO} is higher with pregnant women who reside at high altitudes compared to those who reside at sea level. The increase in D_{CO} supplements the increased MV

and increased hemoglobin concentrations, thus increasing oxygen saturation.[37]

McAuliffe et al. demonstrated no significant differences in mean FVC, FEV1, FEV1/FVC, and PEFR of nonpregnant women at high altitude compared to nonpregnant women living at sea level. Pregnant women living at high altitude had larger mean TLC, IC, FRC ERV and RV than pregnant women living at sea level. Pregnant women living at high altitude compared with pregnant women living at sea level had higher mean FVC and FEV1, but their mean FEV1/FVC was lower. The mean PEFR of pregnant women living at high altitude did not differ significantly from that of pregnant women living at sea level.

TLC, RV, ERV, IC and FRC were elevated in pregnant women at high altitude.[37] Studies by Keyes et al. showing higher incidence of pre-eclampsia and stillbirth in pregnant women living at high altitude than dwellers pregnant living at sea level.[38]

Physiologic Dyspnea of Pregnancy

Shortness of breath at rest or on mild exertion during pregnancy is referred to as physiological dyspnea. By week 30 of pregnancy, 75% of women have exertional dyspnea.[39] The proposed cause is the increase in the work of breathing and minute volume in response to the enlarged uterus. Other factors contributing to the etiology of dyspnea include anemia, nasal congestion, and increased pulmonary blood flow.[40] Psychological studies suggest that dyspnea is due to the increased work of breathing rather than the increase in the sensitivity to mechanical loads.[40] Increasing endurance exercise didn't seem to show any evidence of improving the cardiovascular response compared to postpartum. Fetal response to short duration of exercise is moderate and returns to baseline after exercise. Furthermore, prenatal physical conditioning did affect fetal growth significantly.[41]

Clinicians need to differentiate the normal dyspnea of pregnancy from pathological ones referring to other clinical findings such as respiratory rate higher than 20 bpm, $PaCO_2$ less than 30 or greater than 35, hypoxemia, abnormal spirometry, and cardiac echocardiography.

The Renal System

Pregnancy induces significant functional, anatomical, and structural changes in the renal system. The high increase in progesterone plays a major mediator in many of those anatomical changes, namely reducing ureteral tone, peristalsis, and contraction pressure.

The importance of understanding those changes will not only help monitoring prenatal progress but also distinguishing those changes from any pathological scenarios that may occur.

Changes in renal function during the menstrual cycle are similar to the changes happening at the early phase of pregnancy. Hormonal variations during the midluteal phase include lower mean arterial pressure and systemic vascular resistance, resulting in increased cardiac output, renal plasma flow (RPF), and glomerular filtration rate (GFR).[42]

The kidney size, volume, and length increase to approximately 30% of its original size 1–1.5 cm,[43] due to an increase in vascular and interstitial spaces, water retention, and hydronephrosis, even if the total number of nephrons remains constant. The kidneys start to shrink and return to normal size in up to six months postpartum.[44]

The renal pelvis, the calyces, and ureters are markedly dilated, which is often and misdiagnosed as obstructive uropathy.[45,46] The dilation is due to smooth muscle relaxation from the increased secretions of progesterone.

There is also a slight reduction in cortical width without an ill effect.[46]

Physiological hydronephrosis and hydroureters will be experienced by 80% of pregnant women. This ureteric dilatation develops during the second trimester and is more frequent and pronounced in primigravid women. It is prominent above the linea terminalis.[49] The right ureter is more affected because it crosses the iliac vessel and the ovary at its entrance to the pelvis.[46] Nonobstructive dilatation of the left ureter is often present.[47] The maximal incidence of hydronephrosis is reached at 28 weeks, with an incidence of 63% of overall hydronephrosis.[48] Au et al. found that hormonal balance during pregnancy is of less importance in causing hydroureter.[50]

Ureteric dilatation can be reduced clinically by placing the woman on the side least affected or in the knee-elbow position which will improve drainage while treating the commonly occurring ascending urinary tract

infection during pregnancy.[51] There is a possible relationship with the development of pre-eclampsia as demonstrated by isotopic Reno graphic studies.[52]

A worsening of an existing hydronephrosis or an acute hydronephrosis should be considered as a possible cause of uncertain abdominal pain during pregnancy.[53]

Renal plasma flow (RPF) increases by 80% during early pregnancy and falls to 40–65% during the third trimester. GFR remains at a level 50% above the nonpregnant throughout pregnancy.[54] The increase in GFR causes creatinine level and Blood Urea and Nitrogen (BUN) to decrease to below normal levels at term, and renal disease during pregnancy should be suspicious if serum creatinine level is greater than or equal 1.2 mg/dl.[55]

There is a study suggesting that hyperfiltration continues at levels 20% above normal at postpartum week two and resolves by one month postpartum.[56]

Those physiological and anatomic changes impose a few clinical implications:

- The dilated collecting system can hold 200 to 300 mL of urine, leading to urinary stasis and a 40% increased risk for asymptomatic bacteriuria and pyelonephritis.
- Elective radiologic examination of the urinary tract should be deferred until the anatomical sizes of the renal system return to prepregnancy size. It should be considered during radiological interpretation. Kidney size can take six months to return to prepregnant size.
- Rarely, massive ureteral and renal pelvis dilation might precipitate the "overdistension syndrome."

Changes in Glomerular Filtration Rate (GFR) and Tubular Functions

The GFR and renal plasma flow RPF increase to levels about 50–60% above nonpregnant values. These increases occur shortly after conception and all increments are maximal in the second trimester. There is often a reduction in GFR of 15% during the final month of the third trimester and this must be taken into consideration, especially when assessing the course of pregnancy in a woman with known renal disease.

There are no substantial alterations in the production of creatinine and urea despite the increase in GFR. Creatinine levels fall from a nonpregnant level to 0.86 mg/dl in the first trimester, to 0.81 mg/dl in the second trimester, and to 0.87 mg/dl[57] in the third trimester. An increasing serum creatinine greater than 0.87 mg/dl in pregnancy could indicate an acute kidney injury.[57]

Serum urea is low in pregnancy due to a reduction in protein degradation and an increase in clearance. Average plasma urea levels of 7–12 mg/dl during first trimester, 3–13 mg/dl during the second and 3–11 mg/dl during the third trimester. In nonpregnant healthy woman, BUN is 7–20 mg/dl.

Glucose excretion is increased and tubular reabsorption of glucose is less efficient.

Proteinuria increases due to high RPF and should be considered abnormal when it is twice the normal limit. Normal proteinuria is 150–250 mg/24 hr in healthy women.

Changes in Water and Electrolytes Homeostasis

Arterial vasodilation in pregnancy stimulates the sympathetic nervous systems, baroreceptors and renin-angiotensinogen-aldosterone system (RAAS), leading to a release of arginine vasopressin peptide (AVP) from the posterior hypothalamus. These changes cause sodium and water retention, hypervolemia, and hypo-osmolar state.[58,59,60]

Maternal plasma volume increases by 30–50% with 40% of that volume composing the extracellular volume (ECV). Total plasma volume is expected to be 1600 to 2000 ml above nonpregnant level.[61] Plasma volume reaches a maximum of 50% during the second trimester. There is also fluid within fetal and maternal interstitial spaces, which is greatest at term. The thresholds for thirst and antidiuretic hormone secretion are depressed, resulting in lower osmolality and serum sodium levels 4–5 mEq/L lower than nonpregnant levels.[62]

Salt and water retention in the distal tubule and collecting duct takes place, due to high aldosterone secretions from the activation of the RAAS. The increase in aldosterone is responsible for the increase in plasma volume during pregnancy.[63]

Aldosterone has a high potency for sodium-retention; however, natriuresis is promoted by progesterone, which is an aldosterone antagonist. Renin synthesis increases during pregnancy as upregulation of RAAS. There is an extra renal production of inactive renin precursor which takes place in the ovaries and decidua during early pregnancy. The estrogen produced by the placenta will stimulate the synthesis of angiotensinogen by the liver. This will be converted into angiotensin II (ANG II). Though ANG II is a potent vasopressor, systolic blood pressure in known to be low during pregnancy. This is likely due to other factors that cause the vasodilatory state of pregnancy. This refractoriness to the ANG II can be due to other hormonal effect of progesterone and vascular endothelial growth factor mediated prostacyclin and/or the monomeric state of angiotensin 1 (AT_1) receptors.[64] This explains the reason for low systolic blood pressure despite high renin production. In patients with pre-eclampsia, there is a dysregulation of the RAAS and return of ANG II sensitivity.[64]

Potassium is kept constant during pregnancy despite the increase in total body level of potassium. This is due to a balance between excretion of potassium and increase in tubular reabsorption. Progesterone promotes antikaliuretic function.[65]

Hypothalamic AVP release increases early in pregnancy as a result of increased relaxin levels. AVP mediates an increase in water reabsorption via aquaporin 2 channels in the collecting duct. The threshold for hypothalamic secretion of AVP and the threshold for thirst is reset to a lower plasma osmolality level, creating the hypo-osmolar state characteristic of pregnancy. These changes are mediated by human chorionic gonadotropin (hCG) and relaxin.[66]

The production of aminopeptidase vasopressinase by the placenta increases fourfold in middle and late pregnancy. These changes enhance the metabolic clearance of vasopressin and regulate the levels of active AVP.

In pre-eclampsia or twin pregnancies, a transient diabetes insipidus may develop due to overproduction of vasopressinase, leading to high secretion of atrial natriuretic peptides. The levels of natriuretic peptides are higher in pregnant women with chronic hypertension and pre-eclampsia.[67]

Renal Changes During Pregnancy

Parameters	Changes	Causes / Comments
Kidney size	1–1.5 cm increase	Fluid retention, hydronephrosis, return to normal up to 12 weeks
GFR	Increases 20% at 4 weeks, 40% 9 weeks, 50% at term	Increase renal plasma flow, high progesterone. Normalizes 4–6 weeks postpartum
Blood pH	7.4–7.44 slight alkalosis	
Plasma osmolality	270 mOsm/kg	Increase plasma volume
BUN	9.0 mg/mL 25% decreased	Hyperfiltration high GFR
Serum Creatinine	0.5 mg/dL 25% decreased	Hyperfiltration high GFR
Uric acid	2–3 mg/dl 20–25% reduced	
Ureter diameter	increase	Return to normal 4–6 weeks post delivery
Serum HCO3-	18–20 mEq/L 20% decreased	
Serum Na^+	135 mEq/L (4–5 mEq/L less than nonpregnant)	Normal or slightly low
Serum K^+	3.8 mEq/L	Slightly low due antikaliuretic effect of progesterone
Urine Glucose	Increases	Reduced reabsorption

The Gastrointestinal System

Nausea and vomiting are common in pregnancy with incidence of 50–90%. The etiology is still unknown although it has been inferred to be related to the high production of estrogen and progesterone, hCG, and TSH hormones.[68]

As pregnancy reaches 20 weeks of gestation, the enlarging uterus will encroach into the intra-abdominal area, resulting in displacement of the digestive organs. The stomach is moved upward and to the left and is rotated 45 degrees to the right of its normal vertical position. This causes a displacement of the intra-abdominal portion of the esophagus into the thorax in many patients, resulting in decreased competency of the lower esophageal sphincter. Further, this reduces the ability of the lower

esophageal tone to rise, which typically occurs under high intragastric pressure to prevent reflux. As pregnancy advances into the last trimester the continued cephalad movement of the abdominal contents results in up to 80% of women experiencing pyrosis. Growth of the fetus distends the abdomen stretching the peritoneum, leading to desensitization, which can make diagnosis of acute abdomen and peritonitis more difficult.

Hormonal changes during pregnancy affect GI transit time. Increasing levels of progesterone result in inhibition of GI contractility and a decrease in esophageal peristalsis and LES tone; however, overall gastric emptying is not affected. The placenta produces gastrin, which increases gastric hydrogen ion secretion, further lowering the gastric pH. These physiologic changes result in the incidence of pyrosis and reflux esophagitis symptoms in nearly 50–80% of parturient. Aspiration pneumonia is estimated to affect 0.1% of pregnant women.

The use of opioids, including epidural opioids, in the peripartum period contributes to the reduction of esophageal tone and impaired gastric emptying. Anticholinergics will also contribute to decreased smooth muscle motility and increased risk of aspiration. Due to the changes mentioned above, all pregnant women after 20 weeks gestation should be treated as if they have a full stomach, with a minimum of 6–8 hours fasting before any elective surgery. Rapid sequence intubation, cricoid pressure, and gastric suctioning should be performed for pregnant patients to minimize aspiration risk. Furthermore, the American Society of Anesthesiologists recommends “Timely administration of oral non-particulate antacids, intravenous IV H2-receptor antagonists, and/or metoclopramide for aspiration prophylaxis.” Nonparticulate antacids, such as sodium citrate, work rapidly but can increase gastric volume, so administration should not be immediately prior to induction of anesthesia. Metoclopramide is a dopamine antagonist known to cause increased gastric emptying and a modest increase in LES tone. Within the first day of the postpartum period, gastric emptying and gastric volumes return to prepregnancy state.

Summary of Gastrointestinal Changes During Pregnancy

Parameters	Changes	Causes / comments
Gastric motility	Decrease	Increased progesterone
Gastric emptying time	Increase	
Hyperemesis gravidarum		Increased thyroid hormones, hCG, progesterone, estrogen
Gastroesophageal sphincter tone	Decrease	Anatomical displacement and increased gastrin
Bowel motility	Decrease	Increased gastrin
Bowel transit time	Increase	

The Hepatic System

While there is no change in liver size, morphology, and blood flow in the parturient, there are important changes in hepatic physiology. Plasma protein concentration is reduced secondary to hemodilution described earlier. Plasma albumin concentration decreases from 4.5 to 3.9 g/100 mL in the first trimester and continues to decline to 3.3 g/100 mL by the third trimester. Total protein decreases to 7.0 g/100 mL from 7.8 g/100 mL in the nonpregnant patient. Globulin levels will decrease 10% in the first trimester and then will rise to 10% above normal by the third trimester. Due to these changes the maternal colloid pressure declines 5% in the pregnant patient. There is a 25% decrease in plasma cholinesterase activity during pregnancy; however, this has limited clinical significance in anesthetic management.

The liver produces an assortment of proteins and clotting factors including Factors V, VII, IX, X, XI, antithrombin, Protein C and S, fibrinogen, and prothrombin. As highlighted previously in this chapter, the hepatic changes during pregnancy result in elevated production of coagulation factors I, VII, VIII, IX, X, and XII leading to increased fibrinolysis, clotting, and platelet turnover.

In the pregnant period, alanine and aspartate aminotransferase ALT, AST, LDH, and serum bilirubin will increase to the upper limits of normal. Alkaline phosphatases (ALP) increases to 2–4 times normal values in late pregnancy, attributed to the increased production of isoenzymes by the placenta, bones, liver, kidneys, and small intestine. Due to hormone

mediated changes in smooth muscle tone, there is a slowing of gallbladder emptying, resulting in increases of fasting and residual gallbladder volumes, specifically in the second and third trimester. As the rate of gallbladder emptying slows, the bile concentrates and predisposes the pregnant patient to gallstone formation and further complications.

The Endocrine System

In the pregnant patient, the rapid increase of metabolic demands of both the mother and fetus requires the endocrine system to undergo many changes. The hypothalamic pituitary axis is critical in the coordination of these metabolic activities. The placenta releases increased amounts of corticotropin-releasing hormone (CRH) important for the initiation of labor, and Gonadotropin-releasing hormone (GnRH) which functions primarily to promote further growth of the placenta.

During pregnancy, in response to the increase in hypothalamic releasing hormones, the pituitary gland increases in size by three times. Growth hormone secretion is largely replaced by increased expression of placenta growth hormone. As progesterone and estradiol levels increase, there is decreased gonadotropin secretion.

The anterior lobe of the pituitary gland undergoes hypertrophy in order to produce lactotrophs. The anterior pituitary production of prolactin increases throughout pregnancy in preparation for breastfeeding. In nonbreastfeeding mothers, levels of prolactin will rapidly fall after delivery.

The anterior pituitary release of thyroid-stimulating hormone (TSH) decreases during the first trimester, before returning to normal by term. This initial decrease of TSH is due in large part by the rapid rise in human chorionic gonadotropin hormone (HCG) produced by the placenta. HCG has thyroid stimulating properties resulting in negative feedback suppression of TSH release. Due to the complex hormonal feedback loops mediating TSH levels, TSH should not be used for diagnosis of thyroid dysfunction during pregnancy. Instead, checking free-T4 levels is recommended. This rapid rise of HCG can result in hyperthyroid symptoms, which may contribute to the incidence of hyperemesis gravidarum. Increased levels of estrogen result in 200% increase in synthesis of thyroxine-binding globulin correlating to a resultant 50%

increase in T4 and T3 levels. Due to high metabolic demands of the fetus, there is increased transport of iodine into the fetus, resulting in a state of iodine-deficiency in the mother.

The posterior pituitary gland releases antidiuretic hormone (ADH) and oxytocin. As the placenta enlarges, there is an increased clearance of ADH, which can be associated with increased risk for development of diabetes insipidus in some women. Oxytocin is increased during throughout pregnancy, and is involved in milk production and release.

The placenta produces both CRH and adrenocorticotropic hormone (ACTH), which overrides the typical negative feedback loop, resulting in a hypercortisol state. Corticosteroid binding globulin doubles during gestation due to estrogen induced hepatic synthesis, the elevated corticosteroid binding globulin results in a 100% increase of plasma cortisol concentration during first trimester, and 200% increase at term. Interestingly, and important for diagnosis of metabolic disorders, healthy pregnant women continue to maintain diurnal variation of cortisol and ACTH levels. Normal symptoms of pregnancy (weight gain, fatigue, insulin resistance, vomiting, etc.) can make diagnosis of cortisol-excess (Cushing disease) and adrenal insufficiency nearly impossible to recognize without meticulous analysis of ACTH and Cortisol levels. Untreated adrenal insufficiency is of specific concern to the anesthesiologist as labor and its associated stress response may culminate in adrenal crisis and ensuing profound hypotension response necessitating vasopressor infusion and intravenous hydrocortisone.

The metabolic demands of pregnancy and fetus maturation require changes in carbohydrate and fat metabolism. Hyperplasia of beta cells in the pancreas result in increased insulin secretion and a resultant 10–20% drop of fasting blood glucose levels, most significantly in third trimester. Placental lactogen results in diabetogenic effects. The relative hyperinsulinemia results in mild insulin resistance, this insulin resistance is noted by increase in postprandial glucose levels, especially after high carbohydrate loads. The effects of relative insulin resistance of pregnancy can be confounded in obese patients with pre-existing insulin resistance and patients with low pancreatic reserves resulting in gestational diabetes and higher insulin dose requirements, when compared of nonpregnant women.

Similar to carbohydrate metabolism, fat metabolism changes drastically leading to utilization of fatty acids and glycerol as maternal energy sources.

Glycerol is vital for maternal gluconeogenesis, providing the glucose to cross the placenta for fetal consumption. In the second semester, there is marked increase in storage and accumulation of fat secondary to triglyceride and cholesterol synthesis. As women progress into the third trimester, the increased metabolic demands result in a shift from fat accumulation to consumption with an associated increase in lipolysis. This increase in lipolysis drives the release of fatty acids and glycerol. Fatty acids are involved in energy production during maternal fasting and are converted to ketones by the liver, ketones cross the placenta freely and are utilized by the fetus. Increase in fat cells is also associated with increase in Leptin and Adiponectin, which are important in energy homeostasis, these markers will be abnormal in gestational diabetes.

Summary of the Endocrine Changes During Pregnancy

Parameters	Changes	Causes / Comments
Progesterone	Increase	
Estrogen	Increases	
Pituitary gland size	100% increase	
CRH	Increased	Initiation of Labor
GnRH	Increased	Promote growth of placenta
Adrenal gland size	Unchanged	
Thyroid gland size	10 – 15% increase	
TTH	Increase	Due to high estrogen
TBG	increase	
TSH	Decreased	Suppressed by HCG
FTH	Unchanged	
HPL	Increase	

TTH = total thyroid hormone, TBG = thyroid binding globulins, CRH = corticotropin-releasing hormone, FTH = free thyroid hormone, HPL = human placental lactogen, GnRH = gonadotropin-releasing hormone, TSH = thyroid stimulating hormone, HCG = human gonadotropin hormone

The Central and Peripheral Nervous System

There is an increase in the sensitivity to both local and general anesthetics during pregnancy. The increase in sensitivity to local anesthetic was

demonstrated by Datta et al. in isolated rabbit nerves. A, B, and C fiber types from pregnant and nonpregnant specimens were administered a standardized dose of bupivacaine and times to 50% blockade were recorded. Time to 50% blockade was significantly reduced in pregnant fibers relative to nonpregnant.[69] Butterworth et al demonstrated an analogous differential sensitivity in lidocaine-treated median nerves of pregnant vs. nonpregnant human women.[70]

Consistent with these findings, there is greater sensitivity to local anesthetics when injected in the epidural space. This results in wider dermatomal spread of sensory anesthesia during pregnancy relative to age matched controls.[71] Explanations for the increased sensitivity include the respiratory alkalosis of pregnancy, reduced plasma and CSF protein levels, and hormonal influences.[71]

The increase in sensitivity to general anesthesia during pregnancy is well documented. Palahniuk et al in 1974 observed a 25–40% decrease in minimum alveolar concentration (MAC).[72]

Progesterone may be responsible for increases in sensitivity to both general and local anesthesia. This is implicated in animal models. Injection of progesterone into oophorectomized rabbits resulted in decrease MAC.[73] Chronic exposure to progesterone in these animals resulted in increased sensitivity to local anesthetics as well.[74] It is not currently known when nervous system sensitivity reverts to prepregnancy levels (see Table 1.1).

Table 1.1 Risks of General Anesthesia for Cesarean Delivery

Risk	Reasons	Prevention
Awareness	Often emergent nature of surgery Immediate incision after induction Use of low concentration of volatile agent because of atony, hypotension, hemorrhage, or decreased requirements in pregnancy Avoidance of preoperative sedatives Use of NMBAs	Maintain adequate depth of anesthesia, utilizing IV agents and N_2O when decreasing volatile anesthetic Administer opioids & benzodiazepines after delivery Avoid long-acting NMBAs if possible Consider BIS monitor
Aspiration/aspiration pneumonitis	Possible recent oral intake Decreased gastric transit time in labor Decreased LES tone	Avoid solid food in labor[1] Aspiration prophylaxis RSI OG suction before extubation Extubate awake
Hemorrhage	Impairment of uterine contractility by volatile anesthetics	Decrease volatile agent after delivery TIVA for persistent atony
Difficult/failed airway	Airway edema Increased breast mass Weight gain in pregnancy	Ramped, sniffing position Immediate availability of emergency airway supplies Consider awake intubation for anticipated difficult airway Know airway algorithm Call for help early
Rapid desaturation during apnea	Decreased FRC Increased oxygen consumption	Pre-oxygenate with 3 minutes of TV breaths or 8 deep breaths of 100% FiO_2[2]
Fetal exposure to anesthetic agents	Placental transfer	Facilitate efficient delivery Administer IV anesthetics after delivery if appropriate to wait
Postoperative pain	Absence of neuraxial opioids	Consider pre-emptive truncal block or wound infiltration Multimodal analgesia

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2

The Placenta

Anatomy, Physiology, Uteroplacental Blood Flow, and Drug Transfer

Sandra N. Gonzalez, Easha Patel, and Christa L. Riley

Introduction

The placenta is a fetal–maternal organ critical to the normal implantation and development of the fetus that starts developing early in pregnancy and supports growth and development all the way to term, adjusting dynamically to successfully support fetal growth. Failure of the placenta to develop normally will result in adverse maternal–fetal outcomes such as preeclampsia/eclampsia, intrauterine growth retardation (IUGR), and even loss of the pregnancy. As the interface between the mother and the fetus, the placenta prevents rejection of the fetal allograft, regulates the transfer of nutrients and gases, and eliminates fetal waste products, and it has a pivotal role in regulating transfer of medications to the fetus. It also regulates fetal growth and maternal metabolism by synthesizing peptide and steroid hormones, glycogen, and proteins. Medications are commonly used in pregnancy for both pregnancy-related and nonpregnancy-related conditions.[1] One study states that in 2008 more than 93% of pregnant women took at least one over-the-counter or prescription medication during pregnancy.[2] Anesthetic medications are also commonly used in pregnancy, as surgery for nonpregnancy related conditions occurs in approximately 1–2% of all pregnancies and obstetric surgery occurs in approximately 20% of all pregnancies, with cesarean sections being the most common.[3] Given the prevalence of medication use, it is important to understand the role of the

placenta in the transfer of drugs from the mother to the fetus, and the potential effects of these drugs on the developing fetus. Transport across the placenta takes place at the level of placental villous trees, which are the functional units through which the highly balanced and regulated transfer of nutrients, gases, hormones, antibodies, and medications occurs, involving multiple active and passive cellular transport mechanisms. This chapter will review the development, anatomy, and physiology of the placenta; mechanisms that control placental blood flow; and placental pharmacokinetics and pharmacodynamics.

Maternal Physiologic Changes in Pregnancy

There are multiple changes in maternal physiology that occur during pregnancy. These changes are related to hormonal changes that occur during pregnancy and to the enlarging uterus over the course of pregnancy.[4] These changes affect the metabolism and transport of medications as the pharmacokinetics of drugs can be altered.[5]

Cardiac

There is a 50% overall increase in maternal plasma volume during pregnancy.[6] With the increase in blood volume, there is decreased albumin concentration, which can affect drugs with high protein binding, leading to higher concentration of free drug in circulation. There is also increased maternal arterial pH, which can affect drug-protein binding.[5] The increased plasma volume allows pregnant patients to withstand effects of blood loss during delivery. Uterine blood flow increases as the fetus grows, and by term 20% of the cardiac output is seen by the uterus. This system is highly sensitive to exogenous agents such as catecholamines as well as to loss of maternal intravascular volume.[7]

Respiratory

The major respiratory change in pregnancy is the increase in tidal volume secondary to rising progesterone levels. This results in increased oxygen

consumption as well as increased minute ventilation; however, the respiratory rate does not increase. This change[7] results in a compensated respiratory alkalosis with a pCO_2 of approximately 30 mm Hg and bicarbonate levels in the 19–20 mEq/L.

Gastrointestinal

Increased progesterone levels also decrease gastrointestinal motility along with a decrease in the resting tone of the lower esophageal sphincter. This predisposes pregnant patients to reflux. They are also at an increased risk from aspiration with general anesthesia.[7] Drug absorption can be decreased to due delayed gastric emptying and increase in gastric pH.[5]

Renal

There is an increase in renal blood flow and increased glomerular filtration rate in pregnancy. This can lead to increased clearance of many medications.[5] There is also reduced ureteral tone and peristalsis, which can result in a dilated ureter and hydronephrosis. Hydronephrosis can also be related to be compression from gravid uterus.[7]

Development of the Placenta

Placental development begins between the stages of the morula and blastocyst and progresses in multiple stages:

Pre-Implantation Stage

Between the stages of morula and blastocyst (days 4 to 5 postfertilization), the trophoblast, from which the placenta originates, is the first cell lineage to differentiate.[8] The morula enters the uterus, and on day 5 the blastocyst forms as fluid accumulates and cells become polarized, forming the inner cell mass that will become the embryo and an outer layer of cells that becomes the trophoblast (Figure 2.1).[1]

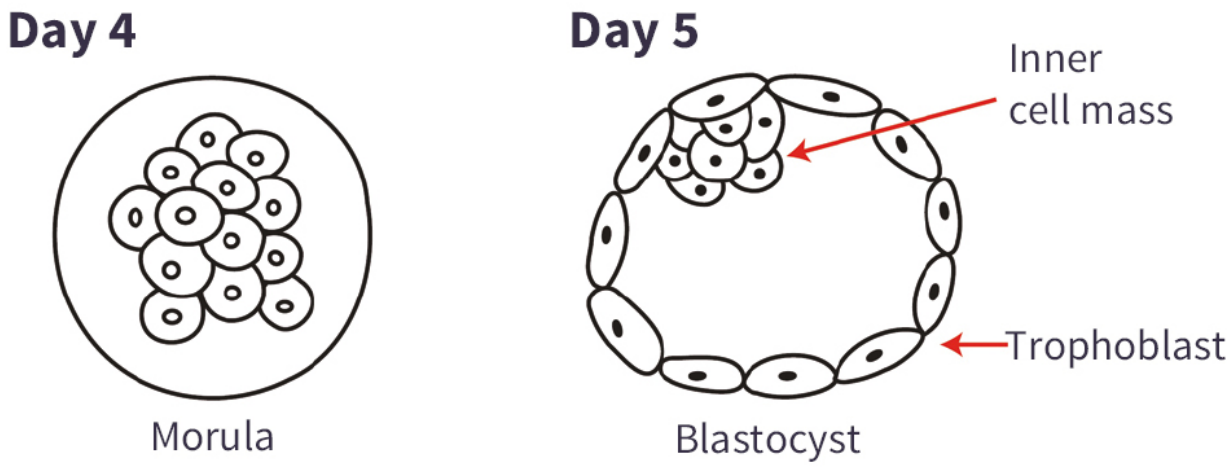

Figure 2.1 Pre-implantation stage.

Pre-Lacunar Stage

The portion of the trophoblast overlying the inner cell mass, the polar trophoblast, will lead to implantation of the blastocyst.[8] The trophoblast will give origin to the cytotrophoblast, which acts as a source of stem cells that differentiate into two pathways: the syncytiotrophoblast and the extravillous trophoblast (EVT). The syncytiotrophoblast, formed from fused cytotrophoblasts, will invade the uterine epithelium and implant the blastocyst into the uterine decidua at approximately 6 days postfertilization.[1] The syncytiotrophoblast completely surrounds the conceptus, preventing it from coming into contact with maternal tissues.[8] Once implanted, the blastocyst will have access to various substrates (e.g., glycogen) that are needed for continued growth (Figure 2.2).[1]

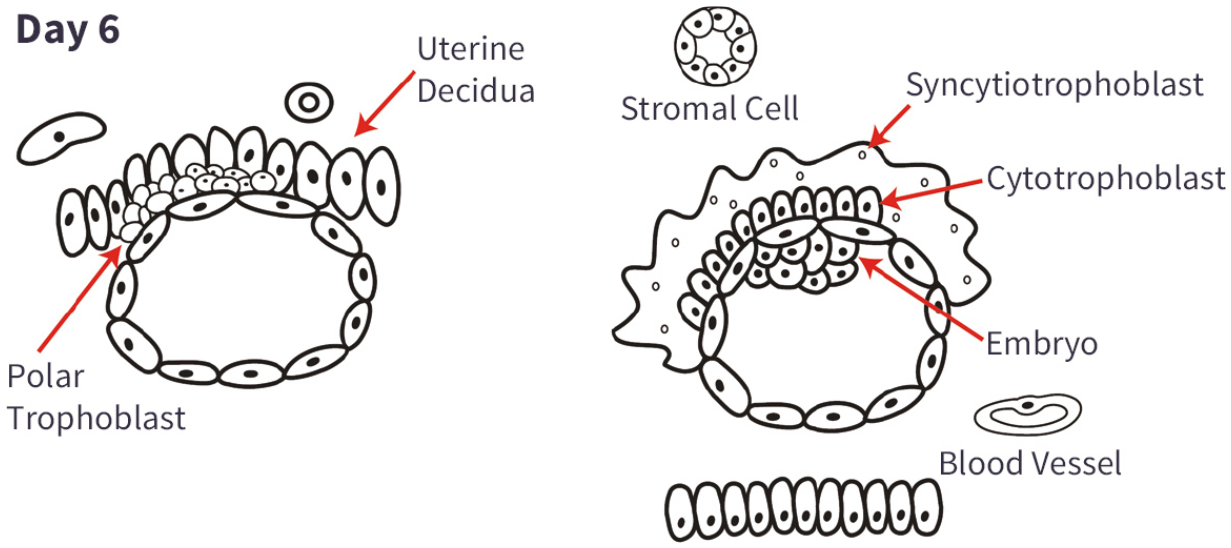

Figure 2.2 Pre-lacunar stage.

Lacunar Stage

Eight days after fertilization, vacuoles form within the syncytiotrophoblast and coalesce to form lacunae. The three fundamental zones of the placenta become more defined: the early chorionic plate facing the embryo, the lacunar system, and trabeculae develop into the intervillous space and villous trees, and the primitive basal plate comes into contact with the endometrium.[8] The EVT divides into the interstitial EVT, which invades the decidua, and the endovascular EVT, which invades and remodels the spiral arteries establishing the foundation for the uteroplacental circulation.[1]

Villous Stage

Approximately 13 days after fertilization, a layer of syncytiotrophoblast with a core of cytotrophoblast evaginates into the lacunar space to form primary villi, which acquire an inner core of embryonic mesoderm to become secondary villi. By day 21, the embryonic mesoderm will form blood vessels that connect to the vessels developing in the umbilical cord and embryo, forming the tertiary villi. Some villi anchor in the decidua, whereas others float free in the intervillous space. There is always a layer of trophoblasts separating the embryonic circulation from the maternal decidua (Figure 2.3).[1]

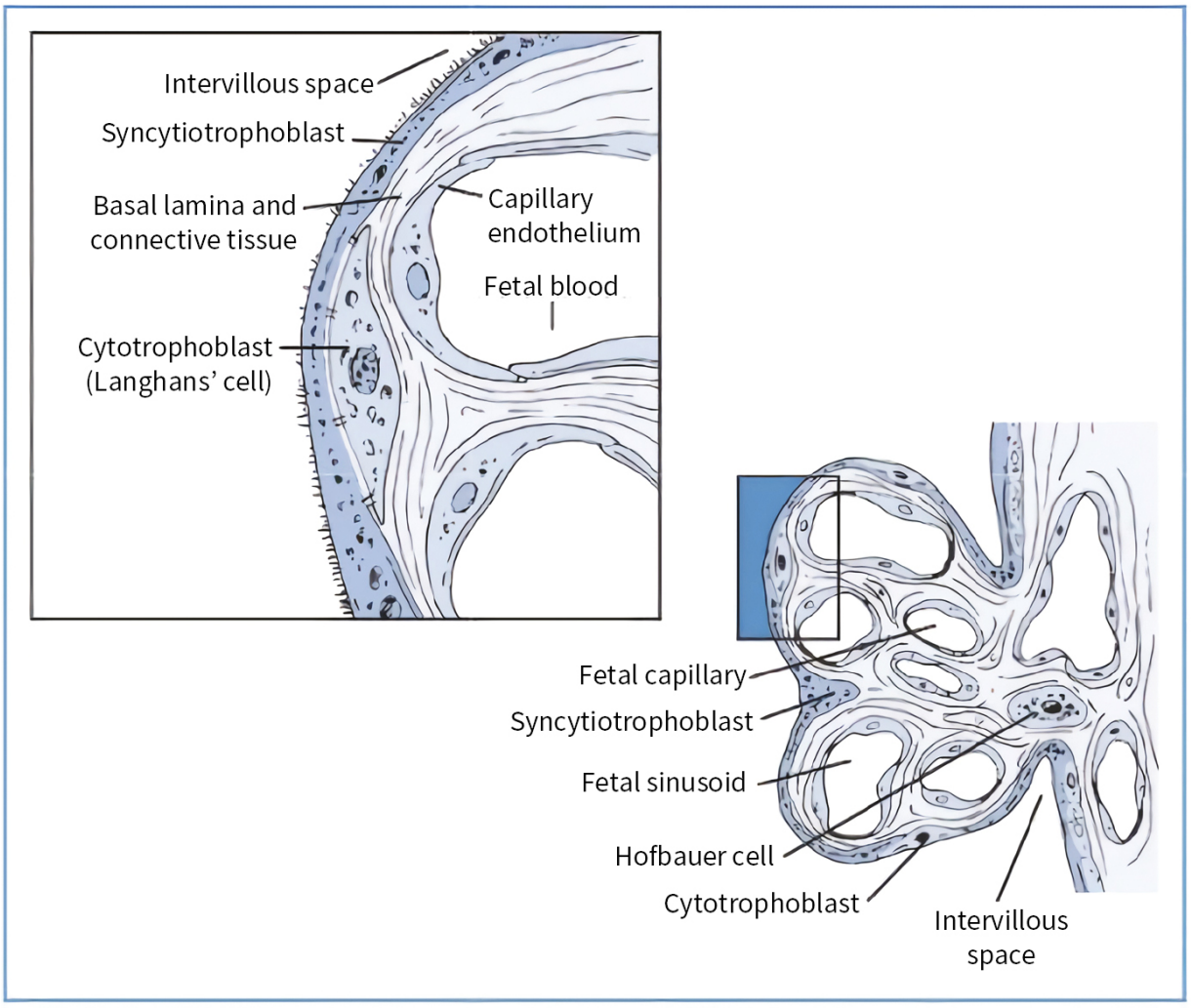

Figure 2.3 *Right:* Cellular morphology of two terminal villi. *Left:* Higher magnification of the boxed region exhibiting the placental barrier between fetal and maternal blood.
Reprinted with permission from *Chestnut's obstetric anesthesia: principles and practice*. 6th ed. Philadelphia, PA: Elsevier; 2019.

Anatomy of the Placenta

The placenta is a highly specialized organ that supports the growth and development of the fetus.[9] The main function of the placenta is to serve as an interface for gas exchange between the mother and the fetus, transfer of nutrients to the fetus and waste products from the fetus, and transfer of immunity via immunoglobulins. Additionally, the placenta secretes hormones that are necessary for the development of the fetus.[10] At term, the

human placenta is a discoid organ with an approximate diameter of 22 cm, a central thickness of 2.5 cm, and an average weight[8] of 470 g. It has two surfaces: a fetal surface and a maternal surface.

Fetal Surface

The chorionic plate is covered by the amnion, which is a single-layer epithelium and amniotic mesenchyme. The chorionic vessels are continuous with the umbilical cord vessels and, deriving from the two umbilical arteries, the chorionic arteries will branch and their terminal branches will supply the villous trees. The chorionic veins are continuous with the veins of the villous trees and will give rise to the umbilical vein (Figure 2.4).[8]

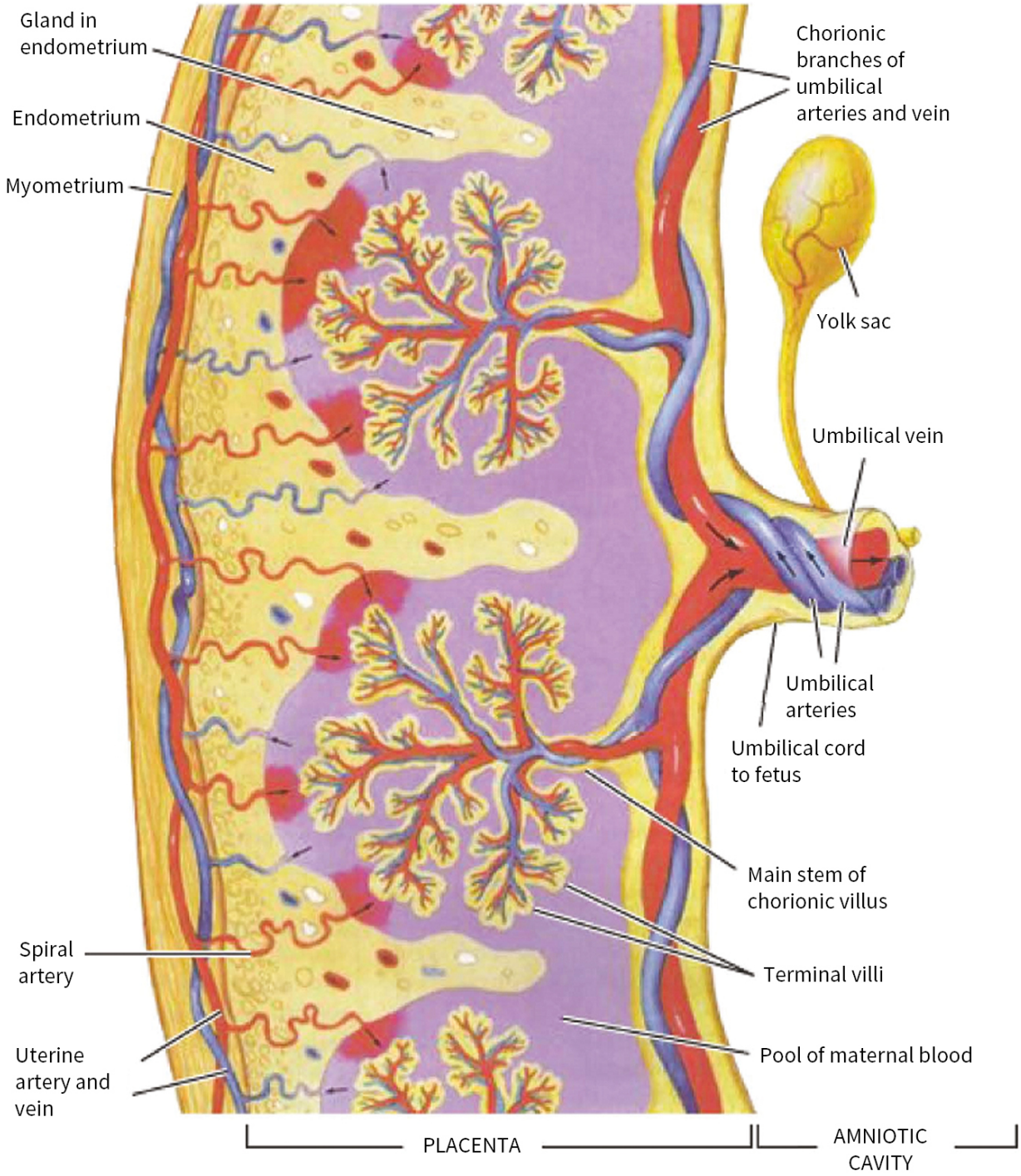

Figure 2.4 Placental vasculature. The terminal branches of the chorionic arteries supply the villous trees. There is continuity between villous trees veins and the chorionic veins. The latter will give rise to the umbilical vein.
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Maternal Surface

The basal plate is the surface that emerges from the separation of the placenta from the uterine wall. It is divided into 10 to 40 lobes that correspond with the position of the villous trees arising from the chorionic plate. Each lobe is divided into one to four lobules (cotyledons), each one containing a villous tree.[8]

Physiology of the Placenta

Placental functions play a critical role in maintaining healthy maternal–fetal physiology. These functions include:

Implantation

Via invasion of the uterine decidua by the syncytiotrophoblast.

Synthesis of Energy Substrates and Hormone Precursors

Glycogen synthesis: The placenta can synthesize significant amounts of glycogen, which is stored as an energy reserve. The uptake of glucose from the maternal circulation involves enzymes and regulators, and it is the rate-limiting step in this process.[1]
Cholesterol synthesis: Placental cholesterol is a precursor for placental production of hormones (progesterone and estrogens).[1]
Protein metabolism: Placental synthesis of proteins is driven by the demands of growth, rising in production to 7.5 g per day by term.[1]
Lactate: The placenta produces large amounts of lactate, which is removed efficiently by L-lactate transporters.[1]

Transport of Nutrients and Gas Exchange

These processes take place in the terminal villi. Maternal blood supplies nutrients, oxygen, water, and electrolytes that are exchanged for fetal

carbon dioxide and other waste products. There are multiple mechanisms by which placental transfer occurs (Table 2.1):

Solvent drag refers to the bulk flow of water that contains solutes and nutrients dissolved in response to hydrostatic pressure changes.[1]

Passive diffusion is the passive transfer of solutes following concentration and electrical gradients. All solutes are transferred by diffusion to a degree determined by molecular properties. For example, respiratory gases and other lipophilic solutes are readily exchanged by simple diffusion.[1]

Transcellular transfer is dependent on transport proteins in the microvilli or basal membrane of the syncytiotrophoblast. There are three different types:

- ***Channels:*** Proteins that form water-filled pores in the plasma membrane. Ions and charged hydrophilic substances can be transported this way. Aquaporins are channels that exemplify this type of transport.
- ***Facilitated diffusion:*** This occurs via saturable carrier proteins that are not dependent on metabolic energy. For example, GLUT transporters facilitate glucose transport.
- ***Active transport (carrier mediated):*** Primary active transport requires ATP to move solutes against a gradient. Na-K ATPase is an example. Secondary active transport, such as Na-amino acid co-transport, uses concentration gradients.[1]

Endocytosis and exocytosis: Endocytosis involves the formation of vesicles that engulf substances by invagination of the cell membrane; exocytosis is the opposite, whereby substances are released by vesicle fusion with the cell membrane. Specific solute–receptor interactions can mediate these processes.[1]

- ***Fatty acid transport:*** Triglycerides are broken down to free fatty acids and glycerol, then re-esterified on the fetal side.[1]
- ***Immunoglobulin G (IgG) transfer:*** IgG is readily transported across the placenta via the fragment crystallizable (FC) receptor. It confers immunity to the fetus. Immunoglobulin M cannot be transported across the syncytiotrophoblast.[1]

Table 2.1 Mechanisms of Placental Transport

Mechanism	Description	Examples
Solvent drag	Bulk flow of water with dissolved solutes and nutrients. Driven by hydrostatic pressure	Water, ions
Simple diffusion	Passive transfer of solutes following concentration gradient	Respiratory gases
Transcellular transfer	Transport proteins	
	Channels (water filled pores in plasma membrane)	Aquaporins (transport of water and small molecules)
	Facilitated diffusion (saturable carrier proteins)	GLUT transporters (glucose)
	Carrier-mediated active transport (active transport, ATP dependent)	Na^+K^+ ATPase
Endocytosis and exocytosis	Endocytosis: engulfment of material within a fluid-filled vesicle	Immunoglobulin G, Liposomes, Nanoformulations
	Exocytosis: fusion of vesicles with cell membrane to release their contents	

Placental Blood Flow

Maintenance of adequate placental blood flow is crucial for a successful pregnancy. The chorionic villi are the functional unit of the placenta, as the majority of the maternal–fetal exchange occurs in these units (see Figure 2.5). The villi are lined with syncytiotrophoblasts. Maternal blood enters the villi via the uterine spiral arteries, bathes the villi, and drains back into maternal circulation via endometrial veins.[9] Fetal capillaries take oxygenated blood from the villi to the umbilical vein, and deoxygenated fetal blood is brought back to the villi via umbilical arteries.[4] Nutrients, certain drugs, and various chemicals in the maternal blood pass from villi through the syncytiotrophoblasts, fetal connective tissues, and the endothelium of fetal capillaries into the fetal bloodstream.[10] See Figure 2.3 for detailed schematic of the placental transfer surface.

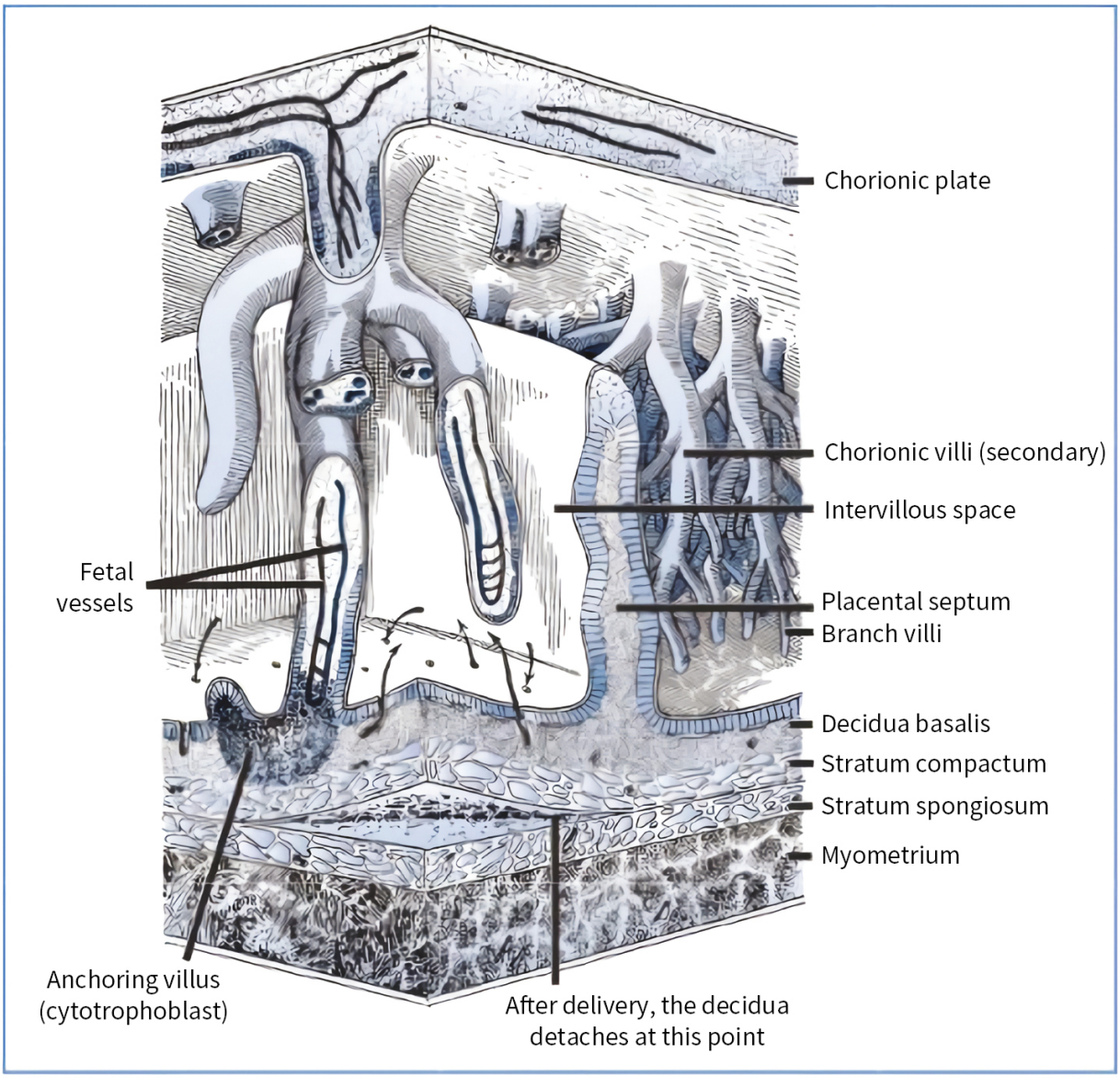

Figure 2.5 The relationship between the villous tree and maternal blood flow. The arrows indicate the maternal blood flow from the spiral arteries into the intervillous space and out through the spiral veins.
Reprinted with permission from *Chestnut's obstetric anesthesia: principles and practice*. 6th ed. Philadelphia, PA: Elsevier; 2019.

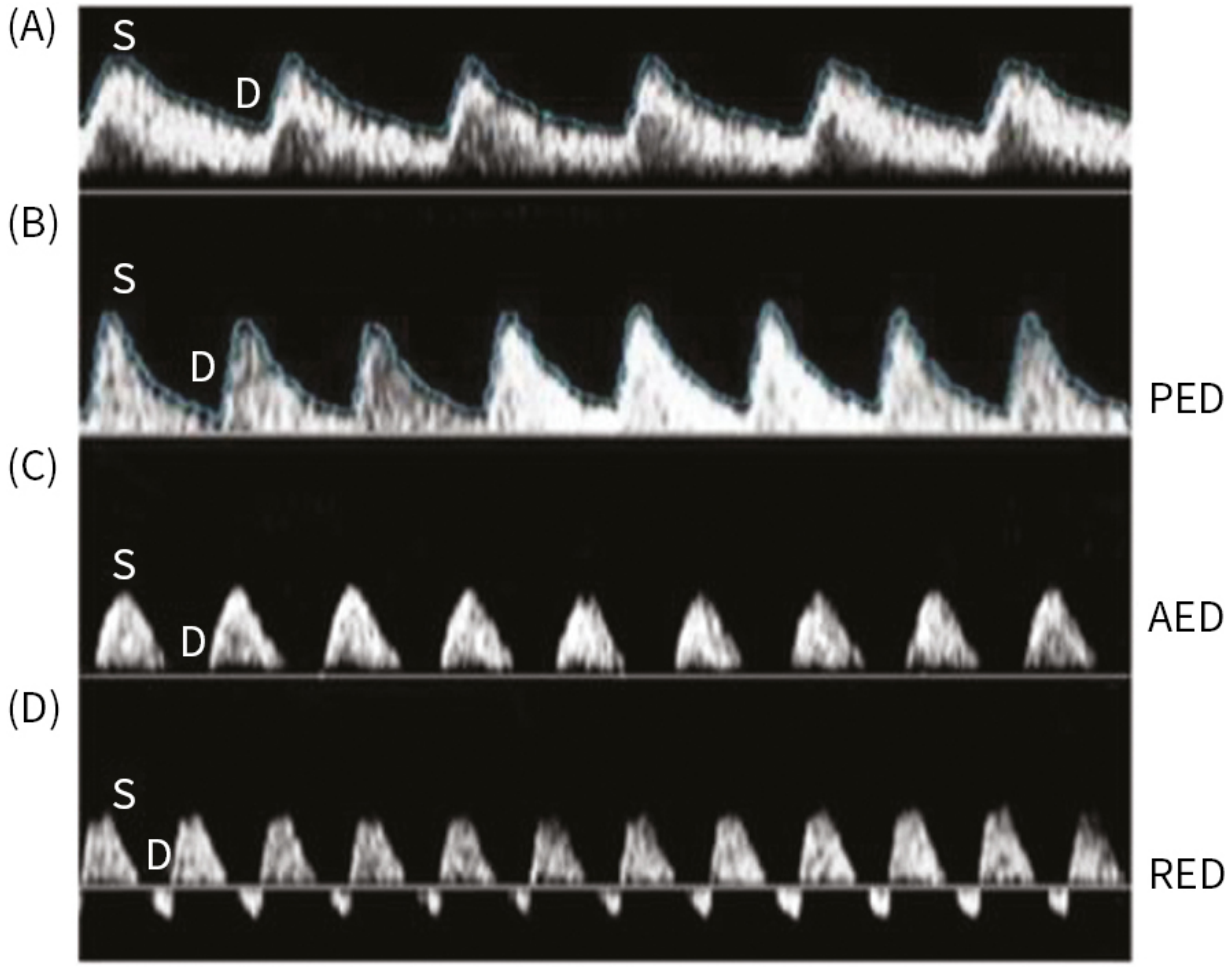

Figure 2.6 Umbilical artery FVW tracings obtained in normal and abnormal third trimester pregnancies. A) Normal: end diastolic velocities are high. B) End diastolic velocities are present, but clearly reduced (compare to A). This pattern is defined as PED. C) End diastolic velocities are absent. This pattern is defined as AED. D) During diastole flow velocities appear in the lower channel, indicating flow in the opposite direction relative to the systolic phase. This pattern is defined as RED. FVWs = flow velocity waveforms, PED = positive end diastole, AED = absent end diastole, RED = reverse end diastole, S = systole, D = diastole.
Reproduced with permission from *Placenta.* Vol 32, March 2011. T Todros, E Piccoli. *Review: Feto-placental vascularization: A multifaceted approach.* Elsevier, 2019.

The placental vasculature is low resistance; increased placental vascular resistance is frequently observed in pregnancies with IUGR, and it is a predictor of poor pregnancy outcomes. Umbilical blood flow rises as a pregnancy develops and can be estimated with Doppler waveform, which shows substantial placental blood flow in diastole. The absence or reversal of placental blood flow during diastole correlates strongly with poor pregnancy outcomes (Figure 2.6). The placenta has no neuronal input, and

agents that are powerful constrictors of other vasculatures (e.g., catecholamines, angiotensin II, oxytocin, and vasopressin) are poor constrictors of fetal placental vessels.[11] Placental blood flow is entirely determined by humoral and structural factors:

Vasoactive Agents

Thromboxane: Data from experimental studies consistently show thromboxane to be a potent vasoconstrictor of the fetal–placental circulation. Aggregating platelets are the most likely source of thromboxane in the placenta; indeed, disorders such as preeclampsia and systemic lupus erythematosus are associated with platelet aggregation and thromboxane release.[11]

Endothelin: A potent constrictor of the fetal–placental vasculature. Elevated fetal serum concentrations of endothelin-1 have been reported at delivery in pregnancies associated with fetal hypoxia.[11]

Vasoactive prostanoids: Prostaglandin E2 and prostaglandin F 2α constrict fetal–placental vessels, but they are far less potent than thromboxane or endothelin.[11]

Vasodilators

Nitric oxide (NO): NO plays an important role in the control of fetal–placental vascular tone. NO is an inhibitor of platelet aggregation and reduces leukocyte adhesion. In pregnancies with IUGR and preeclampsia, NO synthetase levels are elevated, possibly as a compensatory response to poor placental blood flow.[11]

Atrial natriuretic peptide (ANP): ANP may play a role in controlling placental blood flow as its receptors are found in human placenta. In addition, fetal ANP levels rise in response to volume expansion, suggesting an endocrine function.[11]

Prostacyclin: Prostaglandin I2 has a dilator effect on umbilical vessels and may also play a role in controlling placental vascular tone; however, its half-life is very short and prostaglandin I2 is enzymatically inactivated by the placenta.[11]

Fetal–placental blood flow must be considered in conjunction with other events surrounding the pregnancy. The normal process of converting the spiral arteries into vessels of low resistance by the invasion of the trophoblast, if disrupted, will result in abnormally increased resistance within the placenta and abnormally decreased umbilical blood flow. Other pathological events such as the formation of microthrombus and areas of infarction in the placenta occur in pregnancies in women with preeclampsia, systemic lupus erythematosus, and antiphospholipid syndrome, in which placental blood flow is diminished.[11]

Mechanisms of Drug Transfer Across the Placenta

The mechanisms that regulate the passage of substances across the placenta are also involved in controlling the rate and extent of drug transfer across the placenta. Some medications accumulate at a higher concentration in the placenta itself, potentially altering its function. The evidence of placental permeability to drugs was reported earlier in the 20th century, even before the fetal malformations secondary to thalidomide intake during pregnancy were reported. Up until that point, the placenta was viewed as a perfect barrier, when in reality, most drugs cross the placenta to a certain extent.[12] Any drugs, nutrients, and other endogenous compounds that cross the placenta and enter the fetal circulation have to cross the syncytiotrophoblast, basement membrane, and fetal capillary endothelium.[5] The route of transport varies depends on the chemical and physical characteristics of the compound.[4] For example, in animal studies, silicon nanovectors of larger size have been found to not cross the placenta, remaining in the maternal circulation, potentially serving as carriers for harmful medications in order to prevent fetal exposure.[14] Substances in the maternal bloodstream are carried in free form dissolved in plasma, bound to carrier proteins, or bound to red blood cells.[13] Figure 2.7 illustrates the various mechanisms of transport across the human placental barrier, including passive diffusion, facilitated diffusion, active transport, and endocytosis.[5] Most drugs cross the placenta by passive diffusion and to a lesser extent through other mechanisms.

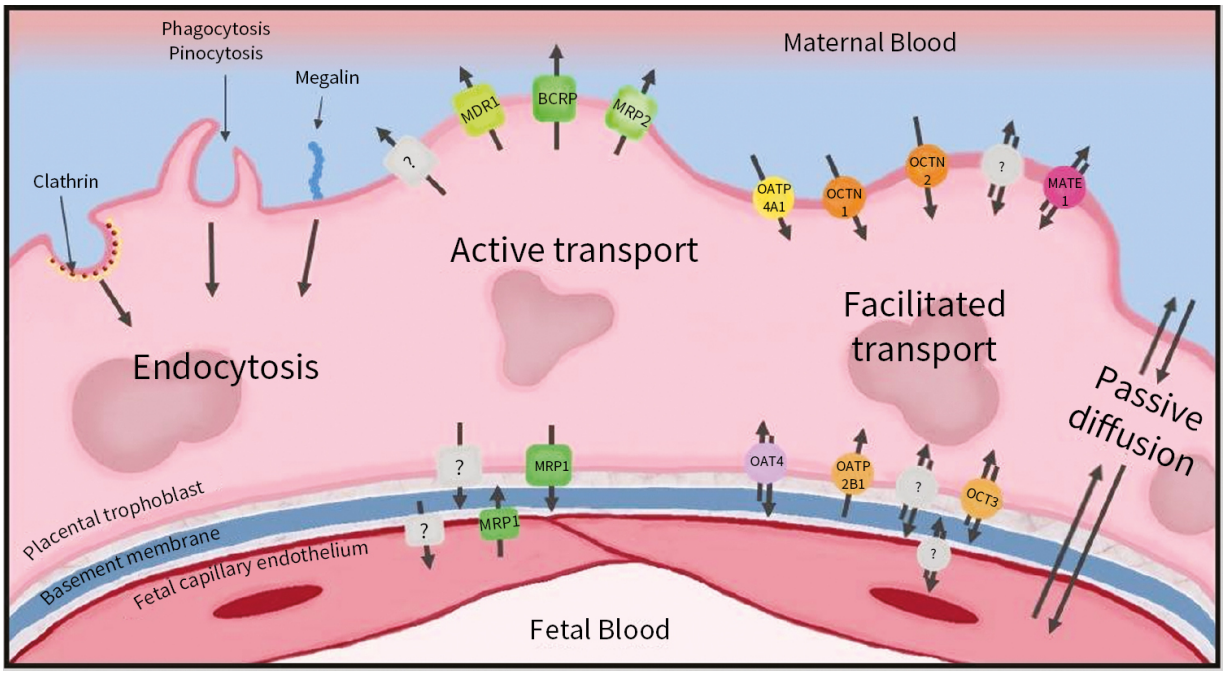

Figure 2.7 The various different transport processes within the human placental barrier. Reprinted from Al-Enazy S, Ali S, Albekairi N, El-Tawil M, Rytting E. Placental control of drug delivery. *Advanced Drug Delivery Reviews*. 2017;116:63-72 with permission from Elsevier.

Passive Diffusion

This is the predominant route through which most drugs cross the placenta, and it applies mainly to hydrophobic molecules of less than 600 Da. Hydrophobic, lipophilic drugs, such as midazolam and paracetamol, cross the placenta by this mechanism.[5,10] Larger compounds, such as low molecular weight heparin, rarely cross the placenta.[15] Drugs with high plasma protein binding are unable to diffuse across the placenta. Compounds that move with this mechanism are more likely to move down a concentration gradient as this is not an energy-dependent process.[5] The concentration of drugs transferred by passive diffusion theoretically should be similar in maternal and fetal blood; however, lower fetal pH causes weakly basic drugs to accumulate in the fetus, more significantly during periods of fetal distress and acidosis, and fetal concentration of the drug may exceed maternal blood levels (e.g., local anesthetics). Drug binding to fetal proteins contributes to longer retention of the drug in the fetal compartment, with prolonged exposure to its effects in the fetus. The rate of transfer of solutes that diffuse rapidly across the placenta (e.g., inhalational

anesthetics) is determined by the rate of placental blood flow, which increases as pregnancy progresses.[11]

Facilitated Diffusion

Various carrier proteins allow for uptake of hormones and nutrients from mother to fetus, as well as the removal of fetal metabolites and waste products to the maternal blood.[5] Energy is not needed for this mechanism, as substances move down a concentration gradient. Drugs such as cephalosporins and glucocorticoids are transported using this mechanism.[10] Carrier proteins have similar saturation kinetics and ability for competitive inhibition but are also distinct in terms of substrate selectivity, placental localization, and transcriptional regulation. These transport proteins share features such as saturation kinetics and the ability to be competitively inhibited but differ regarding substrate selectivity, placental localization, and transcriptional regulation. Most of these proteins are members of the adenosine triphosphate binding cassette and solute carrier transporters.[12]

Active Transport

Transport of substances across the placenta against a concentration or electrochemical gradient with use of energy, through carrier proteins that are present on both the maternal and fetal side. There are multiple different active transporters on the placenta that are involved in the transfer of drugs such as digoxin, dexamethasone, chemotherapeutic drugs, HIV protease inhibitors, norepinephrine, and dopamine.[10]

Endocytosis and Exocytosis

The syncytiotrophoblasts have the ability to use endocytosis as a mechanism of transport for both endogenous compounds as well as xenobiotics.[5] This occurs when the drugs are completely enveloped into the membrane and released on the other side.[10] There are multiple different mechanisms by which this process is carried out. Medications such as gentamicin and endogenous compounds such as albumin are transported with this mechanism.[5] Receptor-mediated endocytosis involves selective

internalization of a specific extracellular ligand into cytoplasmic vesicles via interaction with specific receptors. In addition to IgG, biological agents such as infliximab and adalimumab (IgG1 antibodies), nanoparticles, and liposomes are transferred to the fetus this way.[12]

Drug Transfer to Fetus

Pharmacokinetic Factors

Most studies report fetal exposure in terms of fetal-to-maternal (F/M) drug concentrations. Maternal drug concentrations are measured in peripheral venous blood drawn at delivery. Umbilical vein blood is used to represent fetal blood concentrations. In addition to placental permeability, the pharmacokinetics of drugs determine the maternal metabolism of drugs, transfer of drugs across the placenta, and exposure of the fetus to maternal drugs. Most drugs are transferred across the placenta by passive diffusion. Lipid solubility, maternal and fetal protein and tissue binding, pKa, pH, and placental blood flow all affect fetal exposure to maternal medications.[16]

High lipid solubility facilitates diffusion across cell membranes but can trap drugs in placental tissue.[16,17] Fetal exposure to drugs that are highly protein bound is dependent on both maternal and fetal plasma protein concentrations, which vary by gestational age. The primary binding proteins are albumin and α_1-acid glycoprotein (AAG), and fetal plasma concentrations of both proteins increase over the duration of gestation.[18] The pKa of a medication determines the fraction of ionized drug at physiologic pH. Drugs that are weak bases such as local anesthetics and opioids may be transferred more readily to the fetus in fetal acidemia.[19] Tables 2.2 and 2.3 summarize the placental transfer of medications commonly used in anesthesia.

Table 2.2 Drugs That Readily Cross the Placenta

Anticholinergic Agents	Atropine Scopolamine
Antihypertensive Agents	β-adrenergic receptor antagonists Nitroprusside Nitroglycerin
Benzodiazepines	Diazepam Midazolam
Induction Agents	Propofol Ketamine Etomidate Thiopental Dexmedetomidine
Inhalational Anesthetic Agents	Halothane Isoflurane Sevoflurane Desflurane (presumed) Nitrous oxide
Local Anesthetics Opioids	
Vasopressor	Ephedrine

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Table 2.3 Drugs That Do Not Readily Cross the Placenta

Anticholinergic Agent	**Glycopyrrolate**
Anticoagulant	Heparin
Muscle Relaxants	Succinylcholine Non-depolarizing Agents
Non-depolarizing Agent Binder	Sugammadex
Vasopressor	Phenylephrine

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Anesthetic Agents

Induction Agents: The key feature that makes a drug useful for inducing anesthesia is high lipid solubility, which allows for passage across the blood brain barrier, so these medications also readily cross the placenta. Propofol studies showed an F/M ratio of 0.65 and 0.85, and that there may be sedative effects on the neonate when administered for the induction of anesthesia based on lower Apgar scores at 1 and 5 minutes compared to thiopental.[20,21,22] Propofol is highly protein-bound to albumin and therefore maternal alterations in albumin can affect the transfer of total concentration of propofol.[23] Ketamine readily crosses the placenta with an F/M ratio of 1.26 within 2 minutes of administration to the mother.[24] An induction dose of etomidate resulted[25] in an F/M ratio of 0.5. Dexmedetomidine has an F/M ratio of 0.12 and evidence of high placental tissue binding due to its high lipid solubility.[26] Benzodiazepines vary in their ionization and lipid solubility. Diazepam is the most lipophilic with an F/M ratio of 1 within a few minutes of administration to the mother, while midazolam is the most polar with an F/M ratio of only 0.76 that rapidly decreases.[27,28]

Opioids: Opioid medications cross the placenta and therefore have the potential to cause neonatal respiratory depression. Intravenous (IV) dosing of morphine to the mother results in a lower biophysical profile score of the fetus at 20 minutes due to reduced fetal breathing and fewer heart rate accelerations.[29] Intrathecal morphine actually has an F/M ratio close to 1 but because the typical total intrathecal dose of morphine used is so small, the absolute fetal concentrations of morphine are well below the concentrations associated with neonatal respiratory depression.[30] Fentanyl is highly lipophilic and highly protein bound and rapidly transfers across the placenta.[31] In vitro perfusion of the human placenta shows bidirectional fentanyl transfer with collection of fentanyl in the placenta itself. Sufentanil has a higher F/M ratio than fentanyl but its increased lipid solubility results in rapid uptake by the central nervous system (CNS) when administered in the epidural space, resulting in less vascular absorption in the mother, reducing risk of fetal exposure.[32] Despite a low F/M ratio, alfentanil given at the induction of anesthesia has been shown to decrease Apgar scores at 1 minute.[33] Remifentanil administered by patient-controlled analgesia during labor is more likely to cause maternal respiratory depression than adverse fetal effects. Rapid

metabolism by nonspecific esterases reduces the fetal exposure risk[34] despite an F/M ratio of 0.5. It is important to note that with opioid medications, pharmacokinetics of the specific medication and route of administration influence fetal and neonatal side effects more than a high F/M ratio.

Muscle Relaxants and Reversal Agents: Muscle relaxants are large, ionized quaternary ammonium salts and do not readily cross the placenta. Although muscle relaxants have been detected in fetal blood as time from induction to delivery increases, a single dose of muscle relaxant administered to the mother for the induction of general anesthesia rarely affects muscle tone of the neonate.[35] Succinylcholine is not detectable in blood taken from the umbilical vein when the administered maternal dose[36] is less than 300 mg. Neonatal neuromuscular blockade can occur with a single induction dose of succinylcholine when mother and fetus are homozygous for atypical pseudocholinesterase deficiency.[37] Atropine and scopolamine both readily cross the placenta and may increase fetal heart rate.[38,39] Glycopyrrolate does not cross the placenta easily and does not affect fetal heart rate.[40] Anticholinesterase agents are ionized quaternary ammonium compounds in vivo and do not readily cross the placenta.[41] Sugammadex also does not easily cross the placenta due to its large molecular structure and high molecular weight.[42]

Medications Commonly Used in Pregnancy

Pregnant women often have many chronic medical conditions needing prescription medications.[5] This next section will describe some common classes of medications used in pregnancy.

Selective Serotonin Reuptake Inhibitors/Serotonin-norepinephrine Reuptake Inhibitors: Depression is common in pregnancy with up to 20% of pregnant women affected.[43,44] Studies have shown that 7–13% of pregnancies have some exposure to antidepressant medications, with most being selective serotonin reuptake inhibitors (SSRIs).[43,45] Antidepressants cross the placenta primarily by passive diffusion and enter the intrauterine environment with varying degrees of bioavailability. The effect of antidepressants on the fetus is a syndrome called postnatal adaptation syndrome (PNAS), which is a constellation of behavioral symptoms.[43] This has been found in about 30% of infants exposed to SSRIs or selective norepinephrine reuptake inhibitors (SNRIs). Fluoxetine, paroxetine, and venlafaxine are all associated with PNAS more often than other antidepressants.[46]

Metformin: Gestational diabetes is a common complication in pregnancy, affecting 5–13% of pregnancies in the United States. Metformin is an oral antiglycemic agent that is being used commonly for glucose control in gestational diabetes mellitus (GDM) patients.[47] Metformin readily crosses the placenta barrier.[48] There is a theoretical risk of development of lactic acidosis in a fetus exposed to metformin. Most data does not reflect an increase risk in miscarriage or congenital malformations with exposure to metformin.[49]

Antihypertensive Drugs: Hypertensive disorders are a common medical complication in pregnancy including both pregestational hypertension and pregnancy-induced hypertensive disorders, especially in developing countries,[50] and it is a leading cause of maternal and perinatal morbidity and mortality worldwide.[49] Antihypertensive drugs are often used in pregnancy with the aim of reducing risk of cerebrovascular complications and avoiding progression of pregestational hypertension into superimposed preeclampsia. All antihypertensive medications cross the placental barrier and have varying effects on fetal metabolism. The two classes of medications that are largely avoided in pregnancy are ACE inhibitors and angiotensin II receptor blockers due to neonatal complications, such as renal failure and death.[51]

Anticoagulants: Pregnancy is a hypercoagulable state with a 5-fold increase in the risk of venous thromboembolism (VTE) during pregnancy, a risk that remains until 12 weeks postpartum.[52] Vitamin K

antagonists, such as warfarin, readily cross the placenta with an increased risk of adverse outcomes, such as miscarriage and stillbirth. In special populations, such as those with mechanical heart valves, the risk versus benefits has to be weighed before discontinuation of vitamin K antagonists. An alternative method of anticoagulation is the use of low molecular weight heparin, as it does not readily cross the placenta. It also has better bioavailability than unfractionated heparin.[53]

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3

Fetal Physiology and Antepartum Fetal Surveillance

Agathe Streiff and Yelena Spitzer

Fetal Physiology

In order to understand antepartum fetal surveillance, it is important to be familiar with normal fetal physiology, especially neurologic, respiratory, and cardiac physiology, which are commonly assessed in the third trimester of pregnancy. This section will discuss these topics, with a focus on late-term fetal stages.

Neurophysiology

The neural tube develops by the third to fourth week from conception. This neural tube gives rise to the brain and spinal cord, and errors in formation can lead to many fatal conditions including anencephaly, encephalocele, myeloschisis, and craniorachischisis totalis. Less severe conditions include spina bifida, which may nevertheless result in lifelong disability. The neural tube differentiates into the prosencephalon, mesencephalon, and rhombencephalon, which give rise to the cerebrum and thalamic structures, the midbrain, and the brainstem and cerebellum, respectively. This differentiation occurs during the second to third months of gestation.[1]

The remainder of in utero neurologic development consists of neuron and glial cell proliferation and migration. This portion is not insignificant, with cortical gray matter increasing volume four to five times in the third trimester. Premature birth has been shown to result in decreased cortical volume.[2,3] It is important to note that neurodevelopment does not conclude

until the second decade of life, and fetal insults in the peripartum period can have significant impact. These insults include hypoxia, ischemia, sepsis, and malnutrition.[2] It is estimated that approximately 50% of low birth weight infants born in the United States annually have a degree of cerebral white matter injury.[4] Prematurity is associated with intraventricular hemorrhage, periventricular leukomalacia, hydrocephalus, cerebellar disease, encephalopathy of prematurity, and other neurologic conditions with lifelong implications.[5]

While cerebral blood flow (CBF) in infants, children, and adults is autoregulated across a range of normal blood pressures, CBF in the developing fetus and premature neonate is more pressure-passive. This immature autoregulation renders it vulnerable to sudden decreases in blood pressure that may result in ischemia, as well as sudden increases in blood pressure that may result in rupture of fragile blood vessels. The germinal matrix proliferates in the second and early third trimester and is the most common site of intraventricular hemorrhage. Even small deviations in blood pressure from normal can result in the CBF becoming more pressure-passive.[5]

Fetal movement is often assessed as a measure of fetal well-being and neurologic function. The first fetal movements occur after 7 weeks gestational age (GA) and are typically head and trunk movements.[6] These develop prior to the completion of spinal reflex pathways at weeks 10 to 11. More general movements (GM) of all parts of the body are typically seen at week 10, and increased tone of each movement is appreciated. These GMs persist until 5 months post-term, when they are replaced by more sophisticated goal-directed movements.[6]

Respiratory Physiology

The lung is derived from an invagination of the foregut endoderm. Lung development occurs throughout fetal life, but terminal bronchioles capable of gas exchange do not start to develop until 17 weeks of gestation.[7] Terminal bronchiole development is not complete until after 27 weeks of gestation, thus severely limiting the chances of survival of neonates born before this period despite advances in technology and neonatal care (Table

3.1).[7] Preterm delivery is one of the most important determinants of fetal lung development.

Table 3.1 The Different Stages of Lung Development[a]

Stage	Weeks in utero	Lung structures
Embryonic	0–7	Trachea Main bronchus Bronchi
Pseudoglandular	7–17	Bronchioli Terminal bronchioli
Canalicular	17–27	Alveolar ducts Respiratory bronchioli
Saccular	28–36	Increased gas exchange surface area
Alveolar	36 weeks to 2 years postnatal	Secondary septa Definitive alveoli

[a]Kotecha S. Lung growth for beginners. *Paediatr Respir Rev.* 2000;1(4):308–13.

In utero, respiratory functions include normal fetal breathing movements, as well as the production and clearance of fetal lung fluid. Fetal breathing movements are important in maintaining pressure within airways and in stimulating lung growth and differentiation (Figure 3.1, Box 3.1).[7] Fetal breathing movements may be increased by hypercapnia, hyperglycemia, acidosis, hyperthermia, caffeine, indomethacin, and theophyllines. Conversely, these breathing movements may be decreased by hypoxia, hypoglycemia, prostaglandin E2, maternal smoking, maternal alcohol, intrauterine infection, diazepam, and morphine.[7] When the amniotic fluid volume is inadequate, such as in preterm rupture of membranes and fetal renal disease, pulmonary hypoplasia is seen.[7] The chest cavity must be of adequate size and unoccupied in order to achieve normal fetal lung development. Congenital diaphragmatic hernia is a failure of the diaphragm to close by weeks 10 to 12 of gestation. The presence of bowel in the chest cavity halts lung growth.[8]

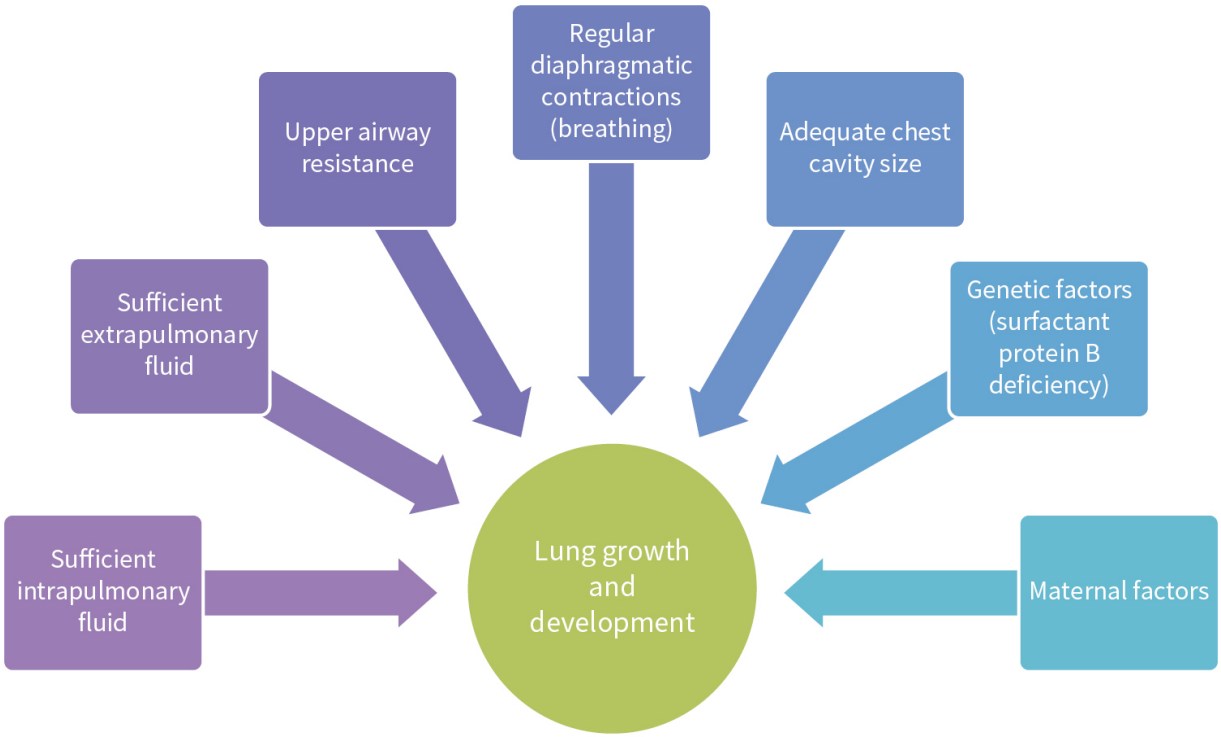

Figure 3.1 Key factors important in promoting fetal lung development.

Box 3.1 Maternal Factors Influencing Fetal Lung Development[a]

Maternal Factors

Nutrition
Endocrine factors
Smoking
Medical comorbidities
Concurrent intrauterine infection

[a]Kotecha S. Lung growth for beginners. *Paediatr Respir Rev*. 2000;1(4):308–13.

The oxygen content formula is as follows:

$$(\text{hemoglobin})(1.34\ \text{mL}\ O_2/\ \text{g of hemoglobin})(SaO_2) + (0.03\ \text{mL}\ O_2)(PaO_2)$$

There are key differences in fetal physiology compared to that of adults.[8] The O_2 dissociation curve is left-shifted and the arterial P_{50} is 18 mm Hg in the fetus, compared to 26 in the adult, and the normal range of arterial

oxygenation saturation is lower in the fetus. The lower P_{50} results in an offloading of oxygen from the maternal circulation to the fetal circulation down a concentration gradient. Oxygenated blood is supplied by the umbilical vein from the placenta, and the lungs do not engage in gas exchange in utero. The pulmonary vascular resistance (PVR) in late gestation is five times greater than that of newborns, and fetal pulmonary arterial blood flow is only 50% of that of newborns. These factors result in markedly different umbilical artery cord blood gas compared to adult arterial blood gases: pH 7.29, $PaCO_2$ 49, PaO_2 18, base deficit 2.7 mmol/L, bicarbonate 23 mmol/L.[9]

Cardiac Physiology

Three key differences exist in the fetal heart compared to the neonatal, infant, and adult heart—sarcomere and myofibril structure, myocardial cytoskeleton, and autonomic innervation. The myofibrils and sarcomeres in the fetus are arranged irregularly and in thinner layers, rendering force generation by the myocardium less efficient compared to later in development.[10] Additionally, the high collagen content of fetal and neonatal myocardium, with relatively high type I collagen compared to type II, results in a noncompliant neonatal and fetal heart.[11] Differences in extracellular matrix and cytoskeleton of the myocardium also are contributory. The neonatal and fetal heart is thus unable to respond as briskly to volume loading.[11] Lastly, sympathetic innervation is immature until the newborn period, leaving a predominance of the parasympathetic nervous system, and reflexive bradycardia is more frequent than tachycardia from the baseline. The maturation of the sympathetic system in term neonates contributes to increased heart rate variability, an indicator of fetal well-being and lack of stress.[12]

Similar to adults, fetal cardiac output is dependent on heart rate and stroke volume. The determinants of ventricular performance are preload, afterload, and myocardial contractility. Due to the relatively noncompliant myocardium, the stroke volume is fixed and the cardiac output is described as heart rate–dependent.[13]

Neonatal asphyxia has a profound effect on the fetus. After only a minute of umbilical cord occlusion, the PaO_2 of the fetus decreases sharply to less