

Placental structure, function and drug transfer



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Key points

The placenta is the interface between mother and fetus.

Functions of the placenta include gas exchange, metabolic transfer, hormone secretion, and fetal protection.

Nutrient and drug transfer across the placenta are by passive diffusion, facilitated diffusion, active transport, and pinocytosis.

Placental drug transfer is dependent on the physical properties of the placental membrane and on the pharmacological properties of the drug.

Almost all anaesthetic drugs cross the placenta easily, with the exception of the neuromuscular blocking agents.

The human placenta is a complex organ that acts as the interface between the mother and fetus. Its functions are:

- (i) gas exchange and the transfer of nutrients and waste products between maternal and fetal plasma;
- (ii) transfer of immunity by transfer of immunoglobulins from the mother to the fetus;
- (iii) secretion of hormones which are important for fetal growth and development.

In the late 1950s and early 1960s, the devastating series of thalidomide-induced birth defects raised awareness of the imperfect state of the placenta as a barrier to drug transfer. Subsequent research has sought to elucidate the precise nature and mechanisms of transplacental drug passage. There has also been increasing interest in the deliberate use of maternally administered drugs designed to cross the placenta and provide therapeutic effects on the fetus.

This article reviews the structure and key functions of the placenta. It also summarizes our current understanding of placental drug transfer, particularly of drugs used for anaesthesia and analgesia in pregnancy.

Placental structure

The placenta is a disc-shaped organ which provides the sole physical link between mother and fetus. During pregnancy, the placenta grows to provide an ever-larger surface area for materno-fetal exchange. At term, the placenta weighs almost 500 g, has a diameter of 15–20 cm, a thickness of 2–3 cm, and a surface area of almost 15 m².¹

The basic structural unit of the placenta is the chorionic villus. The villi are vascular projections of fetal tissue surrounded by chorion. The chorion consists of two cellular layers: the outer syncytiotrophoblast which is in direct contact with maternal blood within the intervillous space, and the inner cytotrophoblast. The intervillous space is a large cavernous expanse into which the

villi reach.² As the villi mature, there is a marked reduction in the cytotrophoblast component so that at term, only a single layer of syncytiotrophoblast separates maternal blood and fetal capillary endothelium.³

The maternal blood supply to the uterus is via the uterine and ovarian arteries that form the arcuate arteries, and from which radial arteries penetrate the myometrium. The radial arteries then divide into spiral arteries that supply the intervillous space, bathing the chorionic villi in maternal blood. The pressure is about 80–100 mm Hg in the uterine arteries, 70 mm Hg in the spiral arteries and only 10 mm Hg within the intervillous space. Two umbilical arteries arising from the fetal internal iliac arteries carry deoxygenated fetal blood via the umbilical cord to the placenta. The umbilical arteries divide into chorionic arteries and end as capillaries within the villi. Substances in the maternal blood pass from the intervillous space through the syncytiotrophoblast, fetal connective tissue, and the endothelium of the fetal capillaries into the fetal blood. The fetal capillaries drain into chorionic veins which empty into a single umbilical vein² (Fig. 1).

Maternal uterine blood flow at term is ~600 ml min⁻¹, 80% of which passes to the placenta. There is no autoregulation in the uteroplacental circulation and therefore flow is directly related to the mean uterine perfusion pressure and inversely related to uterine vascular resistance. Blood flow in the uteroplacental circulation may consequently be reduced by maternal hypotension and increased uterine pressure during uterine contractions. As the uteroplacental arteries contain α -adrenergic receptors, sympathetic stimulation (e.g. by vasopressor drugs) may lead to uterine artery vasoconstriction.²

Functions of the placenta

Gas exchange

The fetal lungs do not take part in gas exchange while *in utero*, so the placenta is wholly

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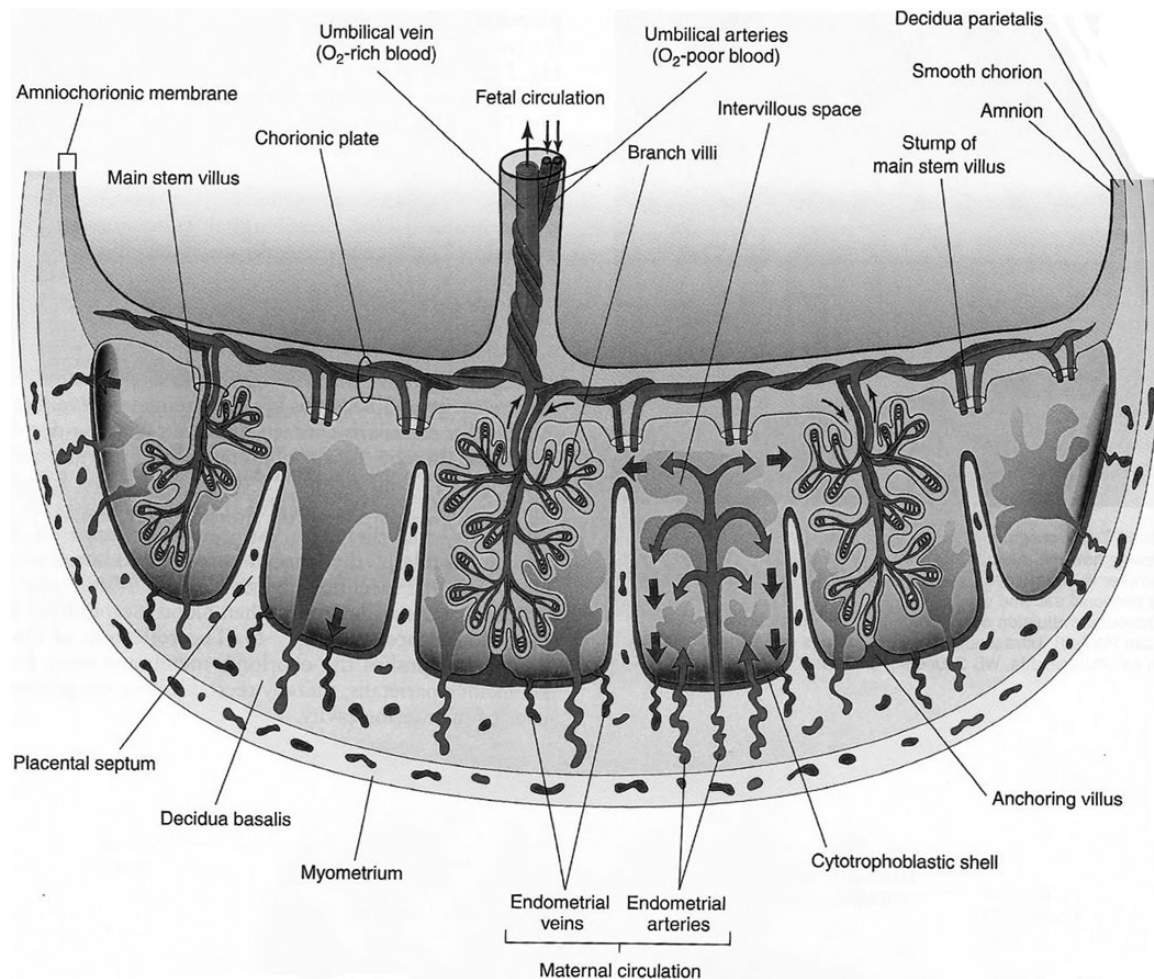


Fig 1 Schematic drawing of a transverse section through a full-term placenta [reproduced from *The Developing Human: Clinically Oriented Embryology* (8th Edn) by K.L. Moore and T.V.N. Persaud¹ with kind permission from Elsevier Inc.].

responsible for the transfer of oxygen and carbon dioxide to and from the developing fetus.

Oxygen

Oxygen is a small molecule which readily crosses the placenta by passive diffusion. Oxygen transfer mainly depends on the oxygen partial pressure gradient between maternal blood in the intervillous space and fetal blood in the umbilical arteries (~ 4 kPa).

Oxygen transfer to the fetus is enhanced by the Bohr effect. At the materno-fetal interface, maternal blood takes up carbon dioxide and becomes more acidotic. This causes a rightward shift of the maternal oxyhaemoglobin dissociation curve which favours oxygen release to the fetus. At the same time, fetal blood releases carbon dioxide and becomes more alkalotic. This leads to a leftward shift of the fetal curve, favouring fetal uptake of oxygen. This phenomenon is called the 'Double Bohr Effect'. The transfer of oxygen from mother to fetus is also favoured by the presence of fetal

haemoglobin which shifts the fetal oxyhaemoglobin dissociation curve further to the left.³

Carbon dioxide

Carbon dioxide also crosses the placenta readily by passive diffusion. Transfer from fetus to mother depends mainly on the partial pressure gradient for carbon dioxide between fetal blood in the umbilical arteries and maternal blood in the intervillous space (~ 1.8 kPa).

Carbon dioxide transfer from the fetus to the mother is facilitated by the Haldane effect (the increased capacity of deoxygenated blood to carry carbon dioxide compared with oxygenated blood). As maternal blood releases oxygen (producing deoxyhaemoglobin), it is able to carry more carbon dioxide as bicarbonate and carbaminohaemoglobin. At the same time, as fetal blood takes up oxygen to form oxyhaemoglobin, it has reduced affinity for carbon dioxide and therefore releases carbon dioxide to the mother. The combination of these two events is called the 'Double Haldane Effect'.³

Metabolic transfer

Glucose

The fetus has very little capacity for gluconeogenesis, so maternal glucose forms its main source of energy. Passive diffusion of glucose across the placenta is insufficient to meet the needs of the fetus and therefore facilitated diffusion using a variety of glucose transporters is required.^{4,5}

Amino acids

Amino acids for fetal protein synthesis are transferred from mother to fetus by active transport. There are several transporter proteins specific for anionic, cationic, and neutral amino acids. Many of these proteins co-transport amino acids with sodium: the transport of sodium down its concentration gradient drags amino acids into the cells.^{4,5}

Fatty acids

Fatty acids are important for the synthesis of compounds involved in cell signalling (e.g. prostaglandins and leukotrienes), and for the production of fetal phospholipids, biological membranes, and myelin. Lipoprotein lipase, an enzyme which cleaves lipoproteins into free fatty acids, is located on the maternal surface of the placenta.⁴ Free fatty acids and glycerol are transferred from mother to fetus mainly by simple diffusion, but also through the use of fatty acid binding proteins.^{4,5}

Electrolytes, vitamins, and water

Sodium and chloride ions are mainly transferred across the placenta by passive diffusion, although active transport may have a role. Calcium ions, iron, and vitamins are transferred by active carrier-mediated transport. Water moves by simple diffusion according to hydrostatic and osmotic pressure gradients. Certain water channel proteins in the trophoblast may aid its passage.⁶

Endocrine function

The placenta is an endocrine organ which produces a number of important peptide and steroid hormones.

Human chorionic gonadotropin

Human chorionic gonadotropin (HCG) is a glycoprotein hormone produced in early pregnancy by the syncytiotrophoblast. Production peaks at ~8 weeks of gestation. HCG stimulates the corpus luteum to secrete progesterone which is required to maintain the viability of the pregnancy.⁶ Detection of HCG in the urine forms the basis of commercial pregnancy testing kits.

Human placental lactogen

Human placental lactogen (HPL) is also produced by the syncytiotrophoblast. It reduces maternal insulin sensitivity, leading to an increase in maternal blood glucose levels. It stimulates the production

of fetal pulmonary surfactant and the synthesis of adrenocorticotrophic hormones and helps to promote maternal breast development for milk production.⁶ HPL converts the mother from being a principal carbohydrate user to a fatty acid user, thereby sparing glucose for the fetus.

Human growth hormone variant

Human growth hormone variant is produced by the syncytiotrophoblast and affects the growth of the placenta itself. It also stimulates maternal gluconeogenesis and lipolysis, optimizing the availability of nutrients for the developing fetus.⁶

Oestrogens and progesterone

Until the end of the eighth week of gestation, the corpus luteum secretes progesterone. The placenta gradually takes over this role and production of progesterone increases until just before labour. Progesterone is important in preventing uterine contractions and the onset of labour. Oestrogens stimulate uterine growth and development of the mammary glands.

Immunological function

Although most proteins are too large to cross the placental barrier, maternal IgG antibodies may cross from mother to fetus by pinocytosis to provide passive immunity in the first few months of life. The syncytiotrophoblast possesses receptors for the Fc fragments of IgG; the bound IgG is then endocytosed into a vesicle before being released by exocytosis into the fetal blood.² This transfer starts in early gestation and increases exponentially in the third trimester.⁷ Antibodies which cause maternal autoimmune disorders (e.g. myasthenia gravis) can also cross the placenta and affect the fetus.²

Placental drug transfer

Almost all drugs will eventually cross the placenta to reach the fetus. In some cases, this transplacental transfer may be beneficial and drugs may be deliberately administered to the mother in order to treat specific fetal conditions. For example, steroids may be given to the mother to promote fetal lung maturation and cardiac drugs may be given to control fetal arrhythmias.

However, the transplacental passage of drugs may also have detrimental effects on the fetus, including teratogenicity or impairment of fetal growth and development. The greatest risk of adverse drug effects on the fetus is probably during organogenesis which takes place in the first trimester. The effects of drugs on the fetus may be either direct or may be mediated via the alteration of uteroplacental blood flow.

Three types of drug transfer across the placenta are recognized:⁸

- (i) Complete transfer (type 1 drugs): for example, thiopental
Drugs exhibiting this type of transfer will rapidly cross the placenta with pharmacologically significant concentrations equilibrating in maternal and fetal blood.

- (ii) Exceeding transfer (type 2 drugs): for example, ketamine
These drugs cross the placenta to reach greater concentrations in fetal compared with maternal blood.
- (iii) Incomplete transfer (type 3 drugs): for example, succinylcholine
These drugs are unable to cross the placenta completely, resulting in higher concentrations in maternal compared with fetal blood.

Mechanisms of drug transfer

Drugs which transfer from the maternal to the fetal blood must be carried into the intervillous space and pass through the syncytiotrophoblast, fetal connective tissue, and the endothelium of fetal capillaries. The rate-limiting barrier for placental drug transfer is the layer of syncytiotrophoblast cells covering the villi. Factors affecting drug transfer across the placenta are listed in Table 1.

There are four main mechanisms of drug transfer across the placenta⁹ (Fig. 2).

Simple diffusion: *e.g. midazolam and paracetamol*

Most drugs (especially type 1 drugs) cross the placenta by this mechanism. Transfer is either transcellularly through the syncytiotrophoblast layer or paracellularly through water channels incorporated into the membrane.¹⁰ Diffusion does not require energy input but is dependent on a concentration gradient across the placenta with drug passively moving from areas of high to low concentration.

The transfer of drugs which passively diffuse from mother to fetus is governed by Fick's law of diffusion.³ This states that the rate of diffusion per unit time is directly proportional to the surface area of the membrane (placenta) and the concentration gradient across it, and inversely proportional to the thickness of the membrane:

$$Q = \frac{k \times SA \times (C_1 - C_2)}{d}$$

where Q is the rate of drug diffusion across the placenta per unit time, k the diffusion constant, SA the surface area of placental

membrane, C_1 the maternal concentration of free drug, C_2 the fetal concentration of free drug, and d the thickness of placental membrane.

In the normal placenta, the villous surface area and blood flow to the placenta increase with gestation. The placental membranes also thin out and the cytotrophoblast layer almost completely disappears. These changes increase the passive diffusion of drugs and nutrients to the growing fetus. Infective processes affecting the placenta may result in an increase in the thickness of placental membranes which will reduce passive diffusion across them.

The diffusion constant, k , incorporates various physicochemical drug properties. These include:

- (i) Molecular weight
Drugs with a molecular weight of <500 Da readily diffuse across the placenta. Most drugs used in anaesthetic practice have molecular weights <500 Da.
- (ii) Lipid solubility
Lipophilic molecules diffuse readily across lipid membranes, of which the placenta is one.
- (iii) Degree of ionization
Only the non-ionized fraction of a partly ionized drug crosses the placental membrane. The degree to which a drug is ionized depends on its pKa and the pH of maternal blood. Most drugs used in anaesthetic practice are poorly ionized in the blood and they therefore diffuse readily across the placenta. The exception is the neuromuscular blocking agents which are highly ionized and therefore their transfer is negligible. If the pH of maternal blood changes (*e.g.* in labour) then changes in the degree of drug ionization and transfer can occur.
- (iv) Protein binding
Drugs which are protein-bound do not diffuse across the placenta; only the free, unbound portion of a drug is free to cross the cell membranes. Protein binding is altered in a

Table 1 Summary of factors affecting drug transfer across the placenta

Physical	
Placental surface area	
Placental thickness	
pH of maternal and fetal blood	
Placental metabolism	
Uteroplacental blood flow	
Presence of placental drug transporters	
Pharmacological	
Molecular weight of drug	
Lipid solubility	
pKa	
Protein binding	
Concentration gradient across placenta	

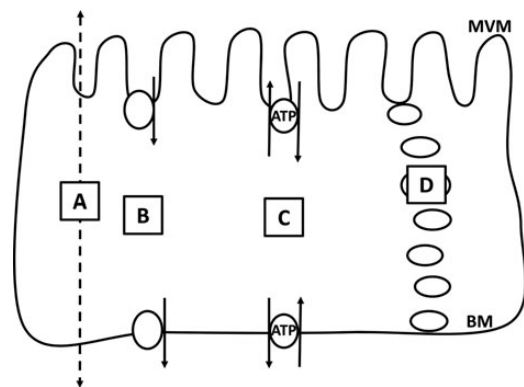


Fig 2 Diagram showing mechanisms of placental drug transfer (A, simple diffusion; B, facilitated diffusion using a carrier; C, active transport using ATP; D, pinocytosis; BM, basal membrane of the syncytiotrophoblast; MVM, microvillous membrane of the syncytiotrophoblast) (adapted from a diagram in Desforges and Sibley⁴ with kind permission from the *International Journal of Developmental Biology*).

range of pathological conditions. For example, low serum albumin in pre-eclampsia will result in a higher proportion of unbound drug and will therefore promote drug transfer across the placenta.

Facilitated diffusion: e.g. cephalosporins and glucocorticoids

Drugs structurally related to endogenous compounds are often transported by facilitated diffusion. This type of transport needs a carrier substance within the placenta to facilitate transfer across it. Again, energy input is not required since drug transfer occurs down a concentration gradient. Facilitated diffusion will be inhibited if the carrier molecules become saturated by both drug and endogenous substrates competing for their use.⁸

Active transport: e.g. norepinephrine and dopamine

Active transport utilizes energy, usually in the form of ATP, to transport substances against a concentration or electrochemical gradient. Transport is carrier-mediated and saturable and there is competition between related molecules. Active drug transporters are located on both the maternal and fetal sides of the placental membranes and can transport drugs from mother to fetus and vice versa.

A wide range of active transporters has been identified within the placenta and includes p-glycoprotein (involved in the transfer of drugs including digoxin, dexamethasone, cyclosporin A, and chemotherapeutic agents like vincristine and vinblastine), and the multi-drug resistance proteins 1–3 (involved in the transfer of drugs such as methotrexate and HIV protease inhibitors).^{8,11} The expression and distribution of drug transporters within the placenta may vary according to gestation.

Pinocytosis

In pinocytosis, drugs become completely enveloped into invaginations of the membrane and are then released on the other side of the cell. Very little is known about this method of transfer and about the drugs which cross the placenta by this mechanism.

Placental transfer of anaesthetic drugs

Induction agents

Thiopental is the most commonly used induction agent in parturients. It is a highly lipid-soluble weak acid which is 61% unionized at plasma pH and 75% bound to plasma albumin. It rapidly crosses the placenta and is quickly cleared by the neonate after delivery.¹² Propofol is also very lipid soluble and able to cross the placenta easily. It has been associated with transient depression of Apgar scores and neurobehavioural effects in the neonate.

Inhalation agents

Volatile anaesthetic agents readily cross the placenta as they are highly lipid soluble and have low molecular weights. A prolonged dose-delivery interval results in greater transfer and therefore a greater sedative effect on the neonate. Nitrous oxide also crosses the

placenta rapidly. Diffusion hypoxia can occur in neonates exposed to nitrous oxide immediately before delivery and therefore supplemental oxygen may be required.

Neuromuscular blocking agents

Neuromuscular blocking agents are large, poorly lipid soluble, and highly ionized molecules. They cross the placenta very slowly and pose no significant clinical problems to the neonate.¹³

Opioids

All opioids cross the placenta in significant amounts. Meperidine is commonly used during labour. It is 50% plasma protein-bound and crosses the placenta readily. Maximal uptake by the fetal tissues occurs 2–3 h after a maternal i.m. dose, and this is the time when neonatal respiratory depression is most likely to occur. Detrimental effects may last 72 h or more after delivery and are attributed to the prolonged half-life of both meperidine and its metabolite, normeperidine, in the neonate.¹⁴ Morphine is less lipid soluble but because of its poor protein binding, it readily crosses the placenta. Fentanyl is very lipid soluble and crosses the placenta rapidly. Remifentanyl crosses the placenta but is rapidly metabolized by the fetus and its use for labour analgesia has not been associated with adverse neonatal effects.

Local anaesthetic agents

In order for local anaesthetic agents administered epidurally to affect the fetus, they must be absorbed into the systemic circulation before placental transfer. Local anaesthetics are weak bases and have relatively low degrees of ionization at physiological pH. Bupivacaine and ropivacaine are highly lipid soluble but have a high degree of protein binding. Some systemic absorption occurs through the large epidural venous plexuses with subsequent transfer across the placenta by simple diffusion. Lidocaine is less lipid soluble than bupivacaine but has a lower degree of protein binding, so it will also cross the placenta.

Local anaesthetics can accumulate in the fetus due to 'ion trapping' if the fetus becomes acidotic. Ion trapping occurs when the decreased pH in the fetus produces an increased proportion of ionized drug which is then unable to cross the placenta.³

Anticholinergics

Transfer of anticholinergic drugs across the placenta mimics the transfer of these drugs across the blood–brain barrier. Glycopyrrolate is a quaternary ammonium compound which is fully ionized and is therefore poorly transferred across the placenta. Atropine is a lipid-soluble tertiary amine which demonstrates complete placental transfer.¹⁵

Neostigmine

Neostigmine is a quaternary ammonium compound but is a small molecule which is able to cross the placenta more rapidly than glycopyrrolate.¹³ In a few cases where neostigmine has been used with glycopyrrolate to reverse non-depolarizing neuromuscular block

in pregnancy, profound fetal bradycardia has been reported.^{13,15} Consequently, for general anaesthesia in pregnancy where the baby is to remain *in utero*, it may be advisable to use neostigmine with atropine rather than with glycopyrrolate.

Benzodiazepines

Benzodiazepines are highly lipid soluble and unionized and therefore exhibit rapid and complete diffusion across the placenta.

Vasoactive drugs

Sympathomimetics such as ephedrine and phenylephrine are commonly used to treat maternal hypotension during regional anaesthesia. Ephedrine increases maternal arterial pressure mainly by increasing cardiac output via cardiac β -1 receptors, with a smaller contribution from vasoconstriction via α -1 receptor stimulation. It has minimal effects on uteroplacental blood flow. It readily crosses the placenta and has been shown to be associated with a decrease in umbilical arterial pH, probably through stimulating an increase in fetal metabolic rate. Phenylephrine increases maternal arterial pressure by vasoconstriction through its direct effect on α -1 receptors. It has been shown to prevent maternal hypotension without causing fetal acidosis, when combined with rapid crystalloid infusion immediately after spinal anaesthetic injection.¹⁶

Summary

The placenta is a remarkable organ which plays a vital role in ensuring the satisfactory growth and development of the fetus. Further research is required to increase our understanding of the molecular mechanisms of transplacental drug transfer, and the ways in which drugs may impact on fetal health and wellbeing.

Declaration of interest

None declared.

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