The placenta, which presents unceremoniously after delivery of the neonate, has been given the undignified name *afterbirth*. This often ignored structure is, in fact, a critical organ that should not be an afterthought in the study of obstetric anesthesia. Revered by ancient cultures as *the seat of the external soul* or *the bundle of life*, the placenta has been the subject of many cultural rituals. However, a true understanding of the indispensable role of the placenta in the development of the fetus did not evolve until the seventeenth century. Much of the placenta’s function remained a mystery until the development of microanatomic, biochemical, and molecular biologic techniques during the past 50 years. The concept of the placenta as a passive sieve (which does little more than serve as a conduit for oxygen, nutrients, and waste) has been dispelled with the realization that the placenta is a complex and dynamic organ.

The placenta brings the maternal and fetal circulations into close apposition, without substantial interchange of maternal and fetal blood, for the physiologic transfer of gases, nutrients, and wastes. This important exchange is accomplished within a complex structure that is almost entirely of fetal origin.

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### PLACENTAL PATHOLOGY

- **ANATOMY**

  **Embryology**

  At implantation, the developing blastocyst erodes the surrounding decidua, leaving the cellular debris on which it survives. The placenta develops in response to the embryo’s outstripping its ability to gain oxygen and nutrients by simple diffusion. The syncytiotrophoblasts (invasive cells located at the margin of the growing conceptus) continue to erode the surrounding decidua and its associated capillaries and arterioles until the blastocyst is surrounded by a sea of circulating maternal blood (trophoblastic lacunae). The vitelline vein system develops in the yolk sac of the embryo to enhance the transport of nutrients, which diffuse from the maternal blood through the trophoblast layer and chorionic plate into the chorionic cavity. The embryo undergoes a dramatic acceleration in growth as its dependence on simple diffusion diminishes.

  At 2 weeks of development, the primitive extraembryonic mesoderm (cytotrophoblast layer) begins to proliferate as cellular columns into the syncytiotrophoblast. These columns with their syncytiotrophoblast covering extend

into the maternal blood lacunae and represent primary villi. Further mesodermal invasion into the core of these primary villi marks the metamorphosis into secondary villi. Cellular differentiation of the villi mesoderm results in the formation of a network of blood cells and vessels; this transition allows their classification as tertiary villi. The vascular components of each villus develop connections within the chorionic plate and into the stalk that connects the developing embryo and primitive placenta. Penetration of the cytotrophoblast continues through the syncytiotrophoblastic layer until many of the villi reach the decidua and form anchoring villi (Figure 4-1).2,3

Villi continue to develop and undergo extensive branching into treelike structures; the branches, which extend into the lacunar (or intervillous) spaces, enlarge the surface area available for exchange. Further villous maturation results in a marked reduction in the cytotrophoblastic component and a shortening of the distance between the fetal villi and maternal intervillus blood.3

The growing embryo within the blastocyst attaches to the chorion through a connecting or body stalk. Mesodermal components of this stalk coalesce to form the allantoic (or rudimentary umbilical) vessels. As the embryo continues its exponential growth phase, the connecting stalk shifts ventrally from its initial posterior attachment. The expansive open region at the ventral surface of the embryo constricts as the body wall grows and closes. By so doing, the body wall surrounds the yolk stalk, allantois, and developing vessels within the connecting stalk to form the primitive umbilicus. As the expanding amnion surrounds and applies itself over the connecting stalk and yolk sac, the cylindrical umbilical cord takes on its mature form.2

The placenta grows dramatically from the third month of gestation until term. A direct correlation exists between the growth of the placenta and the growth of the fetus. By term, the mature placenta is oval and flat, with an average diameter of 18.5 cm, weight of 500 g, and thickness of 23 mm.4 Wide variations in size and shape are within the range of normal and make little difference in function.

Comparative Anatomy

The placentas of different species differ greatly, beginning with their method of uterine attachment, which can include adhesion, interdigitation, and fusion. In addition, the number of tissue layers between the maternal and fetal circulations at their point of apposition can differ. The most commonly used placental categorization system, the Grossner classification, uses the number of tissue layers in the placental barrier to determine the species (Figure 4-2).5 Although still imperfect in modified form, this system remains a useful means of placental classification.

The functional ability of the placenta to transfer various substances differs among species. The markedly thicker epitheliochorial placenta found in sheep, which is the most common animal species used for placental transfer studies, has three maternal layers (epithelium, connective tissues, and endothelium) that separate maternal from fetal blood. By contrast, the human hemochorial placenta lacks these maternal layers, allowing maternal blood to directly bath fetal tissues (see Figure 4-2). As a result, the substances that are able to transfer through the placenta differ; for example, fatty acids cannot cross through the placenta in sheep as they do in humans.6 This wide diversity in placental structure and function among species makes extrapolation from animal investigations to clinical medicine tenuous.

Vascular Architecture

MATERNAL

Under the initial hormonal influences of the corpus luteum, the spiral arteries of the uterus become elongated and more extensively coiled. In the area beneath the developing conceptus, the compression and erosion of the decidua induces lateral looping of the already convoluted spiral arteries.7 These vessels under the placenta gain access to the intervillous spaces. In late pregnancy, the growing demands of the developing fetus require the 200 spiral arteries that directly feed the placenta to handle a blood flow of approximately 600 mL/min.7 The vasodilation required to accommodate this flow is the result of the replacement of the elastic and muscle components of the artery, initially by cytotrophoblast cells and later by fibroid cells. This replacement reduces the vasoconstrictor activity of these arteries and exposes the vessels to the dilating forces of the greater blood volume of pregnancy, especially at the terminal segments, where they form funnel-shaped sacs that enter the intervillous space.7 The increased diameter of the vessels slows blood flow and reduces blood pressure.
The intervillous space is a large cavernous expanse that develops from the fusion of the trophoblastic lacunae and the erosion of the decidua by the expanding blastocyst. This space, which is essentially a huge blood sinus, is bounded by the chorionic plate and the decidua basalis (i.e., the maternal or basal plate). Folds in the basal plate form septa that separate the space into 13 to 30 anatomic compartments known as lobules. Each lobule contains numerous villous trees that are also known as cotyledons or placentones.

Although tightly packed with highly branched villous trees, the intervillous space of the mature placenta can accommodate approximately 350 mL of maternal blood. Maternal arterial blood leaves the funnel-shaped spiral arteries and enters the intervillous space. The blood moves into the nearly hollow, low-resistance area, where villi are very loosely packed (the intercotyledonary space), prior to entering another region of densely packed intermittent and terminal villi (Figure 4-3). The terminal villi represent the areas where placental exchange predominates. After passing through this dense region, maternal venous blood collects between neighboring villous trees in an area called the perilobular zone. Collecting veins penetrate the maternal plate at the periphery of the villous trees to drain perilobular blood from the intervillous space.

Blood from the intervillous space is drained through fenestrations in the decidual veins; however, as pregnancy progresses, the total number of veins contributing to blood return is dramatically reduced by rising uterine wall pressure from intrauterine contents. Of interest, veins exhibit the same changes witnessed in the spiral arteries (i.e., atrophy of the tunica media and replacement with fibroid cells), which reduce vasoconstrictive abilities and enhance the dilation of patent veins to accommodate venous return from the placenta.

FETAL

Two coiled arteries bring fetal blood within the umbilical cord toward the placenta. On the placental surface, these arteries divide into chorionic arteries that ultimately supply the vessels of the 50 villous trees located in the placental lobules (Figure 4-4). At the base of each villous tree, the chorionic arteries are considered the main villous stem or truncal arteries (first-order vessels), which in turn branch into four to eight ramal or cotyledonal arteries (second-order vessels); as they pass toward the maternal plate, they further subdivide into ramulus chori (third-order vessels) and finally, terminal arterioles. The terminal arterioles lead through a neck region into a bulbous enlargement where they form two to four narrow capillary loops. Here the large endothelial surface area and the near absence of connective tissue allow optimal maternal-fetal exchange (Figure 4-5).

The venous end of the capillaries loops, narrows, and returns through the neck region to the collecting venules, which coalesce to form the larger veins in the stem of the villous trees. Each villous tree drains into a large vein,
which, as it perforates the chorionic plate, becomes a chorionic vein. All of the venous tributaries course toward the umbilical cord attachment site, where they empty into one umbilical vein that delivers blood to the fetus.

**PHYSIOLOGY**

**Barrier Function**

The placenta is an imperfect barrier that allows almost all substances to cross, including an occasional red blood cell.

The rate and amount of placental transfer depend on the level of permeability and the ability of various mechanisms to restrict movement. A vast array of cytochrome P-450 isoenzymes are found within the placenta; some of these are inducible, whereas others are constitutive. The inducible enzymes are mainly of the 3-methylcholanthrene-inducible type rather than the phenobarbital-inducing variety found in the liver. These enzymes may play a role in metabolizing agents and decreasing fetal exposure, but the extent to which this involvement occurs is poorly understood. In addition, a number of substances undergo specific or nonspecific binding within the placental tissues, thereby minimizing fetal exposure to and accumulation of the substances. Finally, the thickness of the placental membranes, which diminishes as gestation progresses, may influence the rate of diffusion. Of interest, the rate of transfer of certain substances (e.g., glucose, water) differs very little among species, even though the placental thickness varies greatly.

**Hormonal Function**

A sophisticated transfer of precursor and intermediate compounds in the maternal-fetal-placental unit allows placental enzymes to convert steroid precursors into estrogen and progesterone. This steroidogenic function of the placenta begins very early during pregnancy; by 35 to 47 days after ovulation, the placental production of estrogen and progesterone exceeds that of the corpus luteum (i.e., the ovarian-placental shift).
The placenta also produces a wide array of enzymes, binding proteins, and polypeptide hormones. For example, the placenta produces human chorionic gonadotropin, human placental lactogen (a growth hormone also known as human chorionic somatomammotropin), and factors that control hypothalamic function. This ability to produce proteins and steroid hormones allows the placenta to influence and control the fetal environment.

Regulation of Placental Blood Flow

MATERNAL BLOOD FLOW
The trophoblastic invasion and functional denervation of the musculoelastic lining of the spiral arteries may represent adaptive mechanisms to decrease vascular reactivity and promote vasodilation. These alterations allow the spiral arteries to vasodilate as much as 10 times their normal diameter, thereby lowering resistance for the passage of blood through the intervillous spaces.

Maternal blood enters the intervillous cotyledon space at a pressure of 70 to 80 mm Hg in an area that has relatively few villi. This pressure, and the subsequent velocity of blood flow, rapidly diminishes to approximately 10 mm Hg as the blood passes into an area of higher resistance created by the densely packed villi of the placenta.

FETAL BLOOD FLOW
In contrast to maternoplacental blood flow, the gestational increases in fetoplacental blood flow are more the result of vascular growth, rather than vasodilation, of the villous beds. Fetoplacental blood flow is autoregulated, but the process is not well defined; however, the maintenance of basal arteriolar tone is known to be independent of catecholamines or angiotensin.

Maternal hyperglycemia and hypoxemia are examples of derangements that can alter regional fetal blood flow, probably through vascular mediators. Endothelium-derived relaxing factors, especially prostacyclin and nitric oxide, appear to be important in the control of fetoplacental circulation. Evidence suggests that hypoxia-induced fetoplacental vasoconstriction is mediated by a reduction in the basal release of nitric oxide. This vasoconstrictor activity is functionally similar to that found in the lung and allows optimal fetal oxygenation through redistribution of fetal blood flow to better-perfused lobules.

Transport Mechanisms
Substances are transferred across the placenta by one of several mechanisms. These processes are summarized in this section.

PASSIVE TRANSPORT
The passive transfer of molecules across a membrane depends on (1) concentration and electrochemical differences across the membrane, (2) molecular weight, (3) lipid solubility, (4) level of ionization, and (5) membrane surface area and thickness. This process requires no expenditure of cellular energy, with transfer driven principally by the concentration gradient across a membrane. Simple transmembrane diffusion can occur either through the lipid membrane (e.g., lipophilic molecules and water) or within protein channels that traverse the lipid bilayer (e.g., charged substances such as ions) (Figure 4-6).

FACILITATED TRANSPORT
Carrier-mediated transport of relatively lipid-insoluble molecules down their concentration gradient is called facilitated diffusion. Facilitated diffusion differs from simple diffusion in several ways. Specifically, this mode of transfer exhibits (1) saturation kinetics, (2) competitive and non-competitive inhibition, (3) stereospecificity, and (4) temperature influences (e.g., a higher temperature results in greater transfer). With simple diffusion, the net rate of diffusion is proportional to the difference in concentration between the two sides of the membrane. This rate
limitation is valid for facilitated diffusion only when transmembrane concentration differences are small. At higher concentration gradients, a maximum rate of transfer ($V_{\text{max}}$) is reached; thereafter, further rises in the concentration gradient do not affect the rate of transfer. The rate of transfer is determined by the number of membranous carrier protein complexes and the extent of interaction between the carrier and the substance undergoing transport. An example of facilitated diffusion is the transplacental transfer of glucose.

A special type of facilitated diffusion involves the “uphill” transport of a molecule linked to another substance traveling down its concentration gradient. As such, the transfer is not directly driven by cellular energy expenditure. In most cases, sodium is the molecule that facilitates transport. For the membrane-bound carrier to transfer these molecules, both molecules must be bound to the carrier. This hybrid system is called secondary active transport or cotransport. The transplacental transport of amino acids appears to occur principally through secondary active transport.

**ACTIVE TRANSPORT**

Active transport involves the movement of any substance across a cell membrane being linked with cellular metabolic activity. In general, active transport occurs against a concentration, electrical, or pressure gradient, although not necessarily in all circumstances. Active transport requires cellular energy.

Like facilitated diffusion, active transport requires a protein membrane carrier that exhibits saturation kinetics and competitive inhibition (see Figure 4-6). However, unlike secondary active transport, this movement of a substance against its concentration gradient is directly linked to the hydrolysis of high-energy phosphate bonds of adenosine triphosphate (ATP). The best known example of primary active transport is the translocation of sodium and potassium through the Na+/K+ ATPase pump.

New active transport proteins that have been identified include P-glycoprotein, breast cancer resistance protein, and the sodium/multivitamin transporter, as well as the many proteins involved in monoamine transport and multidrug resistance. These transport proteins play an important role in protecting the fetus from foreign and potentially teratogenic compounds. P-glycoprotein exists on the maternal side of the trophoblastic cell membrane of the placenta, and prevents compounds such as methadone and saquinavir (a protease inhibitor) from leaving the maternal blood, thus limiting fetal exposure. Inhibition of these transporter proteins (e.g., inhibition of P-glycoprotein by verapamil) can significantly increase the fetal transfer of certain drugs, including midazolam, which is a substrate for P-glycoprotein.

**PINOCYTOSIS**

Large macromolecules (e.g., proteins that exhibit negligible diffusion properties) can cross cell membranes via the process of pinocytosis (a type of endocytosis). Pinocytosis is an energy-requiring process whereby the cell membrane invaginates around the macromolecule. Although the contents of pinocytotic vesicles are subject to intracellular digestion, electron microscopic studies have demonstrated that vesicles can move across the cytoplasm and fuse with the membrane at the opposite pole. This appears to be the mechanism by which immunoglobulin G is transferred from the maternal to the fetal circulation.

**OTHER FACTORS THAT INFLUENCE PLACENTAL TRANSPORT**

Other factors that affect maternal-fetal exchange are (1) maternal and fetal blood flow, (2) placental binding, (3) placental metabolism, (4) diffusion capacity, (5) maternal and fetal plasma protein binding, and (6) gestational age (i.e., the placenta is more permeable in early pregnancy). Lipid solubility, pH gradients between the maternal and fetal environments for certain basic drugs (“ion trapping”), and alterations in maternal or fetal plasma protein concentrations found in normal pregnancy and other disease states (e.g., preeclampsia) may also alter placental transport.

**Transfer of Respiratory Gases and Nutrients**

**OXYGEN**

As the “lung” for the fetus, the placenta has only one fifth of the oxygen transfer efficiency of the adult lung, yet must...
provide approximately 8 mL O₂/min per kg fetal body weight for fetal growth and development.¹² To determine the transplacental diffusion capacity for oxygen, the oxygen tension on both sides of the diffusional surface (i.e., within the placenta itself) must be determined. Because this approach is not practical, investigators have used surrogate measurements of oxygen content taken from blood in the uterine and umbilical vessels. One study in sheep demonstrated a transplacental pressure gradient of 37 to 42 mm Hg,¹³ which suggests poor oxygen diffusion capacity. This gradient is believed to be an inaccurate measure of true end-capillary O₂ tensions for at least three reasons. First, approximately 16% and 6% of uterine blood flow and umbilical blood flow, respectively, are shunted through diffusional areas of the placenta, resulting in an admixture.¹⁵ Second, unlike the lung, the placenta consumes a significant amount (20% to 30%) of transferred oxygen.⁴⁴ Third, the uterus also consumes oxygen. Consequently, placental diffusion capacity is significantly higher than a simple measurement of uterine venous P O₂ would suggest.

By contrast, as a gas not used by any organ, carbon monoxide is not affected by shunt or consumption. When placental diffusion capacity was estimated using carbon monoxide, it was found to be four times greater than that obtained with calculations made from arterial-venous P O₂ differences.⁴⁵ Because oxygen and carbon monoxide have similar diffusion coefficients, the placental diffusion capacity for oxygen must be essentially the same as that for carbon monoxide. Therefore, as with carbon monoxide, the transfer of oxygen is limited by flow and not by diffusion.¹⁵

Oxygen transfer across the placenta depends on the oxygen partial pressure gradient between maternal blood and fetal blood. As physically dissolved oxygen diffuses across the villous membranes, bound oxygen is released by maternal hemoglobin in the intervillous space and also diffuses across the placenta. Several factors affect the fetal blood P O₂ once it reaches equilibration in the villi end-capillaries. First, the concurrent and countercurrent arrangements of maternal and fetal blood flow play a key role for placental oxygen transfer in various species. The almost complete equilibration of maternal and fetal P O₂ values suggests that a concurrent (or parallel) relationship between maternal blood and fetal blood exists within the human placenta (Figure 4-7) ¹⁵,⁴⁶; however, one study demonstrated that umbilical venous P O₂ was slightly higher than intervillous P O₂, suggesting a more complex, multivillous pool relationship.⁴⁷ Second, the differences between the oxyhemoglobin dissociation curves of maternal and fetal blood may influence transplacental oxygen transfer to the fetus,⁴⁸ although this proposal is a matter of some dispute.¹⁵ The fetal oxyhemoglobin dissociation curve is positioned to the left of the maternal curve because of the lower P₅₀ (partial pressure of oxygen in the blood at which the hemoglobin is 50% saturated) for fetal blood (see Figure 5-4). In theory, this difference enhances oxygen uptake by fetal red blood cells and promotes the transfer of additional oxygen across the placenta. Third, the Bohr effect may also augment the transfer of oxygen across the placenta. Specifically, fetal-to-maternal transfer of carbon dioxide makes maternal blood more acidic and fetal blood more alkalotic, differences that in turn cause right and left shifts in the maternal and fetal oxyhemoglobin dissociation curves, respectively. This “double” Bohr effect enhances the transfer of oxygen from mother to fetus and accounts for 2% to 8% of the transplacental transfer of oxygen.⁴⁹

The maximum fetal arterial P O₂ (PaO₂) is never greater than 50 to 60 mm Hg, even when maternal fractional inspired oxygen concentration (FIO₂) is 1.0, for several reasons. First, the placenta tends to function as a venous rather than arterial equilibrator. Because of the shape of the maternal oxyhemoglobin dissociation curve, a rise in maternal PaO₂ above 100 mm Hg does not result in a substantial increase in maternal arterial oxygen content.
Therefore, under conditions of constant uterine and umbilical blood flow and fetal oxygen consumption, fetal PaO₂ rises only slightly when maternal PaO₂ is increased. Although this rise in PaO₂ is of limited significance at normal levels of fetal PaO₂, it is more important at decreased levels closer to the P₅₀ of fetal blood (approximately 21 mm Hg in humans) because of the steep slope of the fetal oxyhemoglobin dissociation curve within that range. Second, the placenta has a relatively high rate of oxygen consumption, which lowers the amount of oxygen available for transfer (see Chapter 5). Third, fetal arterial blood represents a mixture of oxygenated umbilical venous blood and deoxygenated inferior vena caval blood (which returns centrally from the fetal lower extremities).

**CARBON DIOXIDE**

The transfer of carbon dioxide occurs through a number of different forms, including dissolved CO₂, carbonic acid (H₂CO₃), bicarbonate ion (HCO₃⁻), carbonate ion (CO₃²⁻), and carbaminohemoglobin. Dissolved CO₂ (8%) and HCO₃⁻ (62%) are the predominant forms involved in transplacental transfer because the concentrations of H₂CO₃ and CO₃²⁻ are almost negligible and carbaminohemoglobin (30%) is present only within red blood cells. Equilibrium between CO₂ and HCO₃⁻ is maintained by a reaction catalyzed by carbonic anhydrase in red blood cells. A difference in PCO₂ normally exists between fetal and maternal blood (i.e., 40 versus 34 mm Hg, respectively); this gradient favors fetal-to-maternal transfer. Carbon dioxide is 20 times more diffusible than oxygen and readily crosses the placenta, although dissolved CO₂ is the form that actually crosses. The rapid movement of CO₂ from fetal capillary to maternal blood invokes a shift in the equilibrium of the carbonic anhydrase reaction (i.e., La Chatelier’s principle) that produces more CO₂ for diffusion. The transfer of CO₂ is augmented further by the production of deoxyhemoglobin in the maternal blood, which has a higher affinity for CO₂ than oxyhemoglobin (i.e., the Haldane effect). The resulting affinity may account for as much as 46% of the transplacental transfer of carbon dioxide.

Although a significant fetal-maternal concentration gradient exists for HCO₃⁻, its charged nature impedes its transfer and contribution to carbon dioxide transport except as a source for CO₂ production through the carbonic anhydrase reaction.

**GLUCOSE**

Simple diffusion alone cannot account for the amount of glucose required to meet the demands of the placenta and fetus. To assist the movement of glucose down its concentration gradient, a stereospecific facilitated diffusion system has been described, which is independent of insulin, a sodium gradient, or cellular energy. In addition, d-glucose transport proteins have been identified within the trophoblast membrane. The placenta, which must maintain its own metabolic processes, competes with the fetus for maternal glucose, and consequently only 28% of the glucose absorbed from the maternal surface is transferred through the umbilical vein to the term fetus. The placenta may also produce glucose via a different mechanism from the conventional hepatic glucose-6-phosphatase reaction.

**AMINO ACIDS**

Concentrations of amino acids are highest in the placenta, followed by umbilical venous blood and then maternal blood. The maternal-fetal transplacental transfer of amino acids is an active process that occurs principally through a linked translocation with sodium. The energy required for this transfer comes from the large sodium gradient established by the Na⁺/K⁺ ATPase pump. This results in increased intracellular concentrations of amino acids, which then “leak” down their gradients into the fetal circulation. This transport mechanism may not be viable for all amino acids and may be susceptible to inhibitors; for example, histidine does not exhibit elevated intracellular concentrations.

**FATTY ACIDS**

Free fatty acids, such as palmitic and linoleic acids, readily cross the human, but not ovine, placenta. A concentration gradient from mother to fetus exists for most fatty acids (with arachidonic acid being a notable exception), and the rate of transfer appears to depend on the magnitude of the gradient. These findings imply that fatty acids cross the placenta by means of simple diffusion, although the actual mechanism remains unclear.

**DRUG TRANSFER**

Placental permeability and pharmacokinetics help determine the fetal exposure to maternal drugs. Animal models (e.g., pregnant ewes, guinea pigs) have been used to assess the placental transport of drugs; however, interspecies differences in placental anatomy and physiology may limit the application of these data to humans. Investigations of transport within the human placenta have been performed on placental slices, isolated villi, membrane vesicles, homogenates, and tissue culture cells. The direct application of these data, however, is in question because these methods do not account for the dual (i.e., maternal and fetal) perfusion of the intact placenta in situ.

The inaccessibility of the placenta in situ and concerns for maternal and fetal safety have limited direct studies of the placenta in humans. Only one published study has reported the real-time transfer pharmacokinetics of an anesthetic drug across the human placenta in vivo. Data regarding the transplacental transfer of anesthetic agents have been extrapolated primarily from single measurements of drug concentrations in maternal and umbilical cord blood samples obtained at delivery. Most studies have reported fetal-maternal (F/M) ratios of the drug concentration. In these studies, the umbilical vein blood concentration represents the fetal blood concentration of the drug.

Single-measurement studies obtain only one set of measurements for each parturient. Maternal and fetal concentrations of a drug are influenced by drug metabolism in the mother, the placenta, and the fetus, and also by changes during delivery (e.g., altered uteroplacental blood flow). Unless a study includes a large number of patients with variable durations of exposure, it is difficult to reach conclusions about the type and time course of transplacental transfer of an individual drug from its results. In addition, single-measurement studies provide information only on the net transfer of a drug across the maternal-placental-fetal unit and do not allow for the determination of unidirectional fluxes at any point (i.e., maternal-to-fetal or fetal-to-maternal). Nonetheless, these studies have provided the best data available for most anesthetic agents.
A dual-perfused, *in vitro* human placental model has been developed to allow for the independent perfusion of the maternal and fetal sides of the placenta and thereby investigate maternal-to-fetal (or fetal-to-maternal) transport. The validity of this method for the study of placental transfer has been well established. Equilibration studies (i.e., recirculating maternal and fetal perfusates) using this model are not directly applicable to the placenta *in vivo*. However, when a nonrecirculating scheme is used, steady-state drug clearance can be determined for either direction (maternal-to-fetal or fetal-to-maternal) and may have direct clinical application. This method has been used to assess the placental transfer of anesthetic agents (e.g., thiopental, methohexital, propofol, bupivacaine, ropivacaine, alfentanil, sufentanil). Transfer across the placenta may be reported as drug clearance or as a ratio referred to as the transfer index (i.e., drug clearance/reference compound clearance). The use of a transfer index allows for interplacental comparisons by accounting for differences between placentas (e.g., lobule sizes). Commonly used reference compounds are either flow-limited (e.g., antipyrine, tritiated water) or membrane-limited (e.g., creatinine). These studies have enhanced our understanding of the placental transfer of anesthetic drugs (Box 4-1).

### Pharmacokinetic Principles

Factors affecting drug transfer across the human placenta include lipid solubility, protein binding, tissue binding, pKa, pH, and blood flow (Table 4-1). High lipid solubility may enable easy cell membrane (lipid bilayer) penetration but may also cause the drug (e.g., sufentanil) to be trapped within the placental tissue. Highly protein-bound drugs are affected by the concentration of maternal and fetal plasma proteins, which varies with gestational age and disease. Some drugs (e.g., diazepam) bind to albumin, whereas others (e.g., sufentanil, cocaine) bind predominantly to alpha-1-acid glycoprotein (Table 4-2). Although the free, unbound fraction of drug equilibrates across the placenta,

| TABLE 4-1 Factors Affecting Placental Transfer of Drug (Maternal to Fetal) |
|---------------------------------|-----------------|-----------------|
| **Size—molecular weight (Da)**  | <1000           | >1000           |
| **Charge of molecule**          | Charged         | Hydrophilic     |
| **Lipid solubility**            | Lipophilic      | Higher proportion of ionized drug in maternal plasma |
| **pH vs. drug pKa**             | Higher proportion of un-ionized drug in maternal plasma | Absent |
| **Placental efflux transporter**| Present         |                |
| **Binding protein type**        | Albumin (lower binding affinity) | Alpha-1-acid glycoprotein (AAG) (higher binding affinity) |
| **Free (unbound) drug fraction**| High            | Low             |

Da, dalton;

*The pH relative to the pKa determines the amount of drug that is ionized and un-ionized in both maternal and fetal plasma. Fetal acidemia enhances the maternal-to-fetal transfer (i.e., “ion trapping”) of basic drugs such as local anesthetics and opioids.

1The efflux transporter pumps substances in a fetal-to-maternal direction.

*Note: albumin concentration is higher in the fetus and AAG concentration is higher in the maternal circulation.*
the total drug concentration is greatly affected by both the extent of protein binding and the quantity of maternal and fetal proteins; fetal blood typically contains less than half the concentration of alpha-1-acid glycoprotein than in maternal blood.73 One study of the placental transfer of sufentanil in vitro noted different results when fresh frozen plasma, rather than albumin, was used as a perfusate.

The pKa of a drug determines the fraction of drug that is nonionized at physiologic pH. Thus, fetal acidemia greatly enhances the maternal-to-fetal transfer (i.e., “ion trapping”) of many basic drugs, such as local anesthetics and opioids (Figure 4-8).74 Most anesthetic drugs are passively transferred, with the rate of blood flow (hence drug delivery) affecting the amount of drug that crosses the placenta.75 One of the authors (M.I.Z.) has used the in vitro perfused human placenta model to perform a number of studies of the placental transfer of opioids (Table 4-3).

**Inhalation Anesthetic Agents**

When general anesthesia is necessary in a pregnant patient, maintenance of anesthesia is often provided with inhalation agents. The lipid solubility and low molecular weight of these agents facilitate rapid transfer across the placenta. A prolonged induction-to-delivery interval results in lower Apgar scores in infants exposed to general anesthesia.76

When administered during cesarean delivery, halothane is detectable in both umbilical venous blood and arterial blood within 1 minute. Even with relatively short induction-to-delivery times, an F/M ratio of 0.71 to 0.87 is established.77,78 Enflurane also exhibits unrestricted transfer across the placenta, with even brief exposures resulting in an F/M ratio of approximately 0.6.79 Isoflurane distributes rapidly across the placenta during cesarean delivery, resulting in an F/M ratio of approximately 0.71.78 To our knowledge, there are no published data regarding the placental transfer of either desflurane or sevoflurane.

Nitrous oxide also rapidly crosses the placenta, with an F/M ratio of 0.83 expected within 3 minutes.80 Maternal administration of nitrous oxide decreases fetal central vascular resistance by 30%,81 and a prolonged induction-to-delivery interval may cause neonatal depression.82 Diffusion hypoxia may occur during the rapid elimination of nitrous oxide from the neonate; therefore, the administration of supplemental oxygen to any neonate exposed to nitrous oxide immediately before delivery appears prudent.83

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**TABLE 4-2 Concentrations of Proteins that Bind Drugs**

<table>
<thead>
<tr>
<th>Protein</th>
<th>Maternal</th>
<th>Umbilical Cord</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>33.1 g/L</td>
<td>37.1 g/L*</td>
</tr>
<tr>
<td>Alpha-1-acid glycoprotein (AGP)</td>
<td>0.77 g/L</td>
<td>0.26 g/L*</td>
</tr>
</tbody>
</table>

*P < .05.


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**FIGURE 4-8** The effects of changes in fetal pH on the transfer of opioids during in vitro perfusion of the human placenta. This figure demonstrates the “ion trapping” of opioids, which is similar to that of local anesthetics. Clearance index = clearance drug/clearance creatinine (a reference compound). (Modified from Zakowski MI, Krishna R, Grant GJ, Turndorf H. Effect of pH on transfer of narcotics in human placenta during in vitro perfusion [abstract]. Anesthesiology 1995; 85:A890.)

**TABLE 4-3 Opioid Transfer during In Vitro Perfusion of the Human Placenta**

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Morphine</th>
<th>Meperidine</th>
<th>Alfentanil</th>
<th>Fentanyl</th>
<th>Sufentanil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid solubility at pH 7.4</td>
<td>1.4</td>
<td>39</td>
<td>129</td>
<td>816</td>
<td>1727</td>
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<tr>
<td>Percent nonionized at pH 7.4</td>
<td>23%</td>
<td>74%</td>
<td>89%</td>
<td>85%</td>
<td>20%</td>
</tr>
<tr>
<td>Percent protein binding</td>
<td>30%</td>
<td>70%</td>
<td>93%</td>
<td>84%</td>
<td>93%</td>
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<tr>
<td>Placenta drug ratio</td>
<td>0.1</td>
<td>0.7</td>
<td>0.53</td>
<td>0.19</td>
<td>0.14</td>
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<tr>
<td>F/M ratio, MTF</td>
<td>0.08</td>
<td>0.27</td>
<td>0.22</td>
<td>0.11</td>
<td>0.18</td>
</tr>
<tr>
<td>F/M ratio, FTM</td>
<td>0.08</td>
<td>0.13</td>
<td>0.11</td>
<td>0.08</td>
<td>0.18</td>
</tr>
<tr>
<td>Minutes to steady state</td>
<td>30</td>
<td>20</td>
<td>20</td>
<td>40-60</td>
<td>40-60</td>
</tr>
<tr>
<td>Clearance index, MTF</td>
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<td>0.95</td>
<td>0.75</td>
<td>0.76</td>
<td>0.41</td>
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<tr>
<td>Clearance index, FTM</td>
<td>0.5</td>
<td>0.91</td>
<td>0.78</td>
<td>0.61</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Clearance index, clearance drug/clearance antipyrine (a flow-limited reference compound); FTM, fetal-to-maternal (direction); MTF, maternal-to-fetal (direction); Placenta drug ratio, placenta drug concentration/g placental tissue/maternal drug concentration.

Data from nonrecirculated experiments, using perfusate Media 199 without protein, with maternal flow 12 mL/min and fetal flow 6 mL/min.57,69,104,107,113
**Induction Agents**

The lipophilic characteristics that make anesthetic agents ideal for the induction of anesthesia also enhance their transfer across the placenta. The understanding of the transplacental transfer of these drugs is better than for any other group of anesthetic agents.

**BARBITURATES**

A popular agent used for the induction of general anesthesia in parturients, thiopental is the most extensively studied barbiturate. An extremely short-acting agent, it quickly appears in umbilical venous blood after maternal injection, with mean F/M ratios between 0.4 and 1.1. High F/M ratios suggest that thiopental is freely diffusible; however, factors other than simple diffusion must play a role, because there is wide intersubject variability in umbilical cord blood concentrations at delivery. Both maternal-to-fetal and fetal-to-materna! transfer of thiopental are strongly influenced by maternal and fetal protein concentrations.

The rapid transfer of the oxybarbiturate methohexital into the fetal circulation, with simultaneous peak concentrations in maternal blood and fetal blood, has been demonstrated by *in vivo* studies. Human placental perfusion studies *in vitro* confirm that methohexital rapidly crosses the placenta in both maternal-to-fetal and fetal-to-maternal directions, with transfer indices of 0.83 and 0.61, respectively, when the concentration of albumin is equal in the two perfusates. This transfer asymmetry disappears when physiologic albumin concentrations in maternal and fetal blood (8 g/100 mL and 4 g/100 mL, respectively) are used; such conditions significantly increase fetal-to-maternal transfer so that it approximates maternal-to-fetal transfer.

**KETAMINE**

Ketamine, a phencyclidine derivative, rapidly crosses the placenta. Although less lipid soluble than thiopental, ketamine (2 mg/kg) reaches a mean F/M ratio of 1.26 in as little as 97 seconds when administered to the mother for vaginal delivery.

**PROPOFOL**

Review of published evidence suggests that the role of propofol in obstetric anesthesia practice remains unclear. Maternal administration of propofol in a bolus dose of 2 to 2.5 mg/kg results in a mean F/M ratio between 0.65 and 0.85. When given as a bolus dose of 2 mg/kg followed by a continuous infusion of either 6 mg/kg/hr or 9 mg/kg/hr, propofol results in mean F/M ratios of 0.50 and 0.54, respectively. These F/M ratios are similar to those found in early gestation (i.e., 12 to 18 weeks). Propofol may have sedative effects on the neonate; the maternal administration of propofol (2.8 mg/kg) for the induction of general anesthesia for elective cesarean delivery has resulted in lower 1- and 5-minute Apgar scores than the administration of thiopental (5 mg/kg). The plasma levels of propofol in the neonate depend on the maternal dose and resulting plasma level as well as on the time elapsed between drug administration and delivery of the neonate. In one study, when delivered within 10 minutes of induction, neonates whose mothers were given propofol (2 mg/kg) had an average umbilical vein propofol concentration of 0.32 μg/mL.

Several factors that affect propofol transfer have been investigated with *in vitro* human placental perfusion models. Increased maternal blood flow and reduced protein binding increase both placental tissue uptake and transplacental transfer of propofol. The effect of propofol’s high protein binding varies with alterations in fetal and maternal protein concentrations. Greater fetal albumin concentrations increase the total, but not free, concentration of propofol in umbilical venous blood, whereas doubling the maternal albumin concentration decreases the umbilical venous blood concentration of propofol by approximately two thirds.

**ETOMIDATE**

The use of etomidate, a carboxylated imidazole, for the induction of general anesthesia in obstetric patients was first described in 1979. A dose of 0.3 to 0.4 mg/kg administered before cesarean delivery results in an F/M ratio of approximately 0.5, which is similar to the ratio found in sheep.

**Benzodiazepines**

Highly un-ionized and lipophilic, diazepam is associated with F/M ratios of 1.0 within 1 hour and 2.0 within 60 minutes of maternal administration. Less lipophilic, lorazepam takes almost 3 hours after administration for the F/M ratio to reach unity. Midazolam is more polarized, with an F/M ratio of 0.76 at 20 minutes after administration. Unlike that of other benzodiazepines, however, midazolam’s F/M ratio falls quickly; by 200 minutes, it is only 0.3.

**Opioids**

Opioids have long been used for systemic pain relief in obstetric patients. More detailed pharmacokinetic data, enhanced monitoring, and the ability to reverse adverse effects with opioid antagonists have reduced the adverse side effects associated with their use. Administration of meperidine has been associated with neonatal central nervous system and respiratory depression. Intravenous administration of meperidine results in rapid transfer across the human placenta; the drug can be detected in the umbilical venous blood as soon as 90 seconds after maternal administration. F/M ratios for meperidine may exceed 1.0 after 2 to 3 hours; maternal levels fall more rapidly than fetal levels because of the mother’s greater capacity for metabolism of the drug. Human placental perfusion studies *in vitro* have demonstrated rapid placental transfer in both maternal-to-fetal and fetal-to-maternal directions with equal clearance profiles, minimal placental tissue binding, and no placental drug metabolism.

Morphine also rapidly crosses the placenta. One study demonstrated a mean F/M ratio of 0.61, a mean umbilical venous blood concentration of 25 ng/mL, and a significant reduction in the biophysical profile score (primarily as a result of decreased fetal breathing movements and fewer fetal heart rate accelerations) within 20 to 30 minutes. Intrathecal administration of morphine results in a high...
not only in the placenta but also in the fetal brain. 116 Maternal administration of fentanyl results in low F/M ratios; maternal administration of sufentanil results in a very high F/M ratio, 0.81. Compared with fentanyl, sufentanil has higher lipid solubility and more rapid uptake by the central nervous system, thereby resulting in less systemic absorption from the epidural space; less systemic absorption lowers both maternal and umbilical vein concentrations and reduces fetal exposure and the associated potential risk for neonatal respiratory depression.114 Human placental perfusion studies in vitro have confirmed the rapid transplacental transfer of sufentanil, which is influenced by differences in maternal and fetal plasma protein binding and fetal pH. High placental tissue uptake suggests that the placenta serves as a drug depot.117

Despite a relatively low F/M ratio (0.30),118 maternal administration of alfentanil has been associated with a reduction of 1-minute Apgar scores.119 Maternal administration of muscle relaxants for the induction of general anesthesia for cesarean delivery rarely affects maternal fetal-to-maternal transfers of alfentanil, with low placental drug uptake and rapid washout.70 At physiologically relevant concentrations and with mean F/M ratios of 0.84 and 0.74 to 0.97, respectively,123-125 In one study, maternal administration of nalbuphine resulted in “flattening” of the FHR tracing in 54% of cases.125

The systemic administration of an opioid agonist/antagonist for labor analgesia has been associated with few maternal, fetal, and neonatal side effects. Both butorphanol and nalbuphine rapidly cross the placenta, with mean F/M ratios of 0.84 and 0.74 to 0.97, respectively.123-125 In one study, maternal administration of nalbuphine resulted in "flattening" of the FHR tracing in 54% of cases.125

Muscle Relaxants

As fully ionized, quaternary ammonium salts, muscle relaxants do not readily cross the placenta; however, maternal administration of single clinical doses of muscle relaxants can result in detectable fetal blood concentrations. Maternal administration of muscle relaxants for the induction of general anesthesia for cesarean delivery rarely affects neonatal muscle tone at delivery. A single induction dose of succinylcholine is not detected in umbilical venous blood at delivery127; maternal doses larger than 300 mg are required before the drug can be detected in umbilical venous blood.128 Neonatal neuromuscular blockade can occur when high doses are given repeatedly or when the fetus has a pseudocholinesterase deficiency.129,130 One report described maternal masseter muscle rigidity and neonatal fasciculations after administration of succinylcholine for an emergency cesarean delivery; however, both the mother and the newborn were diagnosed with central core myopathy and malignant hyperthermia susceptibility.131

The administration of nondepolarizing muscle relaxants results in low F/M ratios: 0.12 for d-tubocurarine132, 0.19 to 0.26 for vecuronium133-135; 0.06 to 0.11 for vecuronium135,136; and 0.07 for atracurium.137 The F/M ratio may be the result of expedient fetal/neonatal blood sampling; in a study in rats, the F/M ratio of vecuronium nearly doubled as the induction-to-delivery interval increased from 180 to 420 seconds.136 To our knowledge, no published study has investigated the placental transfer of the atracurium isomer cisatracurium, Ravaparam, a short-acting analogue of vecuronium advocated as an alternative to succinylcholine for rapid-sequence induction,138,139 has an F/M ratio of 0.09 and is associated with increased maternal heart rate.140 Although no published reports have documented problems with rapacuronium in parturients or neonates, reports of bronchospasm resulted in the withdrawal of rapacuronium from the market. Nondepolarizing muscle relaxants are frequently administered in bolus form; although the transfer rates are low, the fetal blood concentrations increase over time.136 Fetal blood concentrations of nondepolarizing muscle relaxants can be minimized by giving succinylcholine to facilitate intubation, followed by the administration of small doses of either succinylcholine or a nondepolarizing muscle relaxant to maintain paralysis.134

Anticholinergic Agents

The placental transfer rate of anticholinergic agents directly correlates with their ability to cross the blood-brain barrier. Atropine is detected in the umbilical circulation within 1 to 2 minutes of maternal administration, and an F/M ratio of 0.93 is attained at 5 minutes.141 Scopolamine, the other commonly used tertiary amine, also crosses the placenta easily. Intramuscular administration of scopolamine results in an F/M ratio of 1.0 within 55 minutes.142 By contrast, glycopyrrolate is poorly transferred across the placenta with maternal intramuscular administration, resulting in a mean F/M ratio of only 0.22.143 Maternal intravenous administration of glycopyrrolate does not result in a detectable fetal hemodynamic response.144

Local Anesthetics

Local anesthetic agents readily cross the placenta (see Chapter 13). The enantiomers of bupivacaine cross the placenta at the same rate as racemic bupivacaine.126
Anticholinesterase Agents

Neostigmine, pyridostigmine, and edrophonium are quaternary ammonium compounds that are ionized at physiologic pH and consequently undergo limited transplacental transfer. For example, maternal administration of neostigmine does not reverse atropine-induced fetal tachycardia. However, small amounts of these agents do cross the placenta, and fetal bradycardia after maternal administration of neostigmine and glycopyrrolate has been reported. Because neostigmine may cross the placenta to a greater extent than glycopyrrolate, the combination of neostigmine and atropine should be considered for the reversal of nondepolarizing muscle relaxants in pregnant patients.

Antihypertensive Agents

Beta-adrenergic receptor antagonists are commonly used as antihypertensive agents in pregnancy, despite early investigations noting an association with intrauterine growth restriction and neonatal bradycardia, hypoglycemia, and respiratory depression. Although a single dose of propranolol administered 3 hours before cesarean delivery has been shown to lead to an F/M ratio of 0.26, long-term administration during pregnancy results in F/M ratios greater than 1.0. Maternal administration of atenolol and metoprolol leads to mean F/M ratios of 0.94 and 1.0, respectively. The maternal administration of labetalol for the treatment of either chronic or acute hypertension in pregnant women has been supported by a low F/M ratio, 0.38, with long-term oral administration, despite mild neonatal bradycardia. The short-acting beta-adrenergic receptor antagonist esmolol has been used to attenuate the hypertensive response to laryngoscopy and intubation. A mean F/M ratio of 0.2 after maternal administration of esmolol was observed in gravid ewes. However, a few cases of significant and prolonged fetal bradycardia requiring the performance of emergency cesarean delivery have been reported.

Clonidine and methyldopa act through the central stimulation of alpha2-adrenergic receptors; studies have reported mean F/M ratios of 0.89 and 1.17, respectively, for these agents. In concentrations likely present in maternal blood with clinical use, magnesium and nifedipine, but not clonidine, produce fetal vasodilation in human placental perfusion studies. Dexmedetomidine, an alpha2-adrenergic agonist, has an F/M ratio of 0.12, with evidence of significant placental tissue binding due to high lipophilicity.

Phenoxymazine, an alpha-adrenergic receptor antagonist, is commonly used to treat hypertension in patients with pheochromocytoma and has an F/M ratio of 1.6 with long-term maternal administration. Direct-acting vasodilators are used for short-term management of severe hypertension in pregnant women. Administration of hydralazine, which is often given to lower blood pressure in preeclamptic women, results in an F/M ratio of 1.0 and causes fetal vasodilation in in vitro studies. Sodium nitroprusside is lipid soluble, rapidly crosses the placenta, and can produce cyanide as a byproduct. Sodium thiosulfate, the agent used to treat cyanide toxicity, does not cross the placenta in a maternal-to-fetal direction in gravid ewes, but it can treat fetal cyanide toxicity by lowering maternal cyanide levels, thereby enhancing fetal-to-maternal transfer of cyanide. Glycerol trinitrate (nitroglycerin) crosses the placenta to a limited extent, with an F/M ratio of 0.18, and results in minimal changes in fetal umbilical blood flow, blood pressure, heart rate, and blood gas measurements in gravid ewes. However, dinitrate metabolites found in both maternal and fetal venous blood indicate the capacity for placental biotransformation. Indeed, placental tissue production of nitric oxide may be an important factor that enhances the uterine relaxation caused by nitroglycerin in vivo. In one in vitro study, in which prostaglandin F2α was used to create fetal vasoconstriction, the following order of nitrovasodilator compound potency was observed: glyceryl trinitrate $\geq$ sodium nitroprusside $\geq$ sodium nitrate (NaNO₃) $\geq$ S-nitroso-N-acetylpenicillamine (SNAP) = S-nitroso-N-glutathione (SG). SNG and NaNO₂ were significantly more potent under conditions of low oxygen tension. The antioxidants cysteine, glutathione, and superoxide dismutase significantly enhanced the vasodilatory effects of NaNO₂ only. Placental transfer of angiotensin-converting enzyme (ACE) inhibitors may adversely affect fetal renal function. Enalaprilat rapidly crosses the placenta, and its maternal administration in high doses resulted in a 20% reduction in fetal arterial pressure in rhesus monkeys.

Vasopressor Agents

Vasopressor agents are often administered to prevent or treat hypotension during the administration of neuraxial anesthesia in obstetric patients; however, few studies have evaluated their transplacental transfer. Ephedrine easily crosses the placenta and results in an F/M ratio of approximately 0.7. To our knowledge, no studies have evaluated the transfer of phenylephrine across the placenta.

Cocaine, a common drug of abuse during pregnancy (see Chapter 53), has potent vasoconstrictor activity. Human placenta perfusion studies in vitro have demonstrated the rapid transfer of cocaine without metabolism in both maternal-to-fetal and fetal-to-maternal directions; transfer is constant over a wide range of concentrations. The active cocaine metabolites norcocaine and cocaethylene, but not the inactive metabolite benzoylecgonine, are also rapidly transferred across the placenta. Chronic maternal administration of cocaine increases fetal concentrations; however, they remain lower than maternal peak levels. In a study using the in vitro dually perfused human placental lobule, fetal-side administration of vasoconstrictors was found to raise fetal placental perfusion pressure, thus causing a shift of fluid from the fetus to the maternal circulation.

Anticoagulants

Anticoagulation therapy during pregnancy is often necessary despite its association with maternal and fetal morbidity. Maternal administration of warfarin results in a higher rate of fetal loss and congenital anomalies; these
fingernail indirectly confirm the transplacental transfer of warfarin, because no direct measurements of the F/M ratio have been performed. In contrast, heparin does not appear to cross the placenta, as measured by neonatal coagulation studies and the measurement of radiolabeled heparin in fetal lambs. Low-molecular-weight heparin (LMWH) appears to have limited placental transfer; however, maternal administration of enoxaparin does not alter fetal anti-IIa or anti-Xa activity. Even when enoxaparin or fondaparinux (a new pentasaccharide that selectively inhibits factor Xa) are given at doses used for acute thromboembolic therapy, human placental perfusion studies in vitro have demonstrated no placental transfer of the drugs.

Drug Delivery Systems

New drug delivery systems may influence drug transfer and distribution across the human placenta. Liposome encapsulation, depending on the type and ionic charge, can affect placental transfer; anionic and neutral liposomes increase placental transfer, whereas cationic liposomes decrease placental transfer and placental tissue uptake. Liposome encapsulation of valproic acid significantly reduces drug transfer and placental uptake.

Disease States

Disease states, such as diabetes, may affect the placental transfer of drugs. Glyburide, a second-generation sulfonylurea, is partially dependent on a P-glycoprotein active transport mechanism and demonstrates a lower F/M ratio of 0.3 than the first-generation agents, even in the presence of a P-glycoprotein inhibitor. A high level of protein binding (99.8%) may also account for the low transplacental transfer of glyburide; when protein levels are reduced in vitro, higher transfer rates are observed. Some investigators have speculated that the thickened placenta found in diabetic patients is a cause of low transfer rates; however, no difference in maternal-to-fetal transfer of metformin has been observed between placentas from parturients with gestational diabetes and those from healthy parturients.

Gestational age may alter placental transfer, although the direction of the alteration requires further evaluation. Although existing belief holds that placentas from younger fetuses are more likely to transfer substances, one study has demonstrated that methadone transfer is 30% lower in human preterm placentas than in term placentas.

PLACENTAL PATHOLOGY

There has been a growing interest in the clinical-pathologic correlation between placental abnormalities and adverse obstetric outcomes. In some cases, a skilled and systematic examination of the umbilical cord, fetal membranes, and placenta may provide insight into antepartum pathophysiology; in most of these cases, examination of the placenta confirms the clinical diagnosis (e.g., chorioamnionitis). When adverse outcomes occur, often the “disorder that was not suspected clinically may be revealed by placental pathology” (e.g., microabscesses of listeriosis; amnion nodosum, which suggests long-standing oligohydramnios). Drugs may produce placental abnormalities (e.g., cocaine causes chorionic villus hemorrhage and villous edema). The significance of many findings (e.g., villous edema, hemorrhagic endovasculitis, chronic villitis), however, is unclear.

The following factors limit the assessment of placental pathology: (1) “the paucity of properly designed studies of adequate size with appropriate outcome parameters,” which impairs the correlation of placental abnormalities with adverse clinical outcomes; (2) the limited number of pathologists with expertise in the recognition and interpretation of subtle abnormalities of the placenta; and (3) the cost associated with a routine assessment of placental pathology. The American College of Obstetricians and Gynecologists Committee on Obstetrics has concluded, “An examination of the umbilical cord, membranes, and placenta may assist the obstetric care provider in clinical-pathologic correlation when there is an adverse perinatal outcome. However, the scientific basis for clinical correlation with placenta pathology is still evolving, and the benefit of securing specimens on a routine basis is as yet unproven.”

KEY POINTS

- The placenta is a dynamic organ with a complex structure. It brings two circulations close together for the exchange of blood gases, nutrients, and other substances (e.g., drugs).
- During pregnancy, anatomic adaptations result in substantial (near maximal) vasodilation of the uterine spiral arteries; this leads to a low-resistance pathway for the delivery of blood to the placenta. Therefore, adequate uteroplacental blood flow depends on the maintenance of a normal maternal perfusion pressure.
- The marked diversity in placental structure and function among various animal species limits clinicians’ ability to extrapolate the results of animal investigations to human pregnancy and clinical practice.
- Placental transfer involves all of the physiologic transport mechanisms that exist in other organ systems.
- Physical factors (e.g., molecular weight, lipid solubility, level of ionization) affect the placental transfer of drugs and other substances. In addition, other factors affect maternal-fetal exchange, including changes in maternal and fetal blood flow, placental binding, placental metabolism, diffusion capacity, and extent of maternal and fetal plasma protein binding.
- Lipophilicity, which enhances the central nervous system uptake of general anesthetic agents, also heightens the transfer of these drugs across the placenta. However, the placenta itself may take up highly lipophilic drugs, thereby creating a placental drug depot that limits the initial transfer of drug.
- Fetal acidemia can result in the “ion trapping” of both local anesthetics and opioids.
- Vasoactive drugs cross the placenta and may affect the fetal circulation.


