CHAPTER 7: Embryogenesis and Fetal Development

Our knowledge concerning the physiology of the foetus has been markedly enriched during recent years; nevertheless, when compared with the adult, it offers many points concerning which we are but slightly informed or profoundly ignorant.

—J. Whitridge Williams (1903)

INTRODUCTION

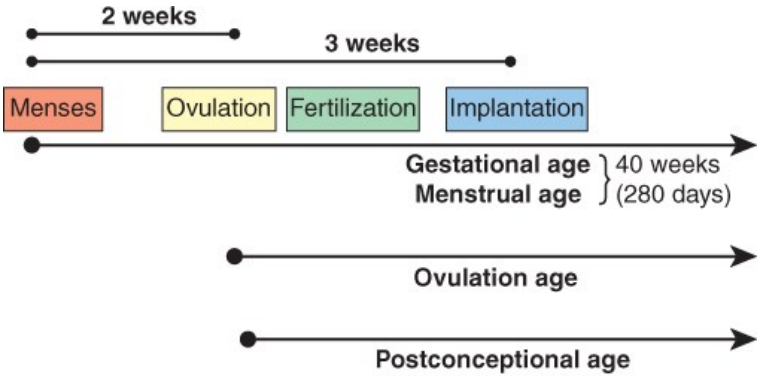
Since these words were written by Williams in 1903, great strides in the understanding of fetal organogenesis and physiology have been gained. Contemporary obstetrics incorporates physiology and pathophysiology of the fetus, its development, and its environment. An important result is that fetal status has been elevated to that of a patient who, in large measure, can be given the same meticulous care that obstetricians provide for gravidas. In our 25th edition, the entirety of Section 5 is dedicated to the fetal patient, as are individual chapters in other sections. Indeed, virtually every aspect of obstetrics can affect the developing fetus.

GESTATIONAL AGE

Several terms define pregnancy duration and thus fetal age (Fig. 7-1). *Gestational age* or *menstrual age* is the time elapsed since the first day of the last menstrual period (LMP), a time that actually precedes conception. This starting time, which is usually approximately 2 weeks before ovulation and fertilization and nearly 3 weeks before blastocyst implantation, has traditionally been used because most women know their approximate last period. Embryologists describe embryofetal development in *ovulation age,* or the time in days or weeks from ovulation. Another term is *postconceptional age,* which is nearly identical to ovulation age.

FIGURE 7-1

Terminology used to describe pregnancy duration.



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Until recently, clinicians customarily calculated menstrual age with term pregnancy averaging approximately 280 days, or 40 weeks between the first day of the LMP and birth. This corresponds to 9 and 1/3 calendar months. However, menstrual cycle length variability among women renders many of these calculations inaccurate. This realization, combined with the frequent use of first-trimester sonography, has led to more accurate gestational age determination (Duryea, 2015). Much of this change hinges on the accuracy of early sonographic measurement. As a result, the American College of Obstetricians and Gynecologists, the American Institute of Ultrasound in Medicine, and the Society for Maternal-Fetal Medicine (Reddy, 2014) together recommend the following:

1. First-trimester sonography is the most accurate method to establish or reaffirm gestational age.
2. In conceptions achieved with assisted-reproductive technology, this gestational age is used.
3. If available, the gestational ages calculated from the LMP and from first-trimester sonography are compared, and the estimated date of confinement (EDC) recorded and discussed with the patient.
4. The best obstetrical estimate of gestational age at delivery is recorded on the birth certificate.

The embryofetal crown-rump length in the first trimester is accurate ±5 to 7 days. Thus, if sonographic assessment of gestational age differs by more than 5 days prior to 9 weeks' gestation, or by more than 7 days later in the first trimester, the estimated delivery date is changed.

Naegele Rule

An EDC based on LMP can be quickly estimated as follows: add 7 days to the first day of the LMP and subtract 3 months. For example, if the first day of the LMP was October 5, the due date is 10–05 minus 3 (months) plus 7 (days) = 7–12, or July 12 of the following year. This calculation has been termed the *Naegele rule*. The period of gestation can also be divided into three units of approximately 14 weeks each. These three *trimesters* are important obstetrical milestones.

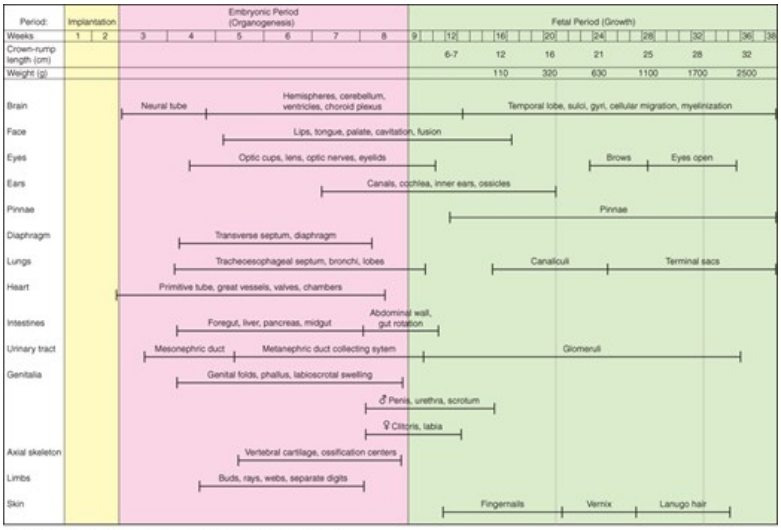
In addition to estimating the EDC with either Naegele rule or pregnancy "wheels," calculator tools in the electronic medical record and smartphone applications can provide a calculated EDC and gestational age. For example, the American College of Obstetricians and Gynecologists (2016) has developed a calculator application that incorporates sonographic criteria and the LMP or embryo transfer date. This is discussed further in Chapter 10 (Gestational Age Assessment).

EMBRYONIC DEVELOPMENT

The complexity of embryofetal development is almost beyond comprehension. Figure 7-2 shows a developmental sequence of various organ systems. New information regarding organ development continues to accrue. For example, imaging techniques help unravel the contributions of gene regulation and tissue interaction to eventual three-dimensional organ morphology (Anderson, 2016; Mohun, 2011). Others have described the sequence of gene activation that underlies cardiac development.

FIGURE 7-2

Embryofetal development according to gestational age determined by the first day of the last menses. Times are approximate.



Zygote and Blastocyst Development

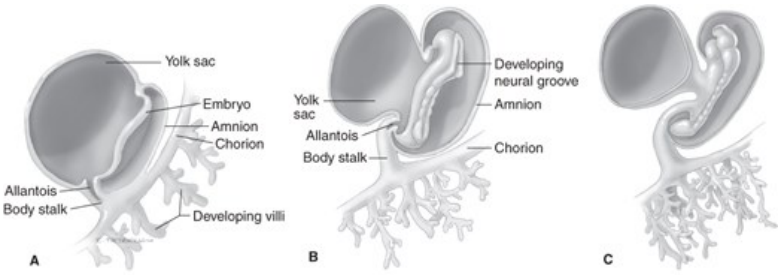
During the first 2 weeks after ovulation and then fertilization, the zygote—or preembryo—develops to the blastocyst stage. The blastocyst implants 6 or 7 days following fertilization. The 58-cell blastocyst differentiates into five embryo-producing cells—*the inner cell mass*—and the remaining 53 cells form placental trophoblast. Details of implantation and early development of the blastocyst and placenta are described in Chapter 5 (Implantation and Early Trophoblast Formation).

Embryonic Period

The conceptus is termed an embryo at the beginning of the third week after ovulation and fertilization. Primitive chorionic villi form, and this coincides with the expected day of menses. The embryonic period, during which time organogenesis takes place, lasts 6 weeks. It begins the third week from the LMP through the eighth week. The embryonic disc is well defined, and most pregnancy tests that measure human chorionic gonadotropin (hCG) become positive by this time. As shown in Figure 7-3, the body stalk is now differentiated. There are villous cores in which angioblastic chorionic mesoderm can be distinguished and a true intervillous space that contains maternal blood.

FIGURE 7-3

Early human embryos. Ovulation ages: **A.** 19 days (presomite). **B.** 21 days (7 somites). **C.** 22 days (17 somites). (After drawings and models in the Carnegie Institute.)



During the third week, fetal blood vessels in the chorionic villi appear. In the fourth week, a cardiovascular system has formed (Fig. 7-4). Thereby, a true circulation is established both within the embryo and between the embryo and the chorionic villi. Partitioning of the primitive heart begins. Also in the fourth week, the neural plate forms, and it subsequently folds to form the neural tube. By the end of the fifth menstrual week, the chorionic sac measures approximately 1 cm in diameter. The embryo is 3 mm long and can be measured sonographically. Arm and leg buds have developed, and the amnion is beginning to ensheathe the body stalk, which thereafter becomes the umbilical cord. At the end of the sixth week, the embryo measures approximately 9 mm long, and the neural tube has closed (Fig. 7-5). Cardiac motion is almost always discernable sonographically (Fig. 7-6). The cranial end of the neural tube closes by 38 days from the LMP, and the caudal end closes by 40 days. Thus, the neural tube has closed by the end of the sixth week. And by the end of the eighth week, the crown-rump length approximates 22 mm. Fingers and toes are present, and the arms bend at the elbows. The upper lip is complete, and the external ears form definitive elevations on either side of the head. Three-dimensional images and videos of human embryos from the MultiDimensional Human Embryo project are found at: http://embryo.soad.umich.edu/index.html.

FIGURE 7-4

Three- to four-week-old embryos. **A, B.** Dorsal views of embryos during 22 to 23 days of development showing 8 and 12 somites, respectively. **C–E.** Lateral views of embryos during 24 to 28 days, showing 16, 27, and 33 somites, respectively. (Redrawn from Moore KL: The Developing Human: Clinically Oriented Embryology, 4th ed. Philadelphia, Saunders, 1988.)

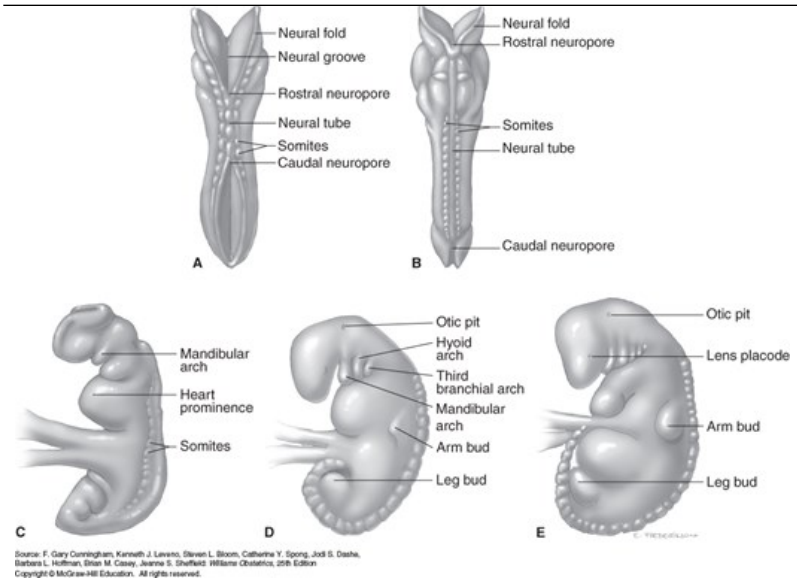


FIGURE 7-5

Embyro photographs. **A.** Dorsal view of an embryo at 24 to 26 days and corresponding to Figure 7-4C. **B.** Lateral view of an embryo at 28 days and corresponding to Figure 7-4D. **C.** Lateral view of embryofetus at 56 days, which marks the end of the embryonic period and the beginning of the fetal period. The liver is within the white, halo circle. (From Werth B, Tsiaras A: From Conception to Birth: A Life Unfolds. New York, Doubleday, 2002.)

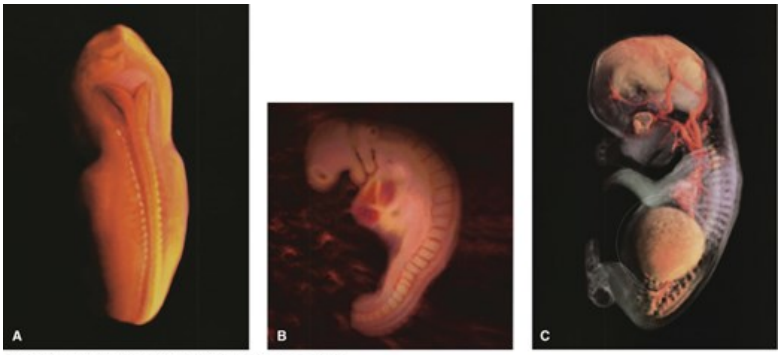
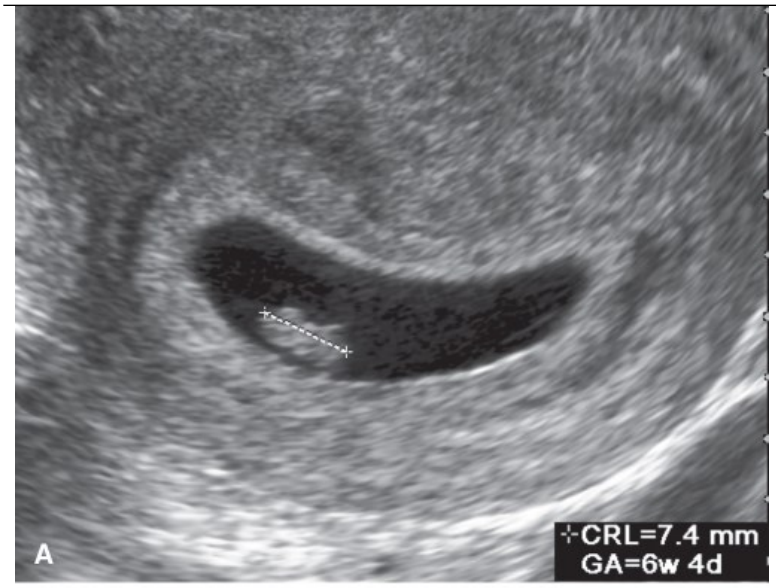
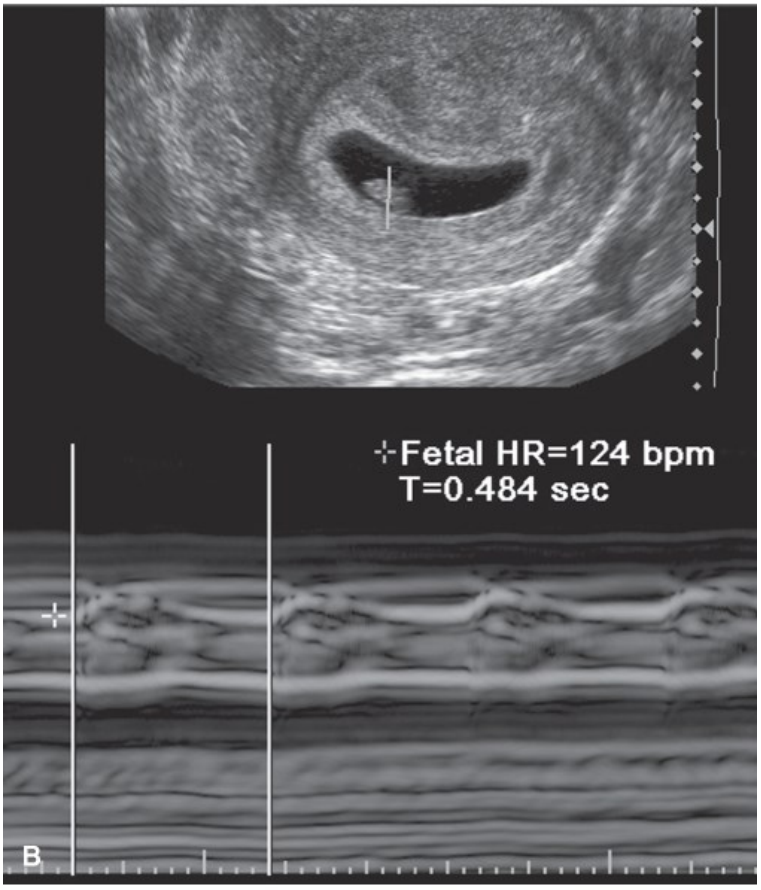


FIGURE 7-6

A. This image of a 6-week, 4-day embryo depicts measurement of the crown-rump length, which is 7.4 mm at this gestational age. **B.** Despite the early gestational age, M-mode imaging readily demonstrates embryonic cardiac activity. The heart rate in this image is 124 beats per minute.





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FETAL DEVELOPMENT AND PHYSIOLOGY

Fetal Period Epochs

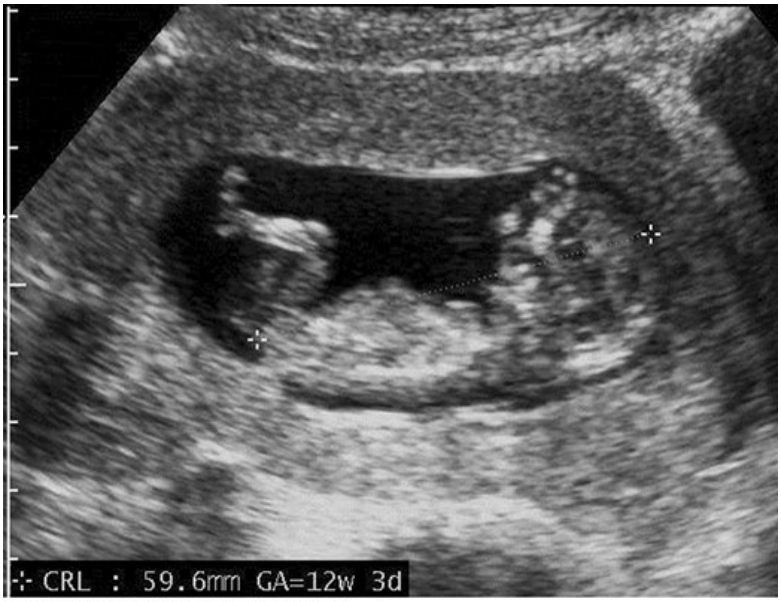
Transition from the embryonic period to the fetal period occurs at 7 weeks after fertilization, corresponding to 9 weeks after onset of the last menses. At this time, the fetus approximates 24 mm in length, most organ systems have developed, and the fetus enters a period of growth and maturation. These phases are outlined in Figure 7-2.

12 Gestational Weeks

The uterus usually is just palpable above the symphysis pubis. Fetal growth is rapid, and the fetal crown-rump length is 5 to 6 cm (Fig. 7-7). Centers of ossification have appeared in most fetal bones, and the fingers and toes have become differentiated. Skin and nails develop, and scattered rudiments of hair appear. The external genitalia are beginning to show definitive signs of male or female gender. The fetus begins to make spontaneous movements.

FIGURE 7-7

This image of a 12-week, 3-day embryo depicts measurement of the crown-rump length. The fetal profile, cranium, and a hand and foot are also visible in this image.



16 Gestational Weeks

Fetal growth slows at this time. The crown-rump length is 12 cm, and the fetal weight approximates 150 g (Hadlock, 1991). Practically speaking, the sonographic crown-rump length is not measured beyond 13 weeks, which corresponds to approximately 8.4 cm. Instead, biparietal diameter, head circumference, abdominal circumference, and femur length are measured. Fetal weight in the second and third trimesters is estimated from a combination of these measurements (Chap. 10, Gestational Age Assessment).

Eye movements begin at 16 to 18 weeks, coinciding with midbrain maturation. By 18 weeks in the female fetus, the uterus is formed and vaginal canalization begins. By 20 weeks in the male, testicles start to descend.

20 Gestational Weeks

This is the midpoint of pregnancy as estimated from the LMP. The fetus now weighs somewhat more than 300 g, and weight increases substantially in a linear manner. From this point onward, the fetus moves approximately every minute and is active 10 to 30 percent of the day (DiPietro, 2005). Brown fat forms, and the fetal skin becomes less transparent. Downy lanugo covers its entire body, and some scalp hair can be seen. Cochlear function develops between 22 and 25 weeks, and its maturation continues for 6 months after delivery.

24 Gestational Weeks

The fetus now weighs almost 700 g (Duryea, 2014). The skin is characteristically wrinkled, and fat deposition begins. The head is still comparatively large, and eyebrows and eyelashes are usually recognizable. By 24 weeks, the secretory type II pneumocytes have initiated surfactant secretion (Chap. 32, Care in the Delivery Room). The canalicular period of lung development, during which the bronchi and bronchioles enlarge and alveolar ducts develop, is nearly completed. Despite this, a fetus born at this time will attempt to breathe, but many will die because the terminal sacs, required for gas exchange, have not yet formed. The overall survival rate at 24 weeks is barely above 50 percent, and only approximately 30 percent survive without severe morbidity (Rysavy, 2015). By 26 weeks, the eyes open. Nociceptors are present over all the body, and the neural pain system is developed (Kadic, 2012). The fetal liver and spleen are important sites for hemopoiesis.

28 Gestational Weeks

The crown-rump length approximates 25 cm, and the fetus weighs about 1100 g. The thin skin is red and covered with **vernix caseosa**. The pupillary membrane has just disappeared from the eyes. Isolated eye blinking peaks at 28 weeks. The bone marrow becomes the major site of hemopoiesis. The otherwise normal neonate born at this age has a 90-percent chance of survival without physical or neurological impairment.

32 and 36 Gestational Weeks

At 32 weeks, the fetus has attained a crown-rump length approximating 28 cm and a weight of about 1800 g. The skin surface is still red and wrinkled. In contrast, by 36 weeks, the fetal crown-rump length averages about 32 cm, and the weight approximates 2800 g (Duryea, 2014). Because of subcutaneous fat deposition, the body has become more rotund, and the previous wrinkled facies is now fuller. Normal fetuses have nearly 100-percent survival rate.

40 Gestational Weeks

This is considered term, and the fetus is now fully developed. The average crown-rump length measures about 36 cm, and the average weight approximates 3500 g.

Central Nervous System Development

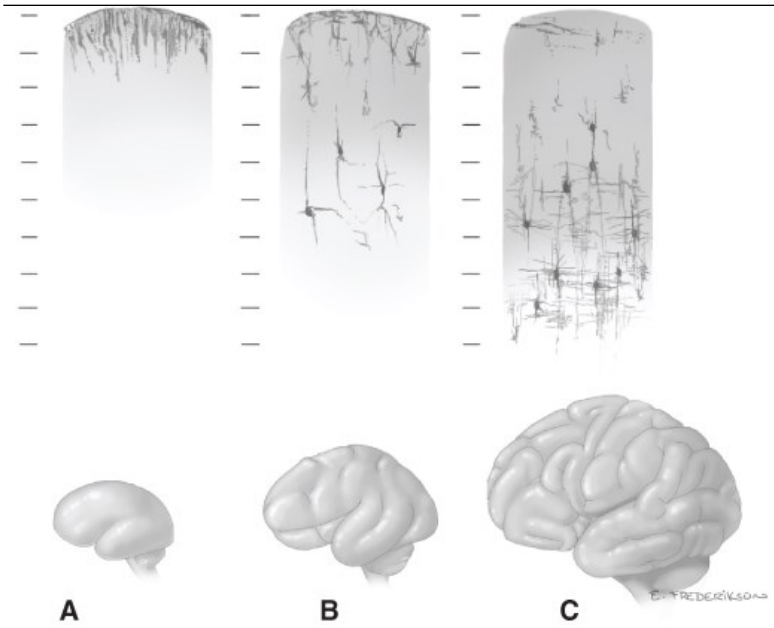
Brain Development

The cranial end of the neural tube closes by 38 days from the LMP, and the caudal end closes by 40 days. Hence, folic acid supplementation to prevent neural-tube defects must be in place before this point to be efficacious (Chap. 9, Pragmatic Nutritional Surveillance). The walls of the neural tube form the brain and spinal cord. The lumen becomes the ventricular system of the brain and the central canal of the spinal cord. During the sixth week, the cranial end of the neural tube forms three primary vesicles. In the seventh week, five secondary vesicles develop: the telencephalon—future cerebral hemispheres; diencephalon—thalami; mesencephalon—midbrain; metencephalon—pons and cerebellum; and myelencephalon—medulla. Meanwhile, flexures develop and fold the brain into its typical configuration. The end of the embryonic period signifies completion of primary and secondary neuralization.

At 3 to 4 months' gestation, *neuronal proliferation* peaks. As expected, disorders in this cerebral development phase profoundly worsen function (Volpe, 2008). *Neuronal migration* occurs almost simultaneously and peaks at 3 to 5 months. This process is characterized by movement of millions of neuronal cells from their ventricular and subventricular zones to areas of the brain in which they reside for life (Fig. 7-8). Upregulation of gene expression for neuronal migration has been described (Iruretagoyena, 2014). Noninvasive methods to study fetal neurodevelopment have also been reported (Goetzl, 2016).

FIGURE 7-8

Neuronal proliferation and migration are complete at 20 to 24 weeks. During the second half of gestation, organizational events proceed with gyral formation and proliferation, differentiation, and migration of cellular elements. Approximate gestational ages are shown. **A.** 20 weeks. **B.** 35 weeks. **C.** 40 weeks.



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As gestation progresses, the fetal brain appearance steadily changes. Thus, it is possible to identify fetal age from its external appearance (Volpe, 2008). Neuronal proliferation and migration proceed along with gyral growth and maturation (see Fig. 7-8). Sequential maturation studies by Manganaro (2007) and Dubois (2014) and their colleagues have characterized the developing fetal brain image using magnetic resonance (MR) imaging. Other recent investigations that also used MR imaging have quantified development of subcortical brain structures from 12 to 22 weeks (Meng, 2012).

Myelination of the ventral roots of the cerebrospinal nerves and brainstem begins at approximately 6 months, but most myelination progresses after birth. This lack of myelin and incomplete skull ossification permit fetal brain structure to be seen sonographically throughout gestation.

Spinal Cord

Whereas the superior two thirds of the neural tube give rise to the brain, the inferior third forms the spinal cord. In the embryo, the spinal cord extends along the entire vertebral column length, but after that it lags behind vertebral growth. Ossification of the entire sacrum is visible sonographically by approximately 21 weeks (Chap. 10, Normal and Abnormal Fetal Anatomy). By 24 weeks, the spinal cord extends to S_1, at birth to L_3, and in the adult to L_1. Spinal cord myelination begins at midgestation and continues through the first year of life. Synaptic function is sufficiently developed by the eighth week to demonstrate flexion of the neck and trunk (Temiras, 1968). During the third trimester, integration of nervous and muscular function proceeds rapidly.

Cardiovascular System

The embryology of the heart is complex. At its earliest stages of formation, the fetal heart undergoes molecular programming, and more than a hundred genes and molecular factors are integral to its morphogenesis. To summarize, the straight cardiac tube is formed by the 23rd day during an intricate morphogenetic sequence, during which each *segment* arises at a unique time. The tube then undergoes *looping,* and the chambers then fuse and form septa (Manner, 2009). The valves develop, and the aortic arch forms by vasculogenesis. For a complete description, refer to Chapter 9 in *Hurst's The Heart* (Keller, 2013).

Fetal Circulation

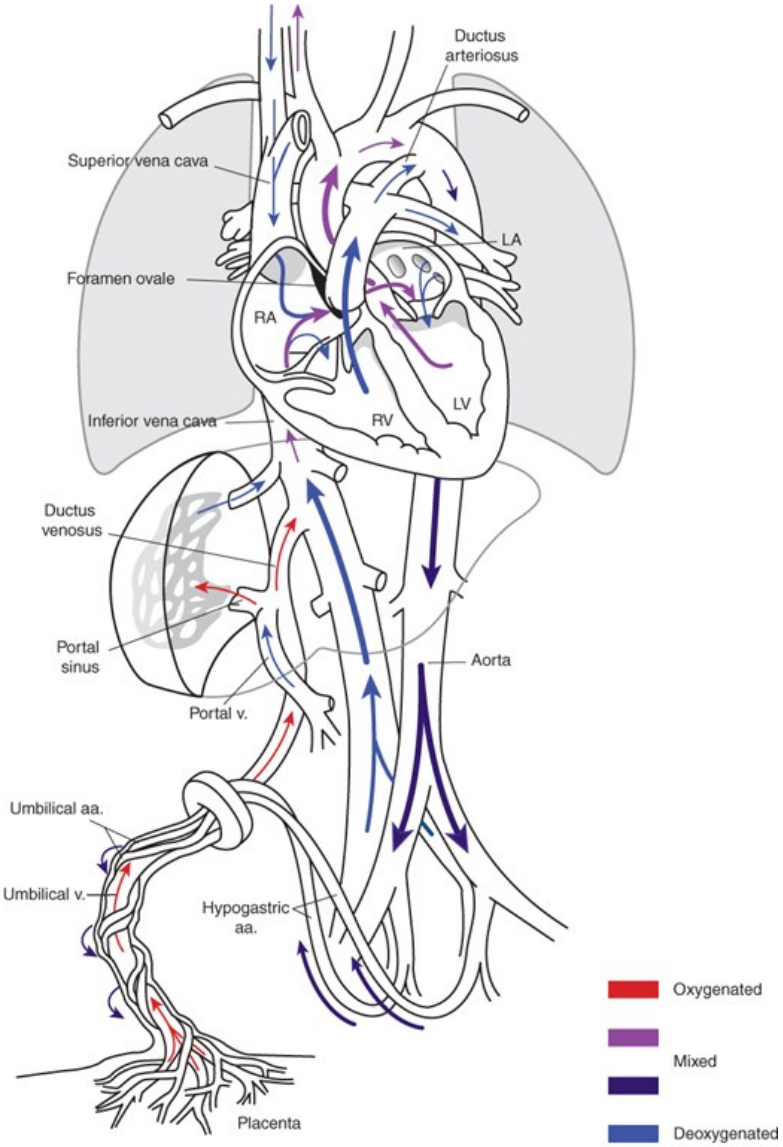
This unique circulation is substantially different from that of the adult and functions until birth, when it changes dramatically. For example, because fetal blood does not need to enter the pulmonary vasculature to be oxygenated, most of the right ventricular output bypasses the lungs. In addition, the fetal heart chambers work in parallel, not in series, which effectively supplies the brain and heart with more highly oxygenated blood than the rest

of the body.

Oxygen and nutrient materials required for fetal growth and maturation are delivered from the placenta by the single umbilical vein (Fig. 7-9). The vein then divides into the ductus venosus and the portal sinus. The ductus venosus is the major branch of the umbilical vein and traverses the liver to enter the inferior vena cava directly. Because it does not supply oxygen to the intervening tissues, it carries well-oxygenated blood directly to the heart. In contrast, the portal sinus carries blood to the hepatic veins primarily on the left side of the liver, and oxygen is extracted. The relatively deoxygenated blood from the liver then flows back into the inferior vena cava, which also receives more deoxygenated blood returning from the lower body. Blood flowing to the fetal heart from the inferior vena cava, therefore, consists of an admixture of arterial-like blood that passes directly through the ductus venosus and less well-oxygenated blood that returns from most of the veins below the level of the diaphragm. The oxygen content of blood delivered to the heart from the inferior vena cava is thus lower than that leaving the placenta.

FIGURE 7-9

The intricate nature of the fetal circulation is evident. The degree of blood oxygenation in various vessels differs appreciably from that in the postnatal state. aa = arteries; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle; v = vein.



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As discussed, the ventricles of the fetal heart work in parallel, not in series. Well-oxygenated blood enters the left ventricle, which supplies the heart

and brain, and less oxygenated blood enters the right ventricle, which supplies the rest of the body. These two separate circulations are maintained by the right atrial structure, which effectively directs entering blood to either the left atrium or the right ventricle, depending on its oxygen content. This separation of blood according to its oxygen content is aided by the pattern of blood flow in the inferior vena cava. The well-oxygenated blood tends to course along the medial aspect of the inferior vena cava and the less oxygenated blood flows along the lateral vessel wall. This aids their shunting into opposite sides of the heart. Once this blood enters the right atrium, the configuration of the upper interatrial septum—the *crista dividens*—preferentially shunts the well-oxygenated blood from the medial side of the inferior vena cava and the ductus venosus through the foramen ovale into the left heart and then to the heart and brain (Dawes, 1962). After these tissues have extracted needed oxygen, the resulting less oxygenated blood returns to the right atrium through the superior vena cava.

The less oxygenated blood coursing along the lateral wall of the inferior vena cava enters the right atrium and is deflected through the tricuspid valve to the right ventricle. The superior vena cava courses inferiorly and anteriorly as it enters the right atrium, ensuring that less well-oxygenated blood returning from the brain and upper body also will be shunted directly to the right ventricle. Similarly, the ostium of the coronary sinus lies just superior to the tricuspid valve so that less oxygenated blood from the heart also returns to the right ventricle. As a result of this blood flow pattern, blood in the right ventricle is 15 to 20 percent less saturated than blood in the left ventricle.

Almost 90 percent of blood exiting the right ventricle is shunted through the ductus arteriosus to the descending aorta. High pulmonary vascular resistance and comparatively lower resistance in the ductus arteriosus and the umbilical–placental vasculature ensure that only about 8 percent of right ventricular output goes to the lungs (Fineman, 2014). Thus, one third of the blood passing through the ductus arteriosus is delivered to the body. The remaining right ventricular output returns to the placenta through the two hypogastric arteries. These two arteries course from the level of the bladder along the abdominal wall to the umbilical ring and into the cord as the umbilical arteries. In the placenta, this blood picks up oxygen and other nutrients and is recirculated through the umbilical vein.

Circulatory Changes at Birth

After birth, the umbilical vessels, ductus arteriosus, foramen ovale, and ductus venosus normally constrict or collapse. With the functional closure of the ductus arteriosus and the expansion of the lungs, blood leaving the right ventricle preferentially enters the pulmonary vasculature to become oxygenated before it returns to the left heart (Hillman, 2012). Virtually instantaneously, the ventricles, which had worked in parallel in fetal life, now effectively work in series. The more distal portions of the hypogastric arteries undergo atrophy and obliteration within 3 to 4 days after birth. These become the umbilical ligaments, whereas the intraabdominal remnants of the umbilical vein form the ligamentum teres. The ductus venosus constricts by 10 to 96 hours after birth and is anatomically closed by 2 to 3 weeks. This ultimately forms the ligamentum venosum (Fineman, 2014).

Fetoplacental Blood Volume

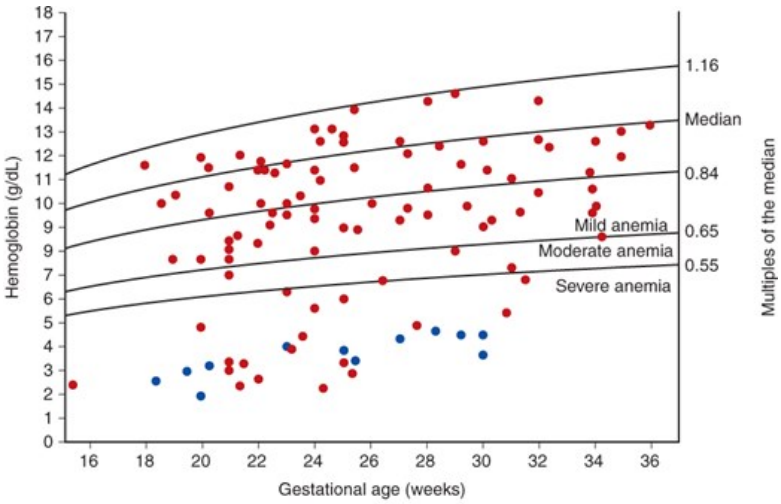
Although precise measurements of human fetoplacental blood volume are lacking, Usher and associates (1963) reported values in term normal newborns to average 78 mL/kg when immediate cord clamping was conducted. Gruenwald (1967) found the fetal blood volume contained in the placenta after prompt cord clamping to average 45 mL/kg of fetal weight. Thus, fetoplacental blood volume at term is approximately 125 mL/kg of fetal weight. This is important when assessing the magnitude of fetomaternal hemorrhage as discussed in Chapter 15 (Fetal Thrombocytopenia).

Hemopoiesis

In the early embryo, hemopoiesis is demonstrable first in the yolk sac, followed by the liver, and finally spleen and bone marrow. Both myeloid and erythroid cells are continually produced by progenitors that are from hematopoietic stem cells (Golub, 2013; Heinig, 2015). The first erythrocytes released into the fetal circulation are nucleated and macrocytic. The mean cell volume is at least 180 fL in the embryo and decreases to 105 to 115 fL at term. The erythrocytes of aneuploid fetuses generally do not undergo this maturation and maintain high mean cell volumes—130 fL on average (Sipes, 1991). As fetal development progresses, more and more of the circulating erythrocytes are smaller and nonnucleated. With fetal growth, both the blood volume in the common fetoplacental circulation and hemoglobin concentration increase. As shown in Figure 7-10, fetal hemoglobin concentrations rise across pregnancy. The Society for Maternal-Fetal Medicine (2015) recommends a cutoff hematocrit value of 30 percent to define anemia.

FIGURE 7-10

Relationship between fetal hemoglobin across gestational age. Blue dots indicate fetuses with hydrops. (Reproduced with permission from Mari G, Deter RL, Carpenter RL, et al: Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. Collaborative Group for Doppler Assessment of the Blood Velocity in Anemic Fetuses (Level II-I), N Engl J Med 2000 Jan 6;342(1):9–14.)



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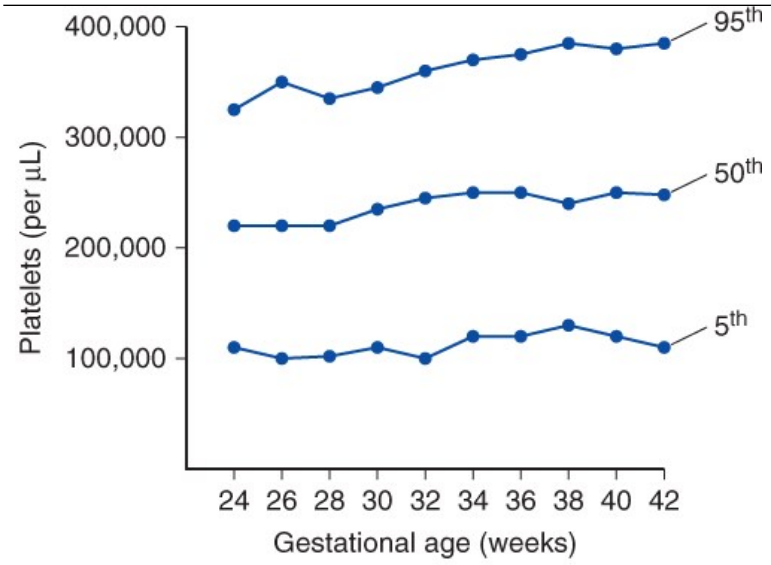
Because of their large size, fetal erythrocytes have a short life span, which progressively lengthens to approximately 90 days at term (Pearson, 1966). As a consequence, red blood cell production rises. Reticulocytes are initially present at high levels, but decrease to 4 to 5 percent of the total at term. Fetal erythrocytes differ structurally and metabolically from those in the adult (Baron, 2012). They are more deformable, which serves to offset their higher viscosity. They also contain several enzymes with appreciably different activities.

Erythropoiesis is controlled primarily by fetal erythropoietin because maternal erythropoietin does not cross the placenta. Fetal hormone production is influenced by testosterone, estrogen, prostaglandins, thyroid hormone, and lipoproteins (Stockman, 1992). Serum erythropoietin levels rise with fetal maturity. Although the exact production site is disputed, the fetal liver appears to be an important source until renal production begins. There is a close correlation between the erythropoietin concentration in amnionic fluid and that in umbilical venous blood obtained by cordocentesis. After birth, erythropoietin normally may not be detectable for up to 3 months.

In contrast, platelet production reaches stable levels by midpregnancy, although there is some variation across gestation (Fig. 7-11). The fetal and neonatal platelet count is subject to various agents as discussed in Chapter 15 (Fetal Thrombocytopenia).

FIGURE 7-11

Platelet counts by gestational age obtained the first day of life. Mean values and 5th and 95th percentiles are shown. (Data from Christensen RD, Henry E, Antonio DV: Thrombocytosis and thrombocytopenia in the NICU: incidence, mechanisms and treatments, J Matern Fetal Neonatal Med 2012 Oct;25 Suppl 4:15–17)



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Fetal Hemoglobin

This tetrameric protein is composed of two copies of two different peptide chains, which determine the type of hemoglobin produced. Normal adult hemoglobin A is made of α and β chains. During embryonic and fetal life, various α and β chain precursors are produced. This results in the serial production of several different embryonic hemoglobins. Genes for β-type chains are on chromosome 11, and those for α-type chains on chromosome 16. Each of these genes is turned on and then off during fetal life, until α and β genes, which direct the production of adult hemoglobin A, are permanently activated.

The timing of production of each of these early hemoglobins corresponds to the site of hemoglobin production. Fetal blood is first produced in the yolk sac, where hemoglobins Gower 1, Gower 2, and Portland are made. Erythropoiesis then moves to the liver, where fetal hemoglobin F is produced. When hemopoiesis finally moves to the bone marrow, adult-type hemoglobin A appears in fetal red blood cells and is present in progressively greater amounts as the fetus matures (Pataryas, 1972).

The final adult version of the α chain is produced exclusively by 6 weeks. After this, there are no functional alternative versions. If an α-gene mutation or deletion occurs, no alternate α-type chain can be substituted to form functional hemoglobin. In contrast, at least two versions of the β chain—δ and γ—remain in production throughout fetal life and beyond. In the case of a β-gene mutation or deletion, these two other versions of the β chain often continue to be produced, resulting in hemoglobin A_2 or hemoglobin F, which substitute for the abnormal or missing hemoglobin.

Genes are turned off by methylation of their control region, which is discussed in Chapter 13 (DNA Triplet Repeat Expansion—Anticipation). In some situations, methylation does not occur. For example, in newborns of diabetic women, hemoglobin F may persist due to hypomethylation of the γ gene (Perrine, 1988). With sickle cell anemia, the γ gene remains unmethylated, and large quantities of fetal hemoglobin continue to be produced. As discussed in Chapter 56 (Polycythemias), elevated hemoglobin F levels are associated with fewer sickle-cell disease symptoms, and pharmacological modification of these levels by hemoglobin F-inducing drugs is one approach to treatment.

As discussed in Placental Transfer, there is a functional difference between hemoglobins A and F. At any given oxygen tension and at identical pH, fetal erythrocytes that contain mostly hemoglobin F bind more oxygen than do those that contain nearly all hemoglobin A (Fig. 47-2). This is because hemoglobin A binds 2,3-diphosphoglycerate (2,3-DPG) more avidly than does hemoglobin F, thus lowering the affinity of hemoglobin A for oxygen. During pregnancy, maternal 2,3-DPG levels are greater, and because fetal erythrocytes have lower concentrations of 2,3-DPG, the latter has increased oxygen affinity.

The amount of hemoglobin F in fetal erythrocytes begins to decrease in the last weeks of pregnancy. At term, approximately three fourths of total hemoglobin levels are hemoglobin F. During the first 6 to 12 months of life, the hemoglobin F proportion continues to decline and eventually reaches

the low levels found in adult erythrocytes.

Coagulation Factors

With the exception of fibrinogen, there are no embryonic forms of the various hemostatic proteins. The fetus starts producing normal, adult-type procoagulant, fibrinolytic, and anticoagulant proteins by 12 weeks. Because they do not cross the placenta, their concentrations at birth are markedly below the levels that develop within a few weeks of life (Corrigan, 1992). In normal neonates, the levels of factors II, VII, IX, X, XI, and of protein S, protein C, antithrombin, and plasminogen all approximate 50 percent of adult levels. In contrast, levels of factors V, VIII, XIII, and fibrinogen are closer to adult values (Saracco, 2009). Without prophylactic treatment, the levels of vitamin K-dependent coagulation factors usually decrease even further during the first few days after birth. This decline is amplified in breastfed infants and may lead to newborn hemorrhage (Chap. 33, Polycythemia and Hyperviscosity).

Fetal fibrinogen, which appears as early as 5 weeks, has the same amino acid composition as adult fibrinogen, however, it has different properties (Klagsbrun, 1988). It forms a less compressible clot, and the fibrin monomer has a lower degree of aggregation (Heimark, 1988). Although plasma fibrinogen levels at birth are less than those in nonpregnant adults, the protein is functionally more active than adult fibrinogen (Ignjatovic, 2011).

Levels of functional fetal factor XIII—fibrin stabilizing factor—are significantly reduced compared with those in adults (Henriksson, 1974). Nielsen (1969) described low levels of plasminogen and elevated fibrinolytic activity in cord plasma compared with that of maternal plasma. Platelet counts in cord blood are in the normal range for nonpregnant adults (see Fig. 7-11).

Despite this relative reduction in procoagulants, the fetus appears to be protected from hemorrhage, and fetal bleeding is rare. Even after invasive fetal procedures such as cordocentesis, excessive bleeding is uncommon. Ney and coworkers (1989) have shown that amnionic fluid thromboplastins and a factor(s) in Wharton jelly combine to aid coagulation at the umbilical cord puncture site.

Various *thrombophilias* may cause thromboses and pregnancy complications in adults (Chap. 52, Acquired Thrombophilias). If the fetus inherits one of these mutations, thrombosis and infarction can develop in the placenta or fetal organs. This is usually seen with homozygous inheritance. One example is homozygous protein C mutation, which causes *purpura fulminans*.

Plasma Proteins

Liver enzymes and other plasma proteins are produced by the fetus, and these levels do not correlate with maternal levels (Weiner, 1992). Concentrations of plasma proteins, which include albumin, lactic dehydrogenase, aspartate aminotransferase, γ-glutamyl transpeptidase, and alanine transferase, all rise. Conversely, prealbumin levels decline with gestational age (Fryer, 1993). At birth, mean total plasma protein and albumin concentrations in fetal blood are similar to maternal levels. This is important because albumin binds unconjugated bilirubin to prevent *kernicterus* in the newborn (Chap. 33, Polycythemia and Hyperviscosity).

Respiratory System

Lung maturation and biochemical indices of functional fetal lung maturity are important predictors of early neonatal outcome. Morphological or functional immaturity at birth leads to the development of the *respiratory distress syndrome* (Chap. 34, Respiratory Distress Syndrome). A sufficient amount of surface-active materials—collectively referred to as *surfactant*—in the amnionic fluid is evidence of fetal lung maturity. As Liggins (1994) emphasized, however, the structural and morphological maturation of fetal lung also is extraordinarily important to proper lung function.

Anatomical Maturation

The limits of viability appear to be determined by the usual process of pulmonary growth. Like the branching of a tree, lung development proceeds along an established timetable that apparently cannot be hastened by antenatal or neonatal therapy. Within this framework, four essential lung development stages are described by Moore (2000). First, the ***pseudoglandular stage*** entails growth of the intrasegmental bronchial tree between the 5th and 17th weeks. During this period, the lung looks microscopically like a gland. Second, during the ***canalicular stage***, from 16 to 25 weeks, the bronchial cartilage plates extend peripherally. Each terminal bronchiole gives rise to several respiratory bronchioles, and each of these in turn divides into multiple saccular ducts. Third, the ***terminal sac stage*** begins after 25 weeks. During this stage, alveoli give rise to primitive pulmonary alveoli, that is, the terminal sacs. Simultaneously, an extracellular matrix develops from proximal to distal lung segments until term. Finally, the

alveolar stage begins during the late fetal period and continues well into childhood. An extensive capillary network is built, the lymph system forms, and type II pneumocytes begin to produce surfactant. At birth, only approximately 15 percent of the adult number of alveoli is present. Thus, the lung continues to grow, adding more alveoli for up to 8 years.

Various insults can upset this process, and their timing determines the sequelae. One example is fetal renal agenesis, in which amnionic fluid is absent at the beginning of lung growth, and major defects occur in all four developmental stages. In another instance, the fetus with membrane rupture and subsequent oligohydramnios before 20 weeks usually exhibits nearly normal bronchial branching and cartilage development but has immature alveoli. In contrast, membrane rupture after 24 weeks may have minimal long-term effect on pulmonary structure. In another example, various growth factors are expressed abnormally in the fetus with a diaphragmatic hernia (Candilira, 2015). Finally, vitamin D is thought to be important for several aspects of lung development (Hart, 2015; Lykkedegn, 2015).

Pulmonary Surfactant

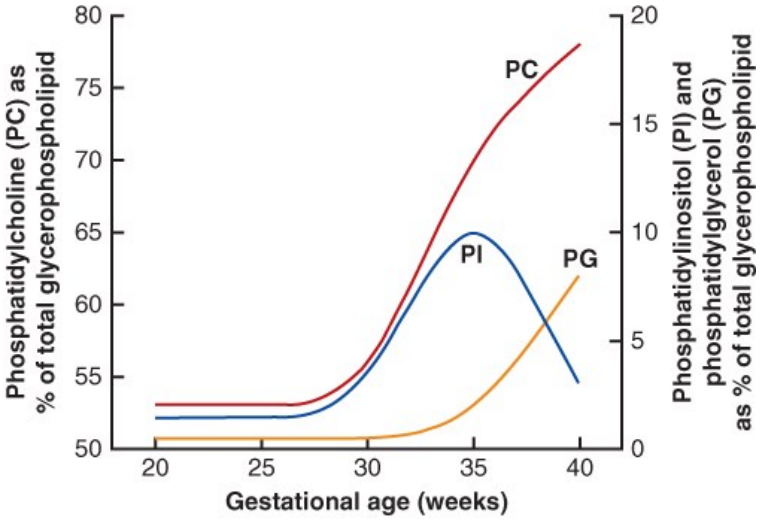
After the first breath, the terminal sacs must remain expanded despite the pressure imparted by the tissue-to-air interface, and surfactant keeps them from collapsing. Surfactant is formed in type II pneumonocytes that line the alveoli. These cells are characterized by multivesicular bodies that produce the lamellar bodies in which surfactant is assembled. During late fetal life, at a time when the alveolus is characterized by a water-to-tissue interface, the intact lamellar bodies are secreted from the lung and swept into the amnionic fluid during respiratory-like movements that are termed fetal breathing. At birth, with the first breath, an air-to-tissue interface is established in the lung alveolus. Surfactant uncoils from the lamellar bodies and spreads to line the alveolus to prevent alveolar collapse during expiration. Thus, the fetal lungs' capacity to produce surfactant establishes lung maturity.

Surfactant Composition

Gluck (1972) and Hallman (1976) and their coworkers approximated that 90 percent of surfactant's dry weight is lipid, specifically glycerophospholipids. Proteins account for the other 10 percent. Nearly 80 percent of the glycerophospholipids are phosphatidylcholines (lecithins). The principal active component that constitutes half of surfactant is a specific lecithin, which is dipalmitoylphosphatidylcholine (DPPC or PC). Phosphatidylglycerol (PG) accounts for another 8 to 15 percent. Its precise role is unclear because newborns without PG usually do well. The other major constituent is phosphatidylinositol (PI). The relative contributions of each component are shown in Figure 7-12.

FIGURE 7-12

Relationship between the levels of lecithin— dipalmitoyl phosphatidylcholine (PC), phosphatidylinositol (PI), and phosphatidylglycerol (PG) in amnionic fluid.



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: *Williams Obstetrics*, 25th Edition

Surfactant Synthesis

Biosynthesis takes place in the type II pneumocytes. The apoproteins are produced in the endoplasmic reticulum, and the glycerophospholipids are synthesized by cooperative interactions of several cellular organelles. Phospholipid is the primary surface tension-lowering component of surfactant, whereas the apoproteins aid the forming and reforming of a surface film.

The major apoprotein is surfactant A (SP-A), which is a glycoprotein with a molecular weight of 28,000 to 35,000 Da (Whitsett, 1992). It is synthesized in the type II cells, and its content in amnionic fluid increases with gestational age and fetal lung maturity. *SP-A* gene expression is demonstrable by 29 weeks (Mendelson, 2005). Specifically, *SP-A1* and *SP-A2* are two separate genes on chromosome 10, but their regulation is distinctive and different (McCormick, 1994).

Several smaller apoproteins such as SP-B and SP-C are likely important in optimizing the action of surfactant. For example, deletions in *SP-B* gene are incompatible with survival despite production of large amounts of surfactant (Hallman, 2013).

Corticosteroids and Fetal Lung Maturation

Since Liggins (1969) observed accelerated lung maturation in lamb fetuses given glucocorticosteroids prior to preterm delivery, many suggested that fetal cortisol stimulates lung maturation and surfactant synthesis. It is unlikely that corticosteroids are the only stimulus for augmented surfactant formation. However, when these are administered at certain critical times, they may improve preterm fetal lung maturation. As fetal lung therapy, antenatal betamethasone and dexamethasone use and neonatal replacement surfactant therapy are discussed in Chapter 34 (Clinical Course).

Breathing

Fetal respiratory muscles develop early, and chest wall movements are detected sonographically as early as 11 weeks (Koos, 2014). From the beginning of the fourth month, the fetus engages in respiratory movement sufficiently intense to move amnionic fluid in and out of the respiratory tract. Some extrauterine events have effects on fetal breathing, for example, maternal exercise stimulates it (Sussman, 2016).

Digestive System

After its embryogenic formation from the yolk sac as the primordial gut, the digestive system forms the intestines and various appendages. The foregut gives rise to the pharynx, lower respiratory system, esophagus, stomach, proximal duodenum, liver, pancreas, and biliary tree. The midgut gives rise to the distal duodenum, jejunum, ileum, cecum, appendix, and the right colon. The hindgut develops into the left colon, rectum, and the superior portion of the anal canal. Numerous malformations develop in these structures from improper rotation, fixation, and partitioning.

Swallowing begins at 10 to 12 weeks, coincident with the ability of the small intestine to undergo peristalsis and actively transport glucose (Koldovsky, 1965). As a correlate, neonates born preterm may have swallowing difficulties because of immature gut motility (Singendonk, 2014). Much of the water in swallowed fluid is absorbed, and unabsorbed matter is propelled to the lower colon. Gitlin (1974) demonstrated that late in pregnancy, approximately 800 mg of soluble protein is ingested daily by the fetus. The stimulus for swallowing is unclear, but the fetal neural analogue of thirst, gastric emptying, and change in the amnionic fluid composition are potential factors (Boyle, 1992). The fetal taste buds may play a role because saccharin injected into amnionic fluid increases swallowing, whereas injection of a noxious chemical inhibits it (Liley, 1972).

Fetal swallowing appears to have little effect on amnionic fluid volume early in pregnancy because the volume swallowed is small compared with the total. However, term fetuses swallow between 200 and 760 mL per day—an amount comparable to that of the term neonate (Pritchard, 1966). Thus at term, amnionic fluid volume regulation can be substantially altered by fetal swallowing. For example, as discussed in Chapter 11 (Hydramnios), if swallowing is inhibited, hydramnios is common.

Hydrochloric acid and some digestive enzymes are present in the stomach and small intestine in minimal amounts in the early fetus. Intrinsic factor is detectable by 11 weeks, and pepsinogen by 16 weeks. The preterm neonate, depending on its gestational age, may have transient deficiencies of these enzymes (Lebenthal, 1983).

Stomach emptying appears to be stimulated primarily by volume. Movement of amnionic fluid through the gastrointestinal system may enhance growth and development of the alimentary canal. That said, other regulatory factors likely are involved. For example, anencephalic fetuses, in which swallowing is limited, often have normal amnionic fluid volume and normal-appearing gastrointestinal tract.

Meconium

Fetal bowel contents consist of various products of secretion, such as glycerophospholipids from the lung, desquamated fetal cells, lanugo, scalp hair, and vernix. It also contains undigested debris from swallowed amnionic fluid. The dark greenish-black color forms from bile pigments, especially biliverdin. Meconium can pass from normal bowel peristalsis in the mature fetus or from vagal stimulation. It can also pass when hypoxia stimulates arginine vasopressin (AVP) release from the fetal pituitary gland. AVP stimulates colonic smooth muscle to contract, resulting in intraamnionic defecation (deVane, 1982; Rosenfeld, 1985). Meconium is toxic to the respiratory system, and its inhalation can result in *meconium aspiration syndrome* (Chap. 33, Neonatal Encephalopathy and Cerebral Palsy).

Liver

The hepatic diverticulum is an outgrowth of the endodermal lining of the foregut. Epithelial liver cords and primordial cells differentiate into hepatic parenchyma. Serum liver enzyme levels increase with gestational age. Still, the fetal liver has a gestational-age-related diminished capacity for converting free unconjugated bilirubin to conjugated bilirubin (Morioka, 2015). Because of hepatic immaturity, the preterm newborn is at particular risk for hyperbilirubinemia (Chap. 33, Polycythemia and Hyperviscosity). And because the life span of normal fetal macrocytic erythrocytes is shorter than that of the adult, relatively more unconjugated bilirubin is produced. As just noted, the fetal liver conjugates only a small fraction, and this is excreted into the intestine and ultimately oxidized to biliverdin. Most of the unconjugated bilirubin is excreted into the amnionic fluid after 12 weeks and transferred across the placenta (Bashore, 1969).

Importantly, placental bilirubin transfer is bidirectional. Thus, a woman with severe hemolysis from any cause has excess unconjugated bilirubin that readily passes to the fetus and then into the amnionic fluid. Conversely, conjugated bilirubin is not exchanged to any significant degree between mother and fetus.

Most fetal cholesterol derives from hepatic synthesis, which satisfies the large demand for low-density lipoprotein (LDL) cholesterol by the fetal adrenal glands. Hepatic glycogen is present in low concentration during the second trimester, but near term, levels rise rapidly and markedly to reach concentrations that are two- to threefold higher than those in the adult liver. After birth, glycogen content falls precipitously.

Pancreas

This organ arises from dorsal and ventral pancreatic buds from the endoderm of the foregut. Gene regulation of its development was recently reviewed (Jennings, 2015). Insulin-containing granules can be identified by 9 to 10 weeks, and insulin is detectable in fetal plasma at 12 weeks (Adam, 1969). The pancreas responds to hyperglycemia by secreting insulin (Obenshain, 1970). Glucagon has been identified in the fetal pancreas at 8 weeks. Although hypoglycemia does not cause an increase in fetal glucagon levels, similar stimuli do so by 12 hours after birth (Chez, 1975). At the same time, however, fetal pancreatic α cells do respond to L-dopa infusions (Epstein, 1977). Therefore, unresponsiveness to hypoglycemia is likely the consequence of failed glucagon release rather than inadequate production. This is consistent with developmental expression of pancreatic genes in the fetus (Mally, 1994).

Most pancreatic enzymes are present by 16 weeks. Trypsin, chymotrypsin, phospholipase A, and lipase are found in the 14-week fetus, and their concentrations increase with gestational age (Werlin, 1992). Amylase has been identified in amnionic fluid at 14 weeks (Davis, 1986). The exocrine function of the fetal pancreas is limited. Physiologically important secretion occurs only after stimulation by a secretagogue such as acetylcholine, which is released locally after vagal stimulation (Werlin, 1992). Cholecystokinin normally is released only after protein ingestion and thus ordinarily would not be found in the fetus.

Urinary System

Renal development involves interaction between pluripotential stem cells, undifferentiated mesenchymal cells, and epithelial components (Fanos, 2015). Two primitive urinary systems—the pronephros and the mesonephros—precede development of the metanephros, which forms the final kidney (Chap. 3, Genitourinary Tract Development). The pronephros involutes by 2 weeks, and the mesonephros produces urine at 5 weeks and degenerates by 11 to 12 weeks. Failure of these two structures either to form or to regress may result in anomalous urinary system development. Between 9 and 12 weeks, the ureteric bud and the nephrogenic blastema interact to produce the metanephros. The kidney and ureter develop from intermediate mesoderm. The bladder and urethra develop from the urogenital sinus. The bladder also develops in part from the allantois.

By week 14, the loop of Henle is functional and reabsorption occurs (Smith, 1992). New nephrons continue to be formed until 36 weeks. In preterm neonates, their formation continues after birth. Although the fetal kidneys produce urine, their ability to concentrate and modify the pH is limited even in the mature fetus. Fetal urine is hypotonic with respect to fetal plasma and has low electrolyte concentrations.

Renal vascular resistance is high, and the filtration fraction is low compared with adult values (Smith, 1992). Fetal renal blood flow and thus urine production are controlled or influenced by the renin-angiotensin system, the sympathetic nervous system, prostaglandins, kallikrein, and atrial natriuretic peptide. The glomerular filtration rate increases with gestational age from less than 0.1 mL/min at 12 weeks to 0.3 mL/min at 20 weeks. In later gestation, the rate remains constant when corrected for fetal weight (Smith, 1992). Hemorrhage or hypoxia generally results in a decrease in renal blood flow, glomerular filtration rate, and urine output.

Urine usually is found in the bladder even in small fetuses. The fetal kidneys start producing urine at 12 weeks. By 18 weeks, they are producing 7 to 14 mL/day, and at term, this increases to 650 mL/day (Wladimiroff, 1974). Maternally administered furosemide increases fetal urine formation, whereas uteroplacental insufficiency, fetal growth restriction, and other fetal disorders can lower it. Obstruction of the urethra, bladder, ureters, or renal pelves can damage renal parenchyma and distort fetal anatomy (Müller Brochut, 2014). Kidneys are not essential for survival in utero but influence control of amnionic fluid composition and volume. Thus, abnormalities that cause chronic fetal anuria are usually accompanied by oligohydramnios and pulmonary hypoplasia. Pathological correlates and prenatal therapy of urinary tract obstruction are discussed in Chapter 16 (Urinary Shunts).

Endocrine Gland Development

Pituitary Gland

The fetal endocrine system is functional for some time before the central nervous system reaches maturity (Mulchahey, 1987). The anterior pituitary gland develops from oral ectoderm—*Rathke pouch*, whereas the posterior pituitary gland derives from neuroectoderm. As with other organ systems, embryonic development involves a complex and highly spatiotemporally regulated network of signaling molecules and transcription factors (Bancalari, 2012; de Moraes, 2012).

Anterior and Intermediate Lobes

The adenohypophysis, or anterior pituitary, differentiates into five cell types that secrete six protein hormones. Of these types, lactotropes produce prolactin (PRL), somatotropes produce growth hormone (GH), corticotropes produce adrenocorticotropic hormone (ACTH), thyrotropes produce thyroid-stimulating hormone (TSH), and gonadotropes produce luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

ACTH is first detected in the fetal pituitary gland at 7 weeks, and GH and LH have been identified by 13 weeks. By the end of the 17th week, the fetal pituitary gland synthesizes and stores all pituitary hormones. Moreover, the fetal pituitary is responsive to tropic hormones and is capable of secreting these early in gestation (Grumbach, 1974). The fetal pituitary secretes β-endorphin, and cord blood levels of β-endorphin and β-lipotrophin rise with fetal P_{CO_2} (Browning, 1983).

The intermediate lobe in the fetal pituitary gland is well developed. The cells of this structure begin to disappear before term and are absent from the adult pituitary. The principal secretory products of the intermediate lobe cells are α-melanocyte–stimulating hormone (α-MSH) and β-endorphin.

Neurohypophysis

The posterior pituitary gland or neurohypophysis is well developed by 10 to 12 weeks, and oxytocin and arginine vasopressin are demonstrable. Both hormones probably function in the fetus to conserve water by actions directed largely at the lung and placenta rather than kidney. Vasopressin levels in umbilical cord plasma are increased strikingly compared with maternal levels (Chard, 1971).

Thyroid Gland

This gland arises from the endoderm of the second pharyngeal pouch. The thyroid migrates to its final position and the obliterated thyroglossal duct connects to the foramen cecum of the tongue. The pituitary–thyroid system is functional by the end of the first trimester. The thyroid gland is able to synthesize hormones by 10 to 12 weeks, and thyrotropin, thyroxine, and thyroid-binding globulin (TBG) have been detected in fetal serum as early as

11 weeks (Bernal, 2007). The placenta actively concentrates iodide on the fetal side, and by 12 weeks and throughout pregnancy, the fetal thyroid concentrates iodide more avidly than does the maternal thyroid. Thus, maternal administration of either radioiodide or appreciable amounts of ordinary iodide is hazardous after this time (Chap. 58, Fetal and Neonatal Effects). Normal fetal levels of free thyroxine (T_4), free triiodothyronine (T_3), and thyroxin-binding globulin increase steadily throughout gestation (Ballabio, 1989). Compared with adult levels, by 36 weeks, fetal serum concentrations of TSH are higher, total and free T_3 concentrations are lower, and T_4 is similar. This suggests that the fetal pituitary may not become sensitive to feedback until late pregnancy (Thorpe-Beeston, 1991).

Fetal thyroid hormone plays a role in the normal development of virtually all fetal tissues, especially the brain (Forhead, 2014; Rovet, 2014). Its influence is illustrated by congenital hyperthyroidism, which develops when maternal thyroid-stimulating antibody crosses the placenta to stimulate the fetal gland to secrete thyroxine (Donnelley, 2015). These fetuses develop large goiters as shown in Figure 58-3. They also display tachycardia, hepatosplenomegaly, hematological abnormalities, craniosynostosis, and growth restriction. As children, they have perceptual motor difficulties, hyperactivity, and reduced growth (Wenstrom, 1990). Fetal thyroid disease and its treatment are discussed in Chapter 16 (Surgical Therapy). Neonatal effects of fetal thyroid deficiency are discussed in Chapter 58 (Iodine Deficiency).

The placenta prevents substantial passage of maternal thyroid hormones to the fetus by rapidly deiodinating maternal T_4 and T_3 to form reverse T_3, a relatively inactive thyroid hormone (Vulsma, 1989). Several antithyroid antibodies cross the placenta when present in high concentrations (Pelag, 2002). Those include the long-acting thyroid stimulators (LATS), LATS-protector (LATS-P), and thyroid-stimulating immunoglobulin (TSI). It was previously believed that normal fetal growth and development, which occurred despite fetal hypothyroidism, provided evidence that T_4 was not essential for fetal growth. It is now known, however, that growth proceeds normally because small quantities of maternal T_4 prevent antenatal cretinism in fetuses with thyroid agenesis (Forhead, 2014; Vulsma, 1989). The fetus with congenital hypothyroidism typically does not develop stigmata of cretinism until after birth (Abduljabbar, 2012). Because administration of thyroid hormone will prevent this, by state law, all newborns are tested for high serum levels of TSH (Chap. 32, Routine Newborn Care).

Immediately after birth, thyroid function and metabolism undergo major change. Cooling to room temperature evokes sudden and marked increase in TSH secretion. This in turn causes a progressive increase in serum T_4 levels that are maximal 24 to 36 hours after birth. There are nearly simultaneous elevations of serum T_3 levels.

Adrenal Glands

These glands develop from two separate tissues. The medulla derives from neural crest ectoderm, whereas the fetal and adult cortex arise from intermediate mesoderm. The gland grows rapidly through cell proliferation and angiogenesis, cellular migration, hypertrophy, and apoptosis (Ishimoto, 2011). Fetal glands are much larger in relation to total body size than in adults. The bulk is made up of the inner or fetal zone of the adrenal cortex and involutes rapidly after birth. This zone is scant to absent in rare instances in which the fetal pituitary gland is congenitally absent. The function of the fetal adrenal glands is discussed in detail in Chapter 5 (Fetal Adrenal Gland–placental Interactions).

Immunological System

Infections in utero have provided an opportunity to examine mechanisms of the fetal immune response. Evidence of immunological competence has been reported as early as 13 weeks (Kohler, 1973; Stabile, 1988). In cord blood at or near term, the average level for most components is approximately half that of the adult values (Adinolfi, 1977).

B cells differentiate from pluripotent hemopoietic stem cells that migrate to the liver (Melchers, 2015; Muzzio, 2013). Despite this, in the absence of a direct antigenic stimulus such as infection, fetal plasma immunoglobulins consist almost totally of transferred maternal immunoglobulin G (IgG). Thus, antibodies in the newborn are most often reflective of maternal immunological experiences (American College of Obstetricians and Gynecologists, 2017). The interaction between maternal and fetal T cells is described in detail in Chapter 5 (Amnion).

Immunoglobulin G

Maternal IgG transport to the fetus begins at approximately 16 weeks and increases thereafter. The bulk of IgG is acquired during the last 4 weeks of pregnancy (Gitlin, 1971). Accordingly, preterm neonates are poorly endowed with protective maternal antibodies. Newborns begin to slowly produce

IgG, and adult values are not attained until age 3 years. In certain situations, the transfer of IgG antibodies from mother to fetus can be harmful rather than protective to the fetus. The classic example is hemolytic disease of the fetus and newborn resulting from Rh-antigen alloimmunization (Chap. 15, Red Cell Alloimmunization).

Immunoglobulins M and A

In the adult, production of immunoglobulin M (IgM) in response to an antigenic stimulus is superseded in a week or so predominantly by IgG production. In contrast, very little IgM is produced by normal fetuses. With infection, the IgM response is dominant in the fetus and remains so for weeks to months in the newborn. And, because IgM is not transported from the mother, any IgM in the fetus or newborn is that which it produced. Thus, specific IgM levels in umbilical cord blood may be useful in fetal infection diagnosis. According to the American College of Obstetricians and Gynecologists (2017), elevated levels of IgM are usually found in newborns with congenital infection such as rubella, cytomegalovirus infection, or toxoplasmosis. In infants, adult levels of IgM are normally attained by age 9 months.

Immunoglobulin A (IgA) ingested in colostrum provides mucosal protection against enteric infections. This may explain the small amount of fetal secretory IgA found in amnionic fluid (Quan, 1999).

Lymphocytes and Monocytes

The immune system develops early, and B lymphocytes appear in fetal liver by 9 weeks and in blood and spleen by 12 weeks. T lymphocytes begin to leave the thymus at approximately 14 weeks. Despite this, the newborn responds poorly to immunization, and especially poorly to bacterial capsular polysaccharides. This immature response may stem from a deficient response of newborn B cells to polyclonal activators or from a lack of T cells that proliferate in response to specific stimuli (Hayward, 1983). In the newborn, monocytes are able to process and present antigen when tested with maternal antigen-specific T cells. DNA methylation patterns are developmentally regulated during monocyte-macrophage differentiation and contribute to the antiinflammatory phenotype in macrophages (Kim, 2012).

Musculoskeletal System

The origin of most muscles and bones is mesodermal. The skeleton arises from condensed mesenchyme—embryonic connective tissue—which eventually forms hyaline cartilage models of the bones. By the end of the embryonic period, ossification centers have developed, and bones harden by endochondral ossification. The limb buds appear by the fourth week. Most skeletal muscle derives from myogenic precursor cells in the somites.

ENERGY AND NUTRITION

Because of the small amount of yolk in the human ovum, growth of the embryofetus is dependent on maternal nutrients during the first 2 months. During the first few days after implantation, blastocyst nutrition comes from the interstitial fluid of the endometrium and the surrounding maternal tissue.

Maternal adaptations to store and transfer nutrients to the fetus are discussed in Chapter 4 and summarized here. Three major maternal storage depots are the liver, muscle, and adipose tissue. These maternal depots and the storage hormone insulin are intimately involved in the metabolism of the nutrients absorbed from the gut. Maternal insulin secretion is sustained by increased serum levels of glucose and amino acids. The net effect is maternal storage of glucose as glycogen primarily in liver and muscle, retention of some amino acids as protein, and storage of the excess as fat. Storage of maternal fat peaks in the second trimester and then declines as fetal energy demands rise in the third trimester (Pipe, 1979). Interestingly, the placenta appears to act as a nutrient sensor, altering transport based on the maternal supply and environmental stimuli (Fowden, 2006; Jansson, 2006b).

During times of fasting, glucose is released from glycogen, but maternal glycogen stores cannot provide an adequate amount of glucose to meet requirements for maternal energy and fetal growth. Augmentation is provided by cleavage of triacylglycerols, stored in adipose tissue, which result in free fatty acids and activation of lipolysis.

Glucose and Fetal Growth

Although dependent on the mother for nutrition, the fetus also actively participates in providing its own nutrition. At midpregnancy, fetal glucose

concentration is independent of maternal levels and may exceed them (Bozzetti, 1988). Glucose is the major nutrient for fetal growth and energy. Logically, mechanisms exist during pregnancy to minimize maternal glucose use so that the limited maternal supply is available to the fetus. Human placental lactogen (hPL), a hormone normally abundant in the mother but not the fetus, has an insulin antagonist effect. It blocks the peripheral uptake and use of glucose, while promoting mobilization and use of free fatty acids by maternal tissues (Chap. 5, Human Placental Lactogen). This hormone is also diabetogenic as discussed in Chapter 57 (Gestational Diabetes).

Glucose Transport

The transfer of d-glucose across cell membranes is accomplished by a carrier-mediated, stereospecific, nonconcentrating process of facilitated diffusion. There are 14 glucose transport proteins (GLUTs) encoded by the *SLC2A* gene family and characterized by tissue-specific distribution (Leonce, 2006). GLUT-1 and GLUT-3 primarily facilitate glucose uptake by the placenta and are located in the plasma membrane of the syncytiotrophoblast microvilli (Acosta, 2015). DNA methylation regulates expression of placental *GLUT* genes, with epigenetic modification across gestation (Novakovic, 2013). It increases as pregnancy advances and is induced by almost all growth factors (Frolova, 2011). GLUT-3 expression is upregulated with fetal growth restriction (Janzen, 2013).

Lactate is a product of glucose metabolism and transported across the placenta also by facilitated diffusion. By way of cotransport with hydrogen ions, lactate is probably transported as lactic acid.

Fetal Macrosomia

The precise biomolecular events in the pathophysiology of fetal macrosomia are not defined. Nonetheless, fetal hyperinsulinemia is clearly one driving force (Luo, 2012). As discussed in Chapter 44 (Normal Birthweight), insulin-like growth factor, fibroblast growth factor, and corticotropin-releasing hormone (CRH) and are important regulators of placental development and function (Gao, 2012; Giudice, 1995). Maternal obesity begets fetal macrosomia (Chap. 44, Definition). In addition, it is hypothesized that maternal obesity affects fetal cardiomyocyte growth that may result in fetal cardiomyopathy or even congenital heart disease (Roberts, 2015).

Leptin

This polypeptide hormone was originally identified as a product of adipocytes and a regulator of energy homeostasis by curbing appetite. It also contributes to angiogenesis, hemopoiesis, osteogenesis, pulmonary maturation, and neuroendocrine, immune, and reproductive functions (Briffa, 2015; Maymó, 2009). Leptin is produced by the mother, fetus, and placenta. It is expressed in syncytiotrophoblast and fetal vascular endothelial cells. Of placental production, 5 percent enters the fetal circulation, whereas 95 percent is transferred to the mother (Hauguel-de Mouzon, 2006). Leptin concentrations peak in amnionic fluid at midpregnancy (Scott-Finley, 2015).

Fetal leptin levels begin rising at approximately 34 weeks and are correlated with fetal weight. This hormone is involved in the development and maturation of the heart, brain, kidneys, and pancreas, and its levels are decreased with fetal growth restriction (Briffa, 2015). Abnormal levels have been associated with fetal growth disorders, gestational diabetes, and preeclampsia (Fasshauer, 2014). Postpartum, leptin levels decline in both the newborn and mother. Perinatal leptin is associated with the development of metabolic syndromes later in life (Briffa, 2015; Granado, 2012).

Free Fatty Acids and Triglycerides

The newborn has a large proportion of fat, which averages 15 percent of body weight (Kimura, 1991). Thus, late in pregnancy, a substantial part of the substrate transferred to the human fetus is stored as fat. Although maternal obesity raises placental fatty acid uptake and fetal fat deposition, it does not appear to affect fetal organ growth (Dubé, 2012). Neutral fat in the form of triglycerides does not cross the placenta, but glycerol does. Despite this, evidence supports that abnormal maternal concentrations of triglycerides—both low and high levels—are associated with major congenital anomalies (Nederlof, 2015).

There is preferential placental-fetal transfer of long-chain polyunsaturated fatty acids (Gil-Sanchez, 2012). Lipoprotein lipase is present on the maternal but not on the fetal side of the placenta. This arrangement favors hydrolysis of triacylglycerols in the maternal intervillous space yet preserves these neutral lipids in fetal blood. Fatty acids transferred to the fetus can be converted to triglycerides in the fetal liver.

The placental uptake and use of LDL is an alternative mechanism for fetal assimilation of essential fatty acids and amino acids (Chap. 5, Placental

Estrogen Production). LDL binds to specific receptors in the coated-pit regions of the syncytiotrophoblast microvilli. The large LDL particle, measuring about 250,000 Da, is taken up by a process of receptor-mediated endocytosis. The apoprotein and cholesterol esters of LDL are hydrolyzed by lysosomal enzymes in the syncytium to yield: (1) cholesterol for progesterone synthesis; (2) free amino acids, including essential amino acids; and (3) essential fatty acids, primarily linoleic acid.

Amino Acids

The placenta concentrates many amino acids in the syncytiotrophoblast, which are then transferred to the fetal side by diffusion. Based on data from cordocentesis blood samples, the amino acid concentration in umbilical cord plasma is greater than in maternal venous or arterial plasma (Morriss, 1994). Transport system activity is influenced by gestational age and environmental factors. These include heat stress, hypoxia, under- and overnutrition, and hormones such as glucocorticoids, growth hormone, and leptin (Briffa, 2015; Fowden, 2006). Trophoblastic mammalian target of rapamycin complex 1 (mTORC1) regulates placental amino acid transporters and modulates transfer across the placenta (Jansson, 2012). In vivo studies suggest an upregulation of transport for certain amino acids and a greater delivery rate of these to the fetuses of women with gestational diabetes associated with fetal overgrowth (Jansson, 2006a).

Proteins

Placental transfer of larger proteins is limited, but there are exceptions. IgG crosses the placenta in large amounts via endocytosis and trophoblast Fc receptors. IgG transfer depends on maternal levels of total IgG, gestational age, placental integrity, IgG subclass, and antigenic potential (Palmeira, 2012). Conversely, the larger immunoglobulins—IgA and IgM—of maternal origin are effectively excluded from the fetus.

Ions and Trace Metals

Calcium and phosphorus are actively transported from mother to fetus. Calcium is transferred for fetal skeletal mineralization (Olausson, 2012). A calcium-binding protein is produced in placenta. Parathyroid hormone-related protein (PTH-rP), as the name implies, acts as a surrogate PTH in many systems (Chap. 5, Placental Progesterone Production). PTH is not found in fetal plasma, but PTH-rP is present, suggesting that PTH-rP is the fetal parathormone. The expression of PTH-rP in cytotrophoblasts is modulated by the extracellular concentration of Ca^{2+} (Hellman, 1992). It seems possible, therefore, that PTH-rP synthesized in decidua, placenta, and other fetal tissues is important in fetal Ca^{2+} transfer and homeostasis.

Iodide transport is clearly attributable to a carrier-mediated, energy-requiring active process. And indeed, the placenta concentrates iodide. The concentrations of zinc in the fetal plasma also are greater than those in maternal plasma. Conversely, copper levels in fetal plasma are less than those in maternal plasma. This fact is of particular interest because important copper-requiring enzymes are necessary for fetal development.

Placental Sequestration of Heavy Metals

The heavy metal–binding protein metallothionein-1 is expressed in human syncytiotrophoblast. This protein binds and sequesters a host of heavy metals, including zinc, copper, lead, and cadmium. Despite this, fetal exposure is variable (Caserta, 2013). For example, lead enters the fetal environment at a level 90 percent of maternal concentrations. In contrast, placental transfer of cadmium is limited (Kopp, 2012). The most common source of environmental cadmium is cigarette smoke.

Metallothionein also binds and sequesters copper (Cu^{2+}) in placental tissue. This accounts for the low levels of Cu^{2+} in cord blood (Iyengar, 2001). It is possible that cadmium provokes metallothionein synthesis in the amnion. This may cause Cu^{2+} sequestration, a pseudo–copper deficiency, and in turn, diminished tensile strength of the amnion.

Vitamins

The concentration of vitamin A (retinol) is greater in fetal than in maternal plasma and is bound to retinol-binding protein and to prealbumin. Retinol-binding protein is transferred from the maternal compartment across the syncytiotrophoblast. The transport of vitamin C—ascorbic acid—from mother to fetus is accomplished by an energy-dependent, carrier-mediated process. Levels of principal vitamin D metabolites, including 1,25-dihydroxycholecalciferol, are greater in maternal plasma than in fetal plasma. The 1β-hydroxylation of 25-hydroxyvitamin D_3 is known to take place in placenta and in decidua.

PLACENTAL ROLE IN EMBRYOFETAL DEVELOPMENT

The placenta is the organ of transfer between mother and fetus. Within this maternal-fetal interface, oxygen and nutrients transfer from the mother to the fetus, whereas CO_2 and metabolic wastes are directed from fetus to mother. Fetal blood, which is contained in the fetal capillaries of the chorionic villi, has no direct contact with maternal blood, which remains in the intervillous space. Instead, bidirectional transfer depends on processes that allow or aid the transport through the syncytiotrophoblast that lines chorionic villi.

Over the past few years, it has become apparent that breaks in the chorionic villi permit escape of fetal cells and other blood-borne material into the maternal circulation. This leakage is the mechanism by which some D-negative women become sensitized by the erythrocytes of their D-positive fetus (Chap. 15, Red Cell Alloimmunization). In fact, after 10 weeks, 10 to 15 percent of cell-free DNA (cfDNA) in maternal plasma is placental in origin, that is, trophoblastic DNA (Norton, 2012). The escape of fetal cells can also lead to fetal microchimerism from entrance of allogeneic fetal cells, including trophoblast, into maternal blood and other organs (Rijnik, 2015). Volumes are estimated to range from 1 to 6 cells/mL at midpregnancy. Some fetal cells become “immortal” in that they persist in the maternal circulation and organs following pregnancy. As discussed in Chapter 59 (Systemic Lupus Erythematosus), the clinical corollary is that some maternal autoimmune diseases may be provoked by such microchimerism.

The Intervillous Space

Maternal blood within the intervillous space is the primary source of maternal–fetal transfer. Blood from the maternal spiral arteries directly bathes the trophoblast layer that surrounds the villi. Substances transferred from mother to fetus first enter the intervillous space and are then transported to the syncytiotrophoblast. As such, the chorionic villi and intervillous space function together as the fetal lung, gastrointestinal tract, and kidney.

Circulation within the intervillous space is described in Chapter 5 (Breaks in the Placental “Barrier”). Intervillous and uteroplacental blood flow increases throughout the first trimester of normal pregnancies (Mercé, 2009). At term, the residual volume of the intervillous space approximates 140 mL. Moreover, uteroplacental blood flow near term is estimated to be 700 to 900 mL/min, and most of this blood apparently goes to the intervillous space (Pates, 2010).

Active labor contractions reduce blood flow into the intervillous space to a degree that depends on contraction intensity. Blood pressure within the intervillous space is significantly less than uterine arterial pressure, but somewhat greater than venous pressure. The latter, in turn, varies depending on several factors, including maternal position (Nelson, 2015). When supine, for example, pressure in the lower part of the inferior vena cava is elevated, and consequently, pressure in the uterine and ovarian veins, and in turn in the intervillous space, is increased.

Placental Transfer

Substances that pass from maternal to fetal blood must first traverse the syncytiotrophoblast, the attenuated cytotrophoblast layer, the villous stroma, and finally, the fetal capillary wall. Although this histological barrier separates maternal and fetal circulations, it is not a simple physical barrier. First, throughout pregnancy, syncytiotrophoblast actively or passively permits, facilitates, and adjusts the amount and rate of substance transfer to the fetus. The maternal-facing syncytiotrophoblast surface is characterized by a complex microvillous structure. The fetal-facing basal cell membrane is the site of transfer to the intravillous space. Finally, the villous capillaries are an additional site for transport from the intravillous space into fetal blood, or vice versa. In determining the effectiveness of the human placenta as an organ of transfer, several variables are important and shown in Table 7-1. Zhao and coworkers (2014) have provided a review of the pharmacology of these interactions.

TABLE 7-1

Variables of Maternal-Fetal Substance Transfer

Maternal plasma concentration and carrier-protein binding of the substance
Maternal blood flow rate through the intervillous space
Trophoblast surface area size available for exchange
Physical trophoblast properties to permit simple diffusion
Trophoblast biochemical machinery for active transport
Substance metabolism by the placenta during transfer
Fetal intervillous capillary surface area size for exchange
Fetal blood concentration of the substance
Specific binding or carrier proteins in the fetal or maternal circulation
Villous capillary blood flow rate

Mechanisms of Transfer

Most substances with a molecular mass <500 Da pass readily through placental tissue by simple diffusion. These include oxygen, CO_2, water, most electrolytes, and anesthetic gases (Carter, 2009). Some low-molecular-weight compounds undergo transfer facilitated by syncytiotrophoblast. These are usually those that have low concentrations in maternal plasma but are essential for normal fetal development.

Insulin, steroid hormones, and thyroid hormones cross the placenta, but very slowly. The hormones synthesized in situ in the syncytiotrophoblast enter both the maternal and fetal circulations, but not equally (Chap. 5, Placental Hormones). Examples are hCG and hPL concentrations, which are much lower in fetal plasma than in maternal plasma. High-molecular-weight substances usually do not traverse the placenta, but there are important exceptions. One is immunoglobulin G—molecular weight 160,000 Da—which is transferred by way of a specific trophoblast receptor–mediated mechanism (Stach, 2014).

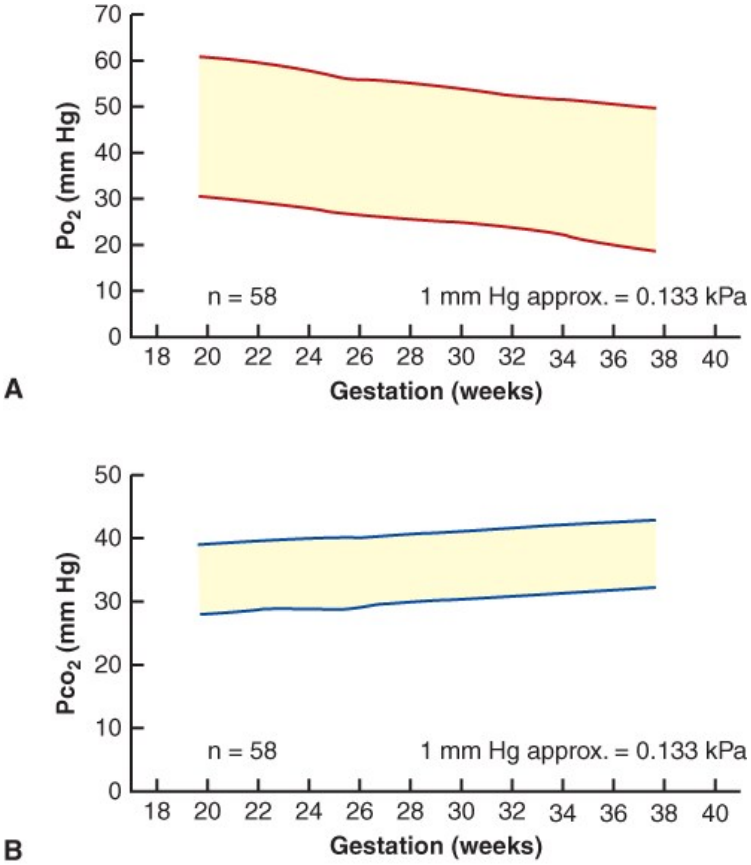
Transfer of Oxygen and Carbon Dioxide

Placental oxygen transfer is blood flow limited. Using estimated uteroplacental blood flow, Longo (1991) calculated oxygen delivery to be approximately 8 mL O_2/min/kg of fetal weight. Normal values for oxygen and CO_2 are presented in Figure 7-13. Because of the continuous passage of oxygen from maternal blood in the intervillous space to the fetus, its oxygen saturation resembles that in maternal capillaries. The average oxygen saturation of intervillous blood is estimated to be 65 to 75 percent, with a partial pressure (P_{O_2}) of 30 to 35 mm Hg. The oxygen saturation of umbilical vein blood is similar but has a somewhat lower oxygen partial pressure. Fetal hemoglobin has a higher oxygen affinity than adult hemoglobin. This is illustrated by the oxyhemoglobin disassociation curve, which is described in Chapter 47 (Positive End-Expiratory Pressure).

FIGURE 7-13

Umbilical venous cordocentesis samples obtained in fetuses being evaluated for possible intrauterine infections or hemolysis, but who were found to be healthy. **A.** Oxygen pressure (P_{O_2}). **B.** Carbon dioxide pressure (P_{CO_2}). Shaded areas represent 5th to 95th percentiles. (Modified from Ramsey, MM:

Normal Values in Pregnancy. Ramsay MM, James DK, Steer PJ, et al (eds). London, Elsevier, 1996, p 106.)



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: *Williams Obstetrics*, 25th Edition

The placenta is highly permeable to CO_2, which traverses the chorionic villus by diffusion more rapidly than oxygen. Near term, the partial pressure of carbon dioxide (Pco_2) in the umbilical arteries averages 50 mm Hg, which is approximately 5 mm Hg higher than in the maternal intervillous blood. Fetal blood has less affinity for CO_2 than does maternal blood, thereby favoring CO_2 transfer from fetus to mother. Also, mild maternal hyperventilation results in a fall in Pco_2 levels, favoring a transfer of CO_2 from the fetal compartment to maternal blood.

Selective Transfer and Facilitated Diffusion

Although simple diffusion is an important method of placental transfer, the trophoblast and chorionic villus unit demonstrate enormous selectivity in transfer. This results in different metabolite concentrations on the two sides of the villus. Importantly, the levels of many substances that are not synthesized by the fetus are several times higher in fetal than in maternal blood. Ascorbic acid is one example. This relatively low-molecular-weight substance might be expected to traverse the placenta by simple diffusion. The concentration of ascorbic acid, however, is two to four times higher in fetal plasma than in maternal plasma (Morriss, 1994). Another example is the unidirectional transfer of iron. Typically, maternal plasma iron concentration is much lower than that in her fetus. Even with severe maternal iron-deficiency anemia, the fetal hemoglobin mass is normal.

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