CHAPTER 40

Maternal & Fetal Physiology & Anesthesia

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KEY CONCEPTS

1. The minimum alveolar concentration (MAC) progressively decreases during pregnancy—at term, by as much as 40%—for all general anesthetic agents; MAC returns to normal by the third day after delivery.
2. Pregnant patients display enhanced sensitivity to local anesthetics during regional anesthesia and analgesia, and neural blockade occurs at reduced concentrations of local anesthetics; dose requirements may be reduced as much as 30%.
3. Obstruction of the inferior vena cava by the enlarging uterus distends the epidural venous plexus and increases the risk of intravascular injection during epidural anesthesia.
4. Approximately 5% of women at term develop the supine hypotension syndrome, which is characterized by hypotension associated with pallor, sweating, or nausea and vomiting. The incidence of maternal hypotension syndrome may be higher in women receiving neuraxial analgesia.
5. The reduction in gastric motility and gastroesophageal sphincter tone place the parturient at high risk for regurgitation and pulmonary aspiration.
6. Ephedrine, which has considerable β-adrenergic activity, has traditionally been considered the vasopressor of choice for hypotension during pregnancy. However, clinical studies suggest that α-adrenergic agonists such as phenylephrine and metaraminol are just as effective in treating hypotension in pregnant patients and are associated with less fetal acidosis than ephedrine.
7. Volatile inhalational anesthetics decrease blood pressure and, potentially, uteroplacental blood flow. In concentrations of less than 1 MAC, however, their effects are generally minor, consisting of dose-dependent uterine relaxation and minor reductions in uterine blood flow.
8. The greatest strain on the parturient's heart occurs immediately after delivery, when intense uterine contraction and involution suddenly relieve inferior vena caval obstruction and increase cardiac output as much as 80% above late third trimester values.
9. Current techniques employing very dilute combinations of a local anesthetic (eg, bupivacaine, 0.125% or less) and an opioid (eg, fentanyl, 5 mcg/mL or less) for epidural or combined spinal–epidural (CSE) analgesia do not appear to prolong the first stage of labor or increase the likelihood of an operative delivery.

This chapter reviews the normal physiological changes associated with pregnancy, labor, and delivery. It concludes with a description of the physiological transition from fetal to neonatal life.

PHYSIOLOGICAL CHANGES DURING PREGNANCY

Pregnancy affects most organ systems (Table 40–1). Many of these physiological changes appear to be adaptive and useful to the mother in tolerating the stresses of pregnancy, labor, and delivery. Other changes lack obvious benefits but nonetheless require special consideration in caring for the parturient.

TABLE 40–1 Average maximum physiological changes associated with pregnancy.[1]

Parameter	Change
Neurological	
MAC	–40%
Respiratory	
Oxygen consumption	+20 to 50%
Airway resistance	–35%
FRC	–20%
Minute ventilation	+50%
Tidal volume	+40%
Respiratory rate	+15%
Pao_2	+10%
$Paco_2$	–15%
HCO_3	–15%
Cardiovascular	
Blood volume	+35%
Plasma volume	+55%
Cardiac output	+40%
Stroke volume	+30%
Heart rate	+20%
Systolic blood pressure	–5%
Diastolic blood pressure	–15%
Peripheral resistance	–15%
Pulmonary resistance	–30%
Hematologic	
Hemoglobin	–20%
Platelets	–10%
Clotting factors[2]	+30 to 250%
Renal	
GFR	+50%

[1]MAC, minimum alveolar concentration; FRC, functional residual capacity; GFR, glomerular filtration rate.

[2]Varies with each factor.

Central Nervous System Effects

1 The minimum alveolar concentration (MAC) progressively decreases during pregnancy—at term, by as much as 40%—for all general anesthetic agents; MAC returns to normal by the third day after delivery. Changes in maternal hormonal and endogenous opioid levels have been implicated. Progesterone, which is sedating when given in pharmacological doses, increases up to 20 times normal at term and is at least partly responsible for this observation. A surge in β-endorphin levels during labor and delivery also likely plays a major role.

2 Pregnant patients also display enhanced sensitivity to local anesthetics during regional anesthesia and analgesia, and neural blockade occurs at reduced concentrations of local anesthetics. The term *minimum local analgesic concentration* (MLAC) is used in obstetric anesthesia to compare the relative potencies of local anesthetics and the effects of additives; MLAC is defined as the local analgesic concentration leading to satisfactory analgesia in 50% of patients (EC_{50}). Local anesthetic dose requirements during epidural anesthesia may be reduced as much as 30%, a phenomenon that appears to be hormonally mediated but may also be related to engorgement of the epidural

3 venous plexus. Obstruction of the inferior vena cava by the enlarging uterus distends the epidural venous plexus and increases epidural blood volume. The latter has three major effects: (1) decreased spinal cerebrospinal fluid volume, (2) decreased potential volume of the epidural space, and (3) increased epidural (space) pressure. The first two effects enhance the cephalad spread of local anesthetic solutions during spinal and epidural anesthesia, respectively, whereas the last may complicate identification of the epidural space (see Chapter 45). Bearing down during labor further accentuates all these effects. Positive (rather than the usual negative) epidural pressures have been recorded in parturients. Engorgement of the epidural veins also increases the likelihood of placing an epidural needle or catheter in a vein, resulting in an unintentional intravascular injection. It is unclear whether pregnancy lowers the seizure threshold for local anesthetics.

Respiratory Effects

Oxygen consumption and minute ventilation progressively increase during pregnancy. Tidal volume and, to a lesser extent, respiratory rate and inspiratory reserve volume also increase. By term, both oxygen consumption and minute ventilation have increased up to 50%. $Paco_2$ decreases to 28–32 mm Hg; significant respiratory alkalosis is prevented by a compensatory decrease in plasma bicarbonate concentration. Hyperventilation may also increase Pao_2 slightly. Elevated levels of 2,3-diphosphoglycerate offset the effect of hyperventilation on hemoglobin's affinity for oxygen (see Chapter 23). The P_{50} for hemoglobin increases from 27 to 30 mm Hg; the combination of the latter with an increase in cardiac output (see section on Cardiovascular Effects below) enhances oxygen delivery to tissues.

The maternal respiratory pattern changes as the uterus enlarges. In the third trimester, elevation of the diaphragm is compensated by an increase in the anteroposterior diameter of the chest; diaphragmatic motion, however, is not restricted. Thoracic breathing is favored over abdominal breathing. Both vital capacity and closing capacity are minimally affected, but functional residual capacity (FRC) decreases up to 20% at term; FRC returns to normal within 48 h of delivery. This decrease is principally due to a reduction in expiratory reserve volume as a result of larger than normal tidal volumes. Flow–volume loops are unaffected, and airway resistance decreases. Physiological dead space decreases but intrapulmonary shunting increases toward term. A chest film may show prominent vascular markings due to increased pulmonary blood volume and an elevated diaphragm. Pulmonary vasodilation prevents pulmonary pressures from rising.

The combination of decreased FRC and increased oxygen consumption promotes rapid oxygen desaturation during periods of apnea. Preoxygenation (denitrogenation) prior to induction of general anesthesia is therefore mandatory to avoid hypoxemia in pregnant patients. Closing volume exceeds FRC in some pregnant women when they are supine at term. Under these conditions, atelectasis and hypoxemia readily occur. The decrease in FRC coupled with the increase in minute ventilation accelerates the uptake of all inhalational anesthetics. The reduction in dead space narrows the arterial end-tidal CO_2 gradient.

Capillary engorgement of the respiratory mucosa during pregnancy predisposes the upper airways to trauma, bleeding, and obstruction. Gentle laryngoscopy and smaller endotracheal tubes (6–6.5 mm) should be employed during general anesthesia.

Cardiovascular Effects

Cardiac output and blood volume increase to meet accelerated maternal and fetal metabolic demands. An increase (55%) in plasma volume in excess of an increase in red cell mass (45%) produces dilutional anemia and reduces blood viscosity. Hemoglobin concentration, however, usually remains greater than 11 g/dL. Moreover, in terms of tissue oxygen delivery, the reduction in hemoglobin concentration is offset by the increase in cardiac output and the rightward shift of the hemoglobin dissociation curve (see the section on Respiratory Effects). A decrease in systemic vascular resistance by the second trimester decreases both diastolic and, to a lesser degree, systolic blood pressure. The response to adrenergic agents and vasoconstrictors is blunted.

At term, blood volume has increased by 1000–1500 mL in most women, allowing them to easily tolerate the blood loss associated with delivery; total blood volume reaches 90 mL/kg. Average blood loss during vaginal delivery is 400–500 mL, compared with 800–1000 mL for a cesarean section. Blood volume does not return to normal until 1–2 weeks after delivery.

The increase in cardiac output (40% at term) is due to increases in both heart rate (20%) and stroke volume (30%). Cardiac chambers enlarge and myocardial hypertrophy is often noted on echocardiography. Pulmonary artery, central venous, and pulmonary artery wedge pressures remain unchanged. Most of these effects are observed in the first and, to a lesser extent, the second trimester. In the third trimester, cardiac output does not appreciably rise, except during labor. The greatest increases in cardiac output are seen during labor and immediately after delivery (see the section on Effect of Labor on Maternal Physiology). Cardiac output often does not return to normal until 2 weeks after delivery.

Decreases in cardiac output can occur in the supine position after week 20 of pregnancy. Such decreases have been shown to be secondary to impeded venous return to the heart as the enlarging uterus compresses the inferior vena cava. 4 Approximately 5% of women at term develop the supine hypotension syndrome (aortocaval compression), which is characterized by hypotension associated with pallor, sweating, or nausea and vomiting. The cause of this syndrome appears to be complete or near-complete occlusion of the inferior vena cava by the gravid uterus. When combined with the hypotensive effects of regional or general anesthesia, aortocaval compression can readily produce fetal asphyxia. Turning the patient on her side typically restores venous return from the lower body and corrects the hypotension in such instances. This maneuver is most readily accomplished by placing a wedge (>15°) under the right hip. The gravid uterus also compresses the aorta in most parturients when they are supine. This latter effect decreases blood flow to the lower extremities and, more importantly, to the uteroplacental circulation. Uterine contraction reduces caval compression but exacerbates aortic compression.

Chronic partial caval obstruction in the third trimester predisposes to venous stasis, phlebitis, and edema in the lower extremities. Moreover, compression of the inferior vena cava below the diaphragm distends and increases blood flow through the paravertebral venous plexus (including the epidural veins), and to a minor degree, the abdominal wall.

Lastly, elevation of the diaphragm shifts the heart's position in the chest, resulting in the appearance of an enlarged heart on a plain chest film and in left axis deviation and T wave changes on the electrocardiogram. Physical examination often reveals a systolic ejection flow murmur (grade I or II) and exaggerated splitting of the first heart sound (S_1); a third heart sound (S_3) may be audible. A few patients develop small, asymptomatic pericardial effusion.

Renal & Gastrointestinal Effects

Renal plasma flow and the glomerular filtration rate increase during pregnancy, and as a result serum creatinine and blood urea nitrogen may decrease to 0.5–0.6 mg/dL and 8–9 mg/dL, respectively. A decreased renal tubular threshold for glucose and amino acids is common and often results in mild glycosuria (1–10 g/d) or proteinuria (<300 mg/d), or both. Plasma osmolality decreases by 8–10 mOsm/kg.

Gastroesophageal reflux and esophagitis are common during pregnancy. Gastric motility is reduced, and upward and anterior displacement of the stomach by the uterus promotes incompetence 5 of the gastroesophageal sphincter. These factors place the parturient at high risk for regurgitation and pulmonary aspiration. However, neither gastric acidity nor gastric volume changes significantly during pregnancy. Opioids and anticholinergics reduce lower esophageal sphincter pressure, may facilitate gastroesophageal reflux, and delay gastric emptying.

Hepatic Effects

Overall hepatic function and blood flow are unchanged; minor elevations in serum transaminases and lactic dehydrogenase levels may be observed in the third trimester. Mild elevations in serum alkaline phosphatase are due to its secretion by the placenta. A mild decrease in serum albumin is due to an expanded plasma volume, and as a result, colloid oncotic pressure is reduced. A 25–30% decrease in serum pseudocholinesterase activity is also present at term but rarely produces significant prolongation of succinylcholine's action. The breakdown of ester-type local anesthetics is not appreciably altered. Pseudocholinesterase activity may not return to normal until up to 6 weeks postpartum. High progesterone levels appear to inhibit the release of cholecystokinin, resulting in incomplete emptying of the gallbladder. The latter, together with altered bile acid composition, can predispose to the formation of cholesterol gallstones during pregnancy.

Hematological Effects

Pregnancy is associated with a hypercoagulable state that may be beneficial in limiting blood loss at delivery. Fibrinogen and concentrations of factors VII, VIII, IX, X, and XII all increase; only factor XI levels may decrease. Accelerated fibrinolysis can be observed late in the third trimester. In addition to the dilutional anemia (see the section on Cardiovascular

Effects), leukocytosis (up to 21,000/μL) and a 10% decrease in platelet count may be encountered during the third trimester. Because of fetal utilization, iron and folate deficiency anemias readily develop if supplements of these nutrients are not taken.

Metabolic Effects

Complex metabolic and hormonal changes occur during pregnancy. Altered carbohydrate, fat, and protein metabolism favors fetal growth and development. These changes resemble starvation, because blood glucose and amino acid levels are low whereas free fatty acids, ketones, and triglyceride levels are high. Nonetheless, pregnancy is a diabetogenic state; insulin levels steadily rise during pregnancy. Secretion of human placental lactogen, also called human chorionic somatomammotropin, by the placenta is probably responsible for the relative insulin resistance associated with pregnancy. Pancreatic beta cell hyperplasia occurs in response to an increased demand for insulin secretion.

Secretion of human chorionic gonadotropin and elevated levels of estrogens promote hypertrophy of the thyroid gland and increase thyroid-binding globulin; although T_4 and T_3 levels are elevated, free T_4, free T_3, and thyrotropin (thyroid-stimulating hormone) remain normal. Serum calcium levels decrease, but ionized calcium concentration remains normal.

Musculoskeletal Effects

Elevated levels of relaxin throughout pregnancy help prepare for delivery by softening the cervix, inhibiting uterine contractions, and relaxing the pubic symphysis and pelvic joints. Ligamentous laxity of the spine increases the risk of back injury. The latter may contribute to the relatively high incidence of back pain during pregnancy.

UTEROPLACENTAL CIRCULATION

A normal uteroplacental circulation (Figure 40–1) is critical in the development and maintenance of a healthy fetus. Uteroplacental insufficiency is an important cause of intrauterine fetal growth retardation, and when severe, can result in fetal demise. The integrity of this circulation is, in turn, dependent on both adequate uterine blood flow and normal placental function.

Uterine Blood Flow

At term, uterine blood flow represents about 10% of the cardiac output, or 600–700 mL/min (compared with 50 mL/min in the nonpregnant uterus). Eighty percent of uterine blood flow normally supplies the placenta; the remainder goes to the myometrium. Pregnancy maximally dilates the uterine vasculature, so that autoregulation is absent, but the uterine vasculature remains sensitive to α-adrenergic agonists. Uterine blood flow is not usually significantly affected by respiratory gas tensions, but extreme hypocapnia ($Paco_2$ <20 mm Hg) can reduce uterine blood flow and causes fetal hypoxemia and acidosis.

Blood flow is directly proportionate to the difference between uterine arterial and venous pressures but inversely proportionate to uterine vascular resistance. Although not under appreciable neural control, the uterine vasculature has α-adrenergic and possibly some β-adrenergic receptors.

Three major factors decrease uterine blood flow during pregnancy: (1) systemic hypotension, (2) uterine vasoconstriction, and (3) uterine contractions. Common causes of hypotension during pregnancy include aortocaval compression, hypovolemia, and sympathetic blockade following regional anesthesia. Stress-induced release of endogenous catecholamines (sympathoadrenal activation) during labor causes uterine arterial vasoconstriction. Any drug with α-adrenergic activity (eg, phenylephrine) potentially is capable of decreasing uterine blood flow by vasoconstriction. Ephedrine, which has considerable β-adrenergic activity, has traditionally been considered the vasopressor of choice for hypotension during pregnancy. However, clinical studies suggest that α-adrenergic agonists such as phenylephrine and metaraminol are just as effective in treating hypotension in pregnant patients and are associated with less fetal acidosis than ephedrine.

Paradoxically, hypertensive disorders are often associated with decreased uterine blood flow due to generalized vasoconstriction. **Uterine contractions decrease uterine blood flow by elevating uterine venous pressure and compressing arterial vessels as they traverse the myometrium.** Hypertonic

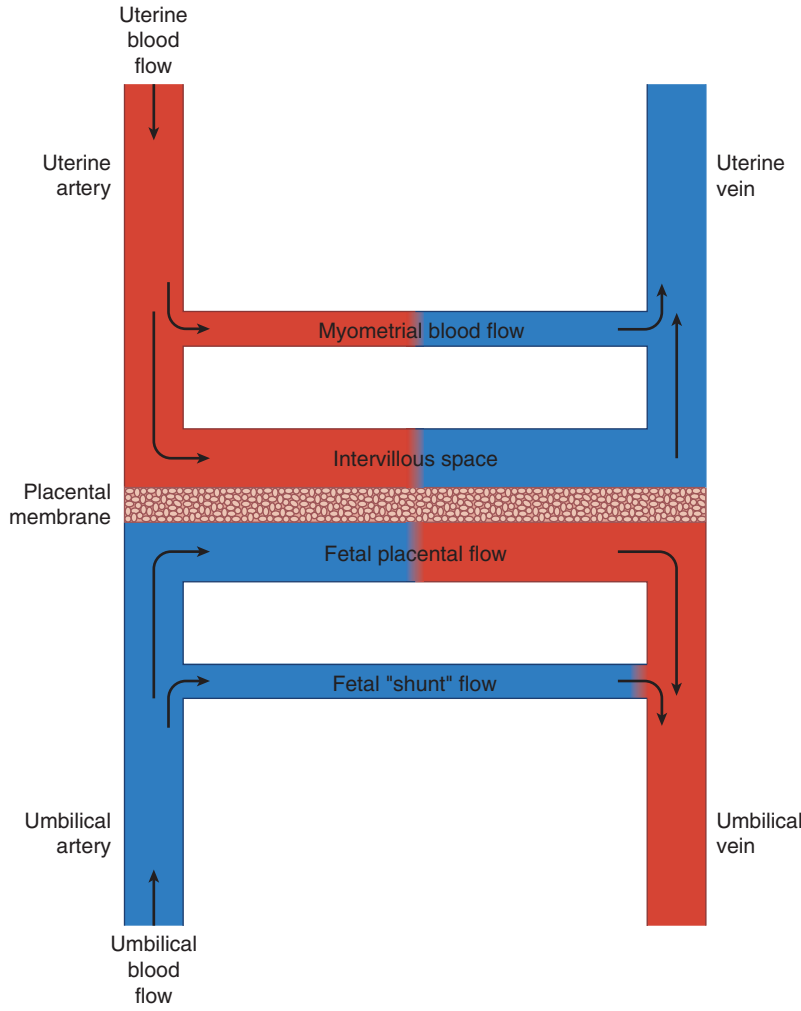

FIGURE 40–1 The uteroplacental circulation. (Reproduced, with permission, from Shnider S, Levinson G: *Anesthesia for Obstetrics*, 2nd ed. Williams & Wilkins, 1987.)

contractions during labor or during oxytocin infusions can critically compromise uterine blood flow.

Placental Function

The fetus is dependent on the placenta for respiratory gas exchange, nutrition, and waste elimination. The placenta is formed by both maternal and fetal tissues and derives a blood supply from each. The resulting exchange membrane has a functional area of about 1.8 m^2.

A. Physiological Anatomy

The placenta (Figure 40–2) is composed of projections of fetal tissue (villi) that lie in maternal vascular spaces (intervillous spaces). As a result of this arrangement, the fetal capillaries within villi readily exchange substances with the maternal blood that bathes them. Maternal blood in the intervillous spaces is derived from spiral branches of the uterine artery and drains into the uterine veins. Fetal blood within villi is derived from the umbilical cord via two umbilical arteries and returns to the fetus via a single umbilical vein.

B. Placental Exchange

Placental exchange can occur by one of six mechanisms:

1. Diffusion—Respiratory gases and small ions are transported by diffusion. Most drugs used in

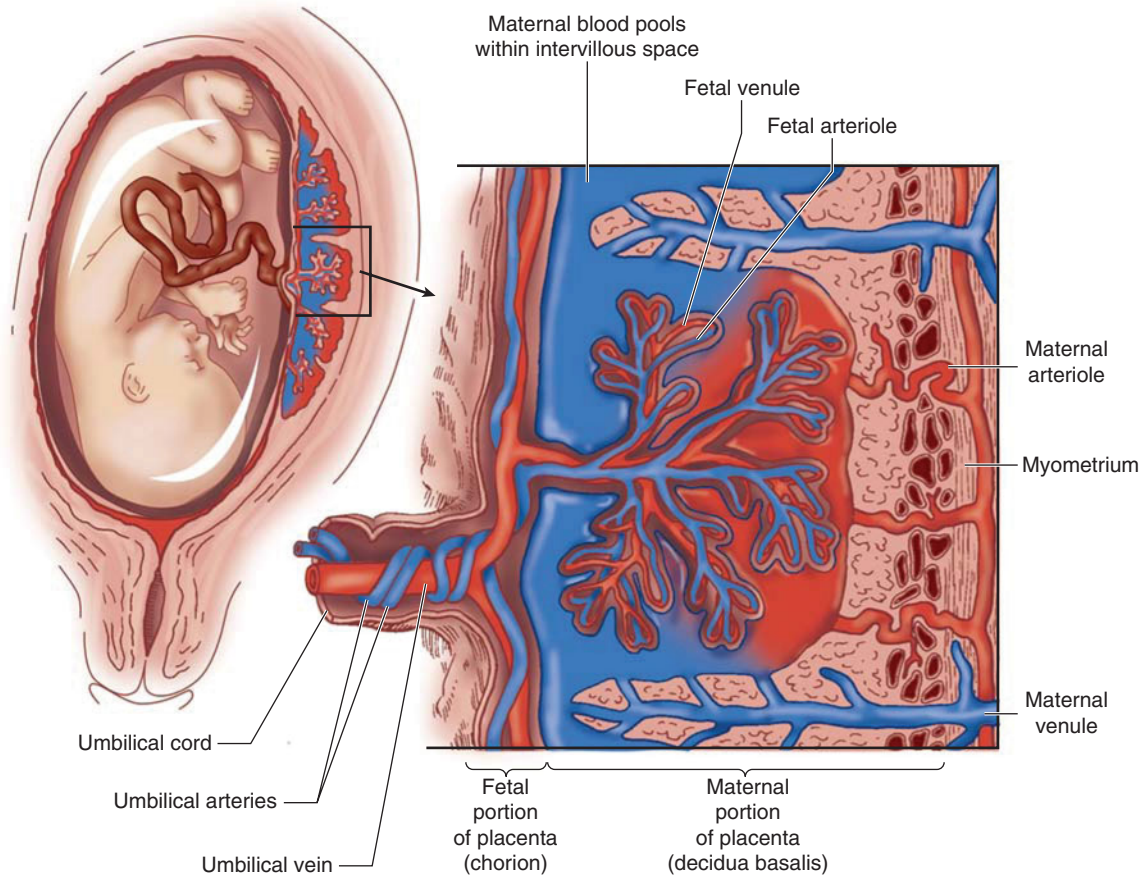

FIGURE 40–2 The placenta.

anesthesia have molecular weights well under 1000 and consequently can readily diffuse across the placenta.

2. Osmotic and hydrostatic pressure (bulk flow)— Water moves across by osmotic and hydrostatic pressures. Water enters the fetal circulation in quantities greater than any other substance.

3. Facilitated diffusion—Glucose enters the fetal circulation down the concentration gradient (no energy is consumed) facilitated by a specific transporter molecule.

4. Active transport—Amino acids, vitamin B_{12}, fatty acids, and some ions (calcium and phosphate) utilize this mechanism.

5. Vesicular transport—Large molecules, such as immunoglobulins, are transported by pinocytosis. Iron enters the fetal circulation in this way, facilitated by ferritin and transferrin.

6. Breaks—Breaks in the placental membrane may permit mixing of maternal and fetal blood. This probably underlies Rh sensitization (see Chapter 51). Rh sensitization occurs most commonly during delivery.

Respiratory Gas Exchange

At term, fetal oxygen consumption averages about 7 mL/min per kilogram of fetal body weight. Fortunately, because of multiple adaptive mechanisms, the normal fetus at term can survive 10 min or longer instead of the expected 2 min in a state of total oxygen deprivation. Partial or complete oxygen deprivation can result from umbilical cord

compression, umbilical cord prolapse, placental abruption, severe maternal hypoxemia, or hypotension. Compensatory fetal mechanisms include redistribution of blood flow primarily to the brain, heart, placenta, and adrenal gland; decreased oxygen consumption; and anaerobic metabolism.

Transfer of oxygen across the placenta is dependent on the ratio of maternal uterine blood flow to fetal umbilical blood flow. The reserve for oxygen transfer is small even during normal pregnancy. Normal fetal blood from the placenta has a Pao_2 of only 30–35 mm Hg. To aid oxygen transfer, the fetal hemoglobin oxygen dissociation curve is shifted to the left such that fetal hemoglobin has greater affinity for oxygen than does maternal hemoglobin (whose curve is already shifted to the right; see the section on Respiratory Effects). In addition, fetal hemoglobin concentration is usually 15 g/dL (compared with approximately 12 g/dL in the mother).

Carbon dioxide readily diffuses across the placenta. Maternal hyperventilation (see the section on Respiratory Effects) increases the gradient for the transfer of carbon dioxide from the fetus into the maternal circulation. Fetal hemoglobin has less affinity for carbon dioxide than do adult forms of hemoglobin. Carbon monoxide readily diffuses across the placenta, and fetal hemoglobin has greater affinity for carbon monoxide than do adult forms.

Placental Transfer of Anesthetic Agents

Transfer of a drug across the placenta is reflected by the ratio of its fetal umbilical vein to maternal venous concentrations (UV/MV), whereas its uptake by fetal tissues can be correlated with the ratio of its fetal umbilical artery to umbilical vein concentrations (UA/UV). Fetal effects of drugs administered to parturients depend on multiple factors, including route of administration (oral, intramuscular, intravenous, epidural, or intrathecal), dose, timing of administration (both relative to delivery as well as contractions), and maturity of the fetal organs (brain and liver). Thus, a drug given hours before delivery or as a single intravenous bolus during a uterine contraction just prior to delivery (when uterine blood flow is maximally reduced) is unlikely to produce high fetal levels. Fortunately, current anesthetic techniques for labor and delivery generally have minimal fetal effects despite significant placental transfer of anesthetic agents and adjuncts.

All inhalational agents and most intravenous agents freely cross the placenta. Inhalational agents generally produce little fetal depression when they are given in limited doses (<1 MAC) and delivery occurs within 10 min of induction. Ketamine, propofol, and benzodiazepines readily cross the placenta and can be detected in the fetal circulation. Fortunately, when these agents (with the exception of benzodiazepines) are administered in usual induction doses, drug distribution, metabolism, and possibly placental uptake may limit fetal effects. Although most opiates readily cross the placenta, their effects on neonates at delivery vary considerably. Newborns appear to be more sensitive to the respiratory depressant effect of morphine compared with other opioids. Although meperidine produces respiratory depression, peaking 1–3 h after administration, it produces less than morphine; butorphanol and nalbuphine produce even less respiratory depression but still may have significant neurobehavioral depressant effects. Although fentanyl readily crosses the placenta, it appears to have minimal neonatal effects unless larger intravenous doses (>1 mcg/kg) are given immediately before delivery. Epidural or intrathecal fentanyl, sufentanil, and, to a lesser extent, morphine, generally produce minimal neonatal effects. Alfentanil causes neonatal depression similar to meperidine. Remifentanil also readily crosses the placenta and has the potential to produce respiratory depression in newborns. Fetal blood concentrations of remifentanil are generally about half those of the mother just prior to delivery. The UA/UV ratio is about 30%, suggesting fairly rapid metabolism of remifentanil in the neonate. The highly ionized nature of muscle relaxants impedes placental transfer, resulting in minimal effects on the fetus.

Local anesthetics are weakly basic drugs that are principally bound to α_1-acid glycoprotein. Placental transfer depends on three factors: (1) pK_a (see Chapter 16), (2) maternal and fetal pH, and (3) degree of protein binding. Except for chloroprocaine, fetal acidosis increases fetal-to-maternal drug ratios because binding of hydrogen ions to the nonionized form causes trapping of the local anesthetic

in the fetal circulation. Highly protein-bound agents diffuse slowly across the placenta; thus, greater protein binding of bupivacaine and ropivacaine, compared with that of lidocaine, likely accounts for their lower fetal blood levels. Chloroprocaine has the least placental transfer because it is rapidly broken down by plasma cholinesterase in the maternal circulation.

Most commonly used anesthetic adjuncts also readily cross the placenta. Thus, maternally administered ephedrine, β-adrenergic blockers (such as labetalol and esmolol), vasodilators, phenothiazines, antihistamines (H_1 and H_2), and metoclopramide are transferred to the fetus. Atropine and scopolamine, but not glycopyrrolate, cross the placenta; the latter's quaternary ammonium (ionized) structure results in only limited transfer.

Effect of Anesthetic Agents on Uteroplacental Blood Flow

Intravenous anesthetic agents have variable effects on uteroplacental blood flow. Propofol and barbiturates are typically associated with small reductions in uterine blood flow due to mild to moderate, dose-dependent decreases in maternal blood pressure. A small induction dose, however, can produce greater reductions in blood flow as a result of sympathoadrenal activation (due to light anesthesia). Ketamine in doses of less than 1.5 mg/kg does not appreciably alter uteroplacental blood flow; its hypertensive effect typically counteracts any vasoconstriction. Uterine hypertonus may occur with ketamine at doses of more than 2 mg/kg. Etomidate likely has minimal effects, but its actions on uteroplacental circulation have not been well-described.

7 Volatile inhalational anesthetics decrease blood pressure and, potentially, uteroplacental blood flow. In concentrations of less than 1 MAC, however, their effects are generally minor, consisting of dose-dependent uterine relaxation and minor reductions in uterine blood flow. Nitrous oxide has minimal effects on uterine blood flow when administered with a volatile agent. In animal studies, nitrous oxide alone can vasoconstrict the uterine arteries.

High blood levels of local anesthetics—particularly lidocaine—cause uterine arterial vasoconstriction. Such levels are seen only with unintentional intravascular injections and occasionally following paracervical blocks (in which the injection site is in close proximity to the uterine arteries), and local absorption or injection into these vessels cannot be ruled out). Spinal and epidural anesthesia typically do not decrease uterine blood flow except when arterial hypotension occurs. Moreover, uterine blood flow during labor may actually improve in preeclamptic patients following epidural anesthesia; a reduction in circulating endogenous catecholamines likely decreases uterine vasoconstriction. The addition of dilute concentrations of epinephrine to local anesthetic solutions does not appreciably alter uterine blood flow. Intravascular uptake of the epinephrine from the epidural space may result in only minor systemic β-adrenergic effects.

PHYSIOLOGY OF NORMAL LABOR

On average, labor commences 40 ± 2 weeks following the last menstrual period. The factors involved in the initiation of labor likely involve distention of the uterus, enhanced myometrial sensitivity to oxytocin, and altered prostaglandin synthesis by fetal membranes and decidual tissues. Although circulating oxytocin levels often do not increase at the beginning of labor, the number of myometrial oxytocin receptors rapidly increases. Several prodromal events usually precede true labor approximately 2–4 weeks prior to delivery: the fetal presenting part settles into the pelvis (lightening); patients develop uterine (Braxton Hicks) contractions that are characteristically irregular in frequency, duration, and intensity; and the cervix softens and thins out (cervical effacement). Approximately 1 week to 1 h before true labor, the cervical mucous plug (which is often bloody) breaks free (*bloody show*).

True labor begins when the sporadic Braxton Hicks contractions increase in strength (25–60 mm Hg), coordination, and frequency (15–20 min apart). Amniotic membranes may rupture spontaneously prior or subsequent to the onset of true labor. Following progressive cervical dilation, the contractions propel first the fetus and then the placenta through the pelvis and perineum. By convention, labor is divided into three stages. The first stage is defined by the onset of true labor and ends with

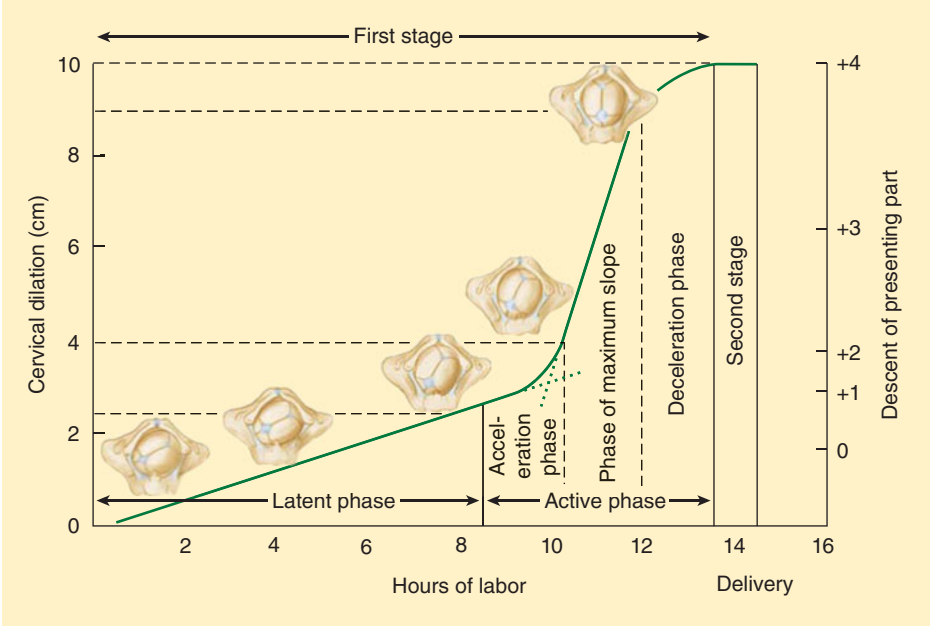

FIGURE 40–3 The course of normal labor. (Reproduced, with permission, from DeCherney AH, Pernoll ML [editors]: *Current Obstetric & Gynecologic Diagnosis & Treatment*, 9th ed. McGraw-Hill, 2001.)

complete cervical dilation. The second stage begins with full cervical dilation, is characterized by fetal descent, and ends with complete delivery of the fetus. Finally, the third stage extends from the birth of the baby to the delivery of the placenta.

Based on the rate of cervical dilation, the first stage is further divided into a slow latent phase followed by a faster active phase (**Figure 40–3**). The latent phase is characterized by progressive cervical effacement and minor dilation (2–4 cm). The subsequent active phase is characterized by more frequent contractions (3–5 min apart) and progressive cervical dilation up to 10 cm. The first stage usually lasts 8–12 h in nulliparous patients and about 5–8 h in multiparous patients.

Contractions during the second stage occur 1.5–2 min apart and last 1–1.5 min. Although contraction intensity does not appreciably change, the parturient, by bearing down, can greatly augment intrauterine pressure and facilitate expulsion of the fetus. The second stage usually lasts 15–120 min and the third stage typically 15–30 min.

The course of labor is monitored by uterine activity, cervical dilation, and fetal descent. Uterine activity refers to the frequency and magnitude of uterine contractions. The latter may be measured directly, with a catheter inserted through the cervix, or indirectly, with a tocodynamometer applied externally around the abdomen. Cervical dilation and fetal descent are assessed by pelvic examination. Fetal station refers to the level of descent (in centimeters) of the presenting part relative to the ischial spines (eg, –1 or +1).

Effect of Labor on Maternal Physiology

During intense painful contractions, maternal minute ventilation may increase up to 300%. Oxygen consumption also increases by an additional 60% above third-trimester values. With excessive hyperventilation, $Paco_2$ may decrease below 20 mm Hg. Marked hypocapnia can cause periods of hypoventilation and transient maternal and fetal hypoxemia between contractions. Excessive maternal hyperventilation also reduces uterine blood flow and promotes fetal acidosis.

Each contraction places an additional burden on the heart by displacing 300–500 mL of blood from the uterus into the central circulation

(analogous to an autotransfusion). Cardiac output rises 45% over third-trimester values. The greatest strain on the heart, however, occurs immediately after delivery, when intense uterine contraction and involution suddenly relieve inferior vena caval obstruction and increase cardiac output as much as 80% above late third trimester values.

Effect of Anesthetic Agents on Uterine Activity & Labor

A. Inhalational Agents

Sevoflurane, desflurane, isoflurane, and halothane depress uterine activity equally at equipotent doses; all cause dose-dependent uterine relaxation. Low doses (<0.75 MAC) of these agents, however, do not interfere with the effect of oxytocin on the uterus. Higher doses can result in uterine atony and increase blood loss at delivery. Nitrous oxide has minimal, if any, effects.

B. Parenteral Agents

Opioids minimally decrease the progression of labor; ketamine, in doses of less than 2 mg/kg, appears to have little effect.

C. Regional Anesthesia

The administration of epidural analgesia is usually based upon the patient's choice, and it is often utilized for patients with maternal or fetal factors that increase the likelihood of prolonged labor or cesarean delivery (Table 40–2). Current evidence indicates that dilute combinations of a local anesthetic (eg, bupivacaine, 0.125% or less) and an opioid (eg, fentanyl, 5 mcg/mL or less) for epidural or combined spinal–epidural (CSE) analgesia do not prolong labor or increase the likelihood of operative delivery.

When greater concentrations of local anesthetic (eg, bupivacaine, 0.25%) are used for continuous epidural analgesia, the second stage of labor may be prolonged by approximately 15–30 min. Intense regional analgesia/anesthesia can remove the urge to bear down during the second stage (Ferguson reflex), and motor weakness can impair expulsive efforts, often prolonging the second stage of delivery. Use of dilute local anesthetic–opioid mixtures can preserve motor function and allow effective pushing. Intravenous fluid loading (crystalloid boluses) is often used to prevent or reduce the severity of hypotension following an epidural injection. So-called fluid loading does not reduce the incidence of hypotension and has been shown to reduce endogenous oxytocin secretion from the pituitary and transiently decrease uterine activity. Epinephrine-containing local anesthetic solutions could theoretically prolong the first stage of labor if absorption of epinephrine from the epidural space results in significant systemic β-adrenergic effects. Prolongation of labor is generally not clinically observed with very dilute (eg, 1:400,000) epinephrine-containing local anesthetics.

TABLE 40–2 Factors that prolong labor, increase the likelihood of cesarean section, and often cause patients to request an epidural.

Primigravida
Prolonged labor
High parenteral analgesic requirements
Use of oxytocin
Large baby
Small pelvis
Fetal malpresentation

D. Vasopressors

Uterine muscle has both α and β receptors. α_1-Receptor stimulation causes uterine contraction, whereas β_2-receptor stimulation produces relaxation. Large doses of α-adrenergic agents, such as phenylephrine, in addition to causing uterine arterial constriction, can produce tetanic uterine contractions. Small doses of phenylephrine (40 mcg) may increase uterine blood flow in normal parturients by raising arterial blood pressure. In contrast, ephedrine has little effect on uterine contractions.

E. Oxytocin

Oxytocin (Pitocin) is usually administered intravenously to induce or augment uterine contractions or to maintain uterine tone postpartum. It has a half-life of 3–5 min. Induction doses for labor are 0.5–8 mU/min. **Complications include fetal distress due to hyperstimulation, uterine tetany, and, less commonly, maternal water retention**

(antidiuretic effect). Rapid intravenous infusion can cause transient systemic hypotension due to relaxation of vascular smooth muscle; reflex tachycardia may also be noted.

Uterine atony is the most common cause of severe postpartum hemorrhage. Immediate administration of oxytocin after delivery is a standard measure to prevent this complication. Despite this practice, uterine atony complicates 4–6% of pregnancies. The concentration of volatile anesthetics should be reduced to 0.5 MAC in obstetric patients undergoing general anesthesia for cesarean delivery to avoid the uterine-relaxing effects of these drugs. Second-line oxytocics are methylergonovine (Methergine) and carboprost tromethamine (Hemabate).

F. Ergot Alkaloids

Methylergonovine (Methergine) causes intense and prolonged uterine contractions. It is therefore given only after delivery (postpartum) to treat uterine atony. Moreover, because it also constricts vascular smooth muscle and can cause severe hypertension if given as an intravenous bolus, it is usually administered only as a single 0.2 mg dose intramuscularly or in dilute form as an intravenous infusion over 10 minutes.

G. Prostaglandins

Carboprost tromethamine (Hemabate, prostaglandin $F_{2\alpha}$) is a synthetic analogue of prostaglandin F_2 that stimulates uterine contractions. It is often used to treat refractory postpartum hemorrhage. An initial dose of 0.25 mg intramuscularly may be repeated every 15–90 min to a maximum of 2 mg. Common side effects include nausea, vomiting, bronchoconstriction, and diarrhea. It is contraindicated in patients with bronchial asthma. Prostaglandin E_1 (Cytotec, rectal suppository) or E_2 (Dinoprostone, vaginal suppository) is sometimes administered and has no bronchoconstricting effect.

H. Magnesium

Magnesium is used in obstetrics both to stop premature labor (tocolysis) and to prevent eclamptic seizures. It is usually administered as a 4 g intravenous loading dose (over 20 min) followed by a 2 g/h infusion. Therapeutic serum levels are considered to be 6–8 mg/dL. Serious side effects include hypotension, heart block, muscle weakness, and sedation. Magnesium in these doses and concentrations intensifies neuromuscular blockade from nondepolarizing agents.

H. β_2 Agonists

The β_2-adrenergic agonists ritodrine and terbutaline inhibit uterine contractions and are used to treat premature labor.

FETAL PHYSIOLOGY

The placenta, which receives nearly half the fetal cardiac output, is responsible for respiratory gas exchange. As a result, the lungs receive little blood flow and the pulmonary and systemic circulations are parallel instead of in series, as in the adult (**Figures 40–4** and **40–5**). This arrangement is made possible by two cardiac shunts—the foramen ovale and the ductus arteriosus:

1. Well-oxygenated blood from the placenta (approximately 80% oxygen saturation) mixes with venous blood returning from the lower body (25% oxygen saturation) and flows via the inferior vena cava into the right atrium.
2. Right atrial anatomy preferentially directs blood flow from the inferior vena cava (67% oxygen saturation) through the foramen ovale into the left atrium.
3. Left atrial blood is then pumped by the left ventricle to the upper body (mainly the brain and the heart).
4. Poorly oxygenated blood from the upper body returns via the superior vena cava to the right atrium.
5. Right atrial anatomy preferentially directs flow from the superior vena cava into the right ventricle.
6. Right ventricular blood is pumped into the pulmonary artery.
7. Because of high pulmonary vascular resistance, 95% of the blood ejected from the right ventricle (60% oxygen saturation) is shunted across the ductus arteriosus, into the descending aorta, and back to the placenta and lower body.

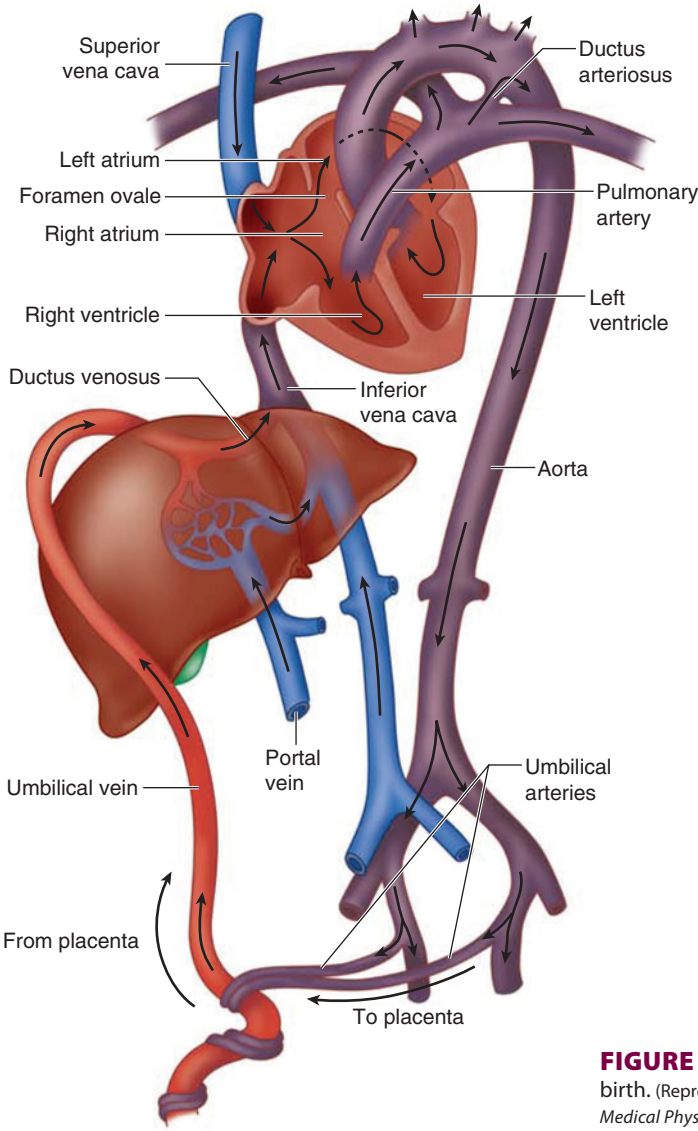

FIGURE 40–4 The fetal circulation before and after birth. (Reproduced, with permission, from Ganong WF: *Review of Medical Physiology*, 24th ed. McGraw-Hill, 2012.)

The parallel circulation results in unequal ventricular flows; the right ventricle ejects two thirds of the combined ventricular outputs, whereas the left ventricle ejects only one third.

Up to 50% of the well-oxygenated blood in the umbilical vein can pass directly to the heart via the ductus venosus, bypassing the liver. The remainder of the blood flow from the placenta mixes with blood from the portal vein (via the portal sinus) and passes through the liver before reaching the heart. The latter may be important in allowing relatively rapid hepatic degradation of drugs (or toxins) that are absorbed from the maternal circulation.

In contrast to the fetal circulation, which is established very early during intrauterine life, maturation of the lungs lags behind. Extrauterine survival is not possible until after 24–25 weeks of gestation, when pulmonary capillaries are formed and come to lie in close approximation to an immature alveolar epithelium. At 30 weeks, the cuboidal alveolar epithelium

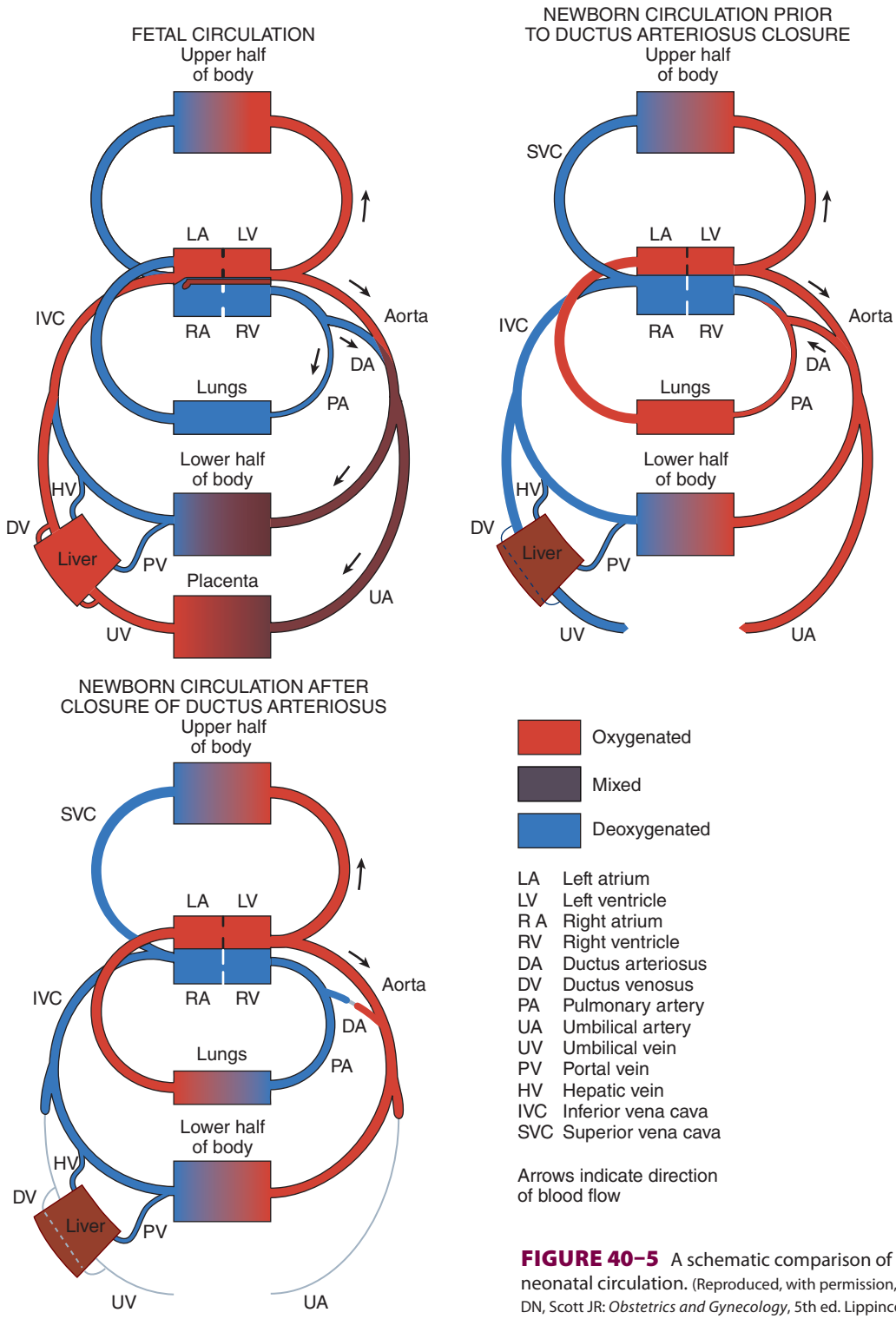

FIGURE 40–5 A schematic comparison of fetal and neonatal circulation. (Reproduced, with permission, from Danforth DN, Scott JR: *Obstetrics and Gynecology*, 5th ed. Lippincott, 1986.)

flattens out and begins to produce pulmonary surfactant. This substance provides alveolar stability and is necessary to maintain normal lung expansion after birth (see Chapter 23). Sufficient pulmonary surfactant is usually present after 34 weeks of gestation. Administration of glucocorticoids to the mother may accelerate fetal surfactant production.

PHYSIOLOGICAL TRANSITION OF THE FETUS AT BIRTH

The most profound adaptive changes at birth involve the circulatory and respiratory systems. Failure to make this transition successfully results in fetal death or permanent neurological damage.

At term, the fetal lungs are developed but contain about 90 mL of a plasma ultrafiltrate. During expulsion of the fetus at delivery, this fluid is normally squeezed from the lungs by the forces of the pelvic muscles and the vagina acting on the baby (the vaginal squeeze). Any remaining fluid is reabsorbed by the pulmonary capillaries and lymphatics. Small (preterm) neonates and neonates delivered via cesarean section do not benefit from the vaginal squeeze and thus typically have greater difficulty in maintaining respirations (transient tachypnea of the newborn). Respiratory efforts are normally initiated within 30 s after birth and become sustained within 90 s. Mild hypoxia and acidosis as well as sensory stimulation—cord clamping, pain, touch, and noise—help initiate and sustain respirations, whereas the outward recoil of the chest at delivery aids in filling the lungs with air.

Lung expansion increases both alveolar and arterial oxygen tensions and decreases pulmonary vascular resistance. The increase in oxygen tension is a potent stimulus for pulmonary arterial vasodilation. The resultant increase in pulmonary blood flow and augmented flow to the left heart elevates left atrial pressure and functionally closes the foramen ovale. The increase in arterial oxygen tension also causes the ductus arteriosus to contract and functionally close. Other chemical mediators that may play a role in ductal closure include acetylcholine, bradykinin, and prostaglandins. The overall result is elimination of right-to-left shunting and establishment of the adult circulation (Figure 40–5). Anatomic closure of the ductus arteriosus does not usually occur until about 2–3 weeks, whereas closure of the foramen ovale takes months if it occurs at all.

Hypoxia or acidosis during the first few days of life can prevent or reverse these physiological changes, resulting in persistence of (or return to) the fetal circulation, or **persistent pulmonary hypertension of the newborn.** A vicious circle is established where the right-to-left shunting promotes hypoxemia and acidosis, which in turn promote more shunting (Figure 40–6). Right-to-left shunting may occur across the foramen ovale, the ductus arteriosus, or both. Unless this circle is broken, neonatal demise can occur rapidly.

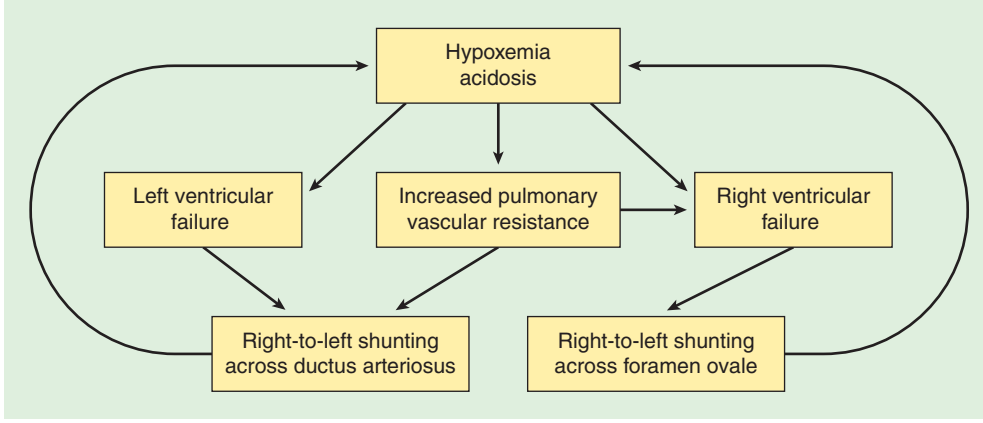

FIGURE 40–6 Pathophysiology of persistent pulmonary hypertension of the newborn (persistent fetal circulation). (Modified from Gregory GA: *Pediatric Anesthesia*, 2nd ed. Churchill Livingstone, 1989.)

CASE DISCUSSION

Postpartum Tubal Ligation

A 36-year-old woman is scheduled for bilateral tubal ligation 12 h after delivery of a healthy baby.

Is this patient still at increased risk for pulmonary aspiration?

Controversy exists over when the increased risk for pulmonary aspiration diminishes following pregnancy. Certainly, many factors contributing to delayed gastric emptying are alleviated shortly after delivery: mechanical distortion of the stomach is relieved, labor pains cease, and the circulating progesterone level rapidly declines. In addition, a period of 8–12 h of elective fasting is possible. Some studies suggest that the risk of pulmonary aspiration as judged by gastric volume and gastric fluid pH (see the section on Renal and Gastrointestinal Effects) normalizes within 24 h. Gastric volume and acidity usually do not differ in pregnant compared with nonpregnant women, although 30–60% of pregnant patients have a gastric volume greater than 25 mL or a gastric fluid pH less than 2.5. Therefore, most clinicians still consider the postpartum patient to be at increased risk for pulmonary aspiration and take appropriate precautions (see Chapters 17 and 41). It is not known when the risk returns to the level associated with elective surgical patients. Although some physiological changes associated with pregnancy may require up to 6 weeks for resolution, the increased risk of pulmonary aspiration probably returns to "normal" well before that time.

Other than aspiration risk, what factors determine the "optimal" time for postpartum sterilization?

The decision about when to perform postpartum tubal ligation (or laparoscopic fulguration) is complex and varies according to patient and obstetrician preferences as well as local practices. Factors influencing the decision include whether the patient had a vaginal or cesarean delivery and whether an anesthetic was administered for labor (epidural anesthesia) or delivery (epidural or general anesthesia).

Postpartum tubal ligation or fulguration may be (1) performed immediately following delivery of the baby and repair of the uterus during a cesarean section, (2) delayed 8–48 h following delivery to allow an elective fasting period, or (3) deferred until after the postpartum period (generally 6 weeks). Many obstetricians are reluctant to perform sterilizations immediately postpartum because the patient may change her mind later, particularly if something untoward happens to the baby. Furthermore, they want to ensure that the patient is stable, particularly after a complicated delivery. On the other hand, sterilization is technically much easier to perform in the immediate postpartum period because of the enlargement of the uterus and tubes. Postpartum sterilizations following natural vaginal delivery are generally performed within 48 h of delivery, because bacterial colonization of the reproductive tract thereafter is thought to increase the risk of postoperative infection.

What factors determine selection of an anesthetic technique for postpartum sterilization?

When continuous epidural anesthesia is administered for labor and vaginal delivery, the epidural catheter may be left in place up to 48 h for subsequent tubal ligation. The delay allows a period of elective fasting. A T4–5 sensory level with regional anesthesia is usually necessary to ensure a pain-free anesthetic experience. Lower sensory levels (as low as T10) may be adequate but sometimes fail to prevent pain during surgical traction on viscera.

When the patient has not had anesthesia for delivery, postpartum sterilization may be performed under either regional or general anesthesia. Because of the increased risk of pulmonary aspiration, regional anesthesia usually is preferred for bilateral tubal ligation via a minilaparotomy. Many clinicians prefer spinal over epidural anesthesia in this setting because of the risk of unintentional intravascular or intrathecal injections with the latter (see Chapter 45). Moreover, the risk of a precipitous decrease in blood pressure following spinal anesthesia may be significantly diminished following delivery (particularly when preceded by an intravenous fluid bolus). In addition, the incidence

of postdural puncture headache is as low as 1% when a 25-gauge or smaller pencil-point needle is used. Dosage requirements for regional anesthesia generally return to normal within 24–36 h after delivery. Bupivacaine, 8–12 mg, or lidocaine, 60–75 mg, may be used for spinal anesthesia. For epidural anesthesia, 15–30 mL of lidocaine 1.5–2% or chloroprocaine 3% is most commonly used.

In contrast, when laparoscopic tubal fulguration is planned, general endotracheal anesthesia is usually preferred. Insufflation of gas during laparoscopy impairs pulmonary gas exchange and predisposes the patient to nausea, vomiting, and possibly pulmonary aspiration. Endotracheal intubation generally ensures adequate ventilation and protects the airway.

What considerations are important for postpartum patients undergoing general anesthesia?

Preoperative concerns include a decreased blood hemoglobin concentration and the persistent increased risk of pulmonary aspiration. Anemia is nearly always present as a result of the physiological effects of pregnancy combined with blood loss during and following delivery. Hemoglobin concentrations are usually greater than 9 g/dL, but levels as low as 7 g/dL are generally considered safe. Fortunately, sterilization procedures are rarely associated with significant blood loss.

The risk of pulmonary aspiration is diminished by a minimum of 8 h of fasting, premedication with an H_2 blocker (ranitidine), a clear antacid (sodium citrate), or metoclopramide (see Chapters 17 and 41). In addition, induction of anesthesia should employ a rapid-sequence technique with cricoid pressure prior to endotracheal intubation, and the patient should be extubated only when she is awake. Decreased plasma cholinesterase levels persist after delivery (see the section on Hepatic Effects), modestly prolonging the effect of succinylcholine. The duration of vecuronium but not atracurium (or cisatracurium) has also been reported to be prolonged in postpartum women. High concentrations of volatile agents should be avoided because of the at least theoretical risk of increasing uterine blood loss or inducing postpartum hemorrhage secondary to uterine relaxation. Intravenous opioids may be used to supplement inhalational agents. Intravenous drugs administered intraoperatively to mothers who are breast-feeding appear to have minimal if any effects on their neonates. Nonetheless, it may be prudent to avoid breast-feeding 12–24 h following general anesthesia. Mothers are advised by some anesthetists to "pump and dump" breast milk for 24 hours before resuming breast feeding.

SUGGESTED READING

Chestnut DH, Polley LS, Tsen LC, et al: *Chestnut's Obstetric Anesthesia: Principals and Practice*, 4th ed. Mosby, 2009.

Suresh M: *Shnider and Levinson's Anesthesia for Obstetrics*, 5th ed. Lippincott, Williams & Wilkins, 2012.