Functions of the placenta

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Abstract

The placenta is an ephemeral materno-fetal organ with chorionic (fetal) villi bathed in maternal blood spaces, which allows restricted transfer of metabolites and drugs across specialized transfer areas. The placenta develops respiratory, nutritive and excretory functions while the fetal organs mature, and is also an important endocrine organ.

Keywords Function; physiology; placenta

Royal College of Anaesthetists CPD Matrix: 1A01

Learning objectives

After reading this article, you should be able to describe:

- the structure and development of the placenta and the relationship between structure and function
- how adequate gas exchange, supplies of nutrients and mineral salts, water balance and removal of waste products are achieved by the placenta
- the endocrine role of the placenta during pregnancy and the kinds of drug that are counter-indicated for the mother during this time

Structure of the placenta

The hemichorial placenta forms at the interface of the maternal uterine tissues and those of the implanted embryo, specifically that part of the modified endometrium apposed to the chorionic vesicle, the *decidua basalis*, and the associated part of the fetal trophoblast, which eventually develops leafy villi and is known as the *chorion frondosum*.

The trophoblast rapidly differentiates into two layers: the syncytiotrophoblast and the cytotrophoblast. The multinucleated syncytiotrophoblast develops lacunae, between which the cytotrophoblastic layer projects villi. The syncytiotrophoblast becomes progressively compressed into a layer covering each villus and separating the cytotrophoblastic layer (which itself becomes discontinuous) from the lacunae, which merge to form intervillous spaces. Trophoblastic enzymes erode about 100 spiral arteries and veins of the uterine wall, and so the branched villi become bathed in approximately 150 ml of maternal blood (Figure 1a), which is replaced three to four times a minute. Fetal mesenchymal cells invade the villi and generate vascular networks connecting the umbilical arteries and vein. The fetal and maternal circulations, therefore, come to be separated, in specialized transfer areas between cytotrophoblastic cells, by only the endothelial cells lining the microvessels of the fetal villi, associated basement membrane, and thin areas of syncytiotrophoblast (Figure 1b). These areas may constitute 5–10% of the 16 m^2 surface area within the term placenta.

The apices of the villi tend not to develop a mesenchymal core, but remain as solid cytotrophoblastic cell columns. While others remain free-floating in the intervillous space, some villi take on an anchoring function by abutting onto the maternal decidual cells. Moreover, the cytotrophoblastic cells spread over the *decidua basalis* to form a complete layer – the cytotrophoblastic shell. Specialized cytotrophoblastic cells further invade the spiral arteries and cause them to become remodelled[1,2] so that blood enters the intervillous space at a lower than normal arterial pressure. In this way, the placenta progressively and temporarily assumes the eventual functions of the fetal lungs (gaseous exchange), gastrointestinal tract (uptake of nutrients), and kidneys (regulation of fluid volume and elimination of waste metabolites) while these organs are developing. It also acts as an endocrine organ in its own right, releasing steroid and peptide hormones into both circulations.

Transfer of a substance across the maternofetal barrier depends on the thickness and extent of the barrier as well as the concentration gradient of the substance, or the presence of active transfer mechanisms, as detailed below.

Gas exchange across the placenta

Respiratory gases are relatively small molecules, which cross the maternofetal barrier by flow-limited passive diffusion. This placental blood–blood barrier, however, is much thicker than the blood–gas barrier of the lung (3.5 μm versus 0.5 μm) and has a much smaller surface area (about 16 m^2 versus 50–60 m^2).

The fetus compensates by:

- having an increased concentration of fetal haemoglobin (HbF; 170 g/litre versus 120 g/litre in the mother, an increase of about 40%)
- HbF having a higher affinity for oxygen, resulting in 50% saturation (P_{50}) at a lower partial pressure of oxygen (PO_2). This represents an arterial oxygen tension of 18–20 mmHg in the fetus versus 26.6 mmHg in the adult. The end result of all this is a higher oxygen content in fetal blood at any given PO_2 (Figure 2). This left shift in the oxyhaemoglobin dissociation curve occurs because HbF is a tetramer of α and γ subunits ($\alpha_2\ \gamma_2$) and does not contain β subunits found in adult haemoglobin (HbA; $\alpha_2\ \beta_2$). The β subunits of HbA (especially deoxyHbA) bind strongly to 2,3-diphosphoglycerate (a by-product of glycolysis, which approaches similar molar concentrations to HbA in the vicinity of respiring tissues, and displaces oxygen)
- a double Bohr effect (i.e. the direct effect of pH on haemoglobin's affinity for oxygen). Carbon dioxide is very soluble and, within red blood cells, the majority (60%)

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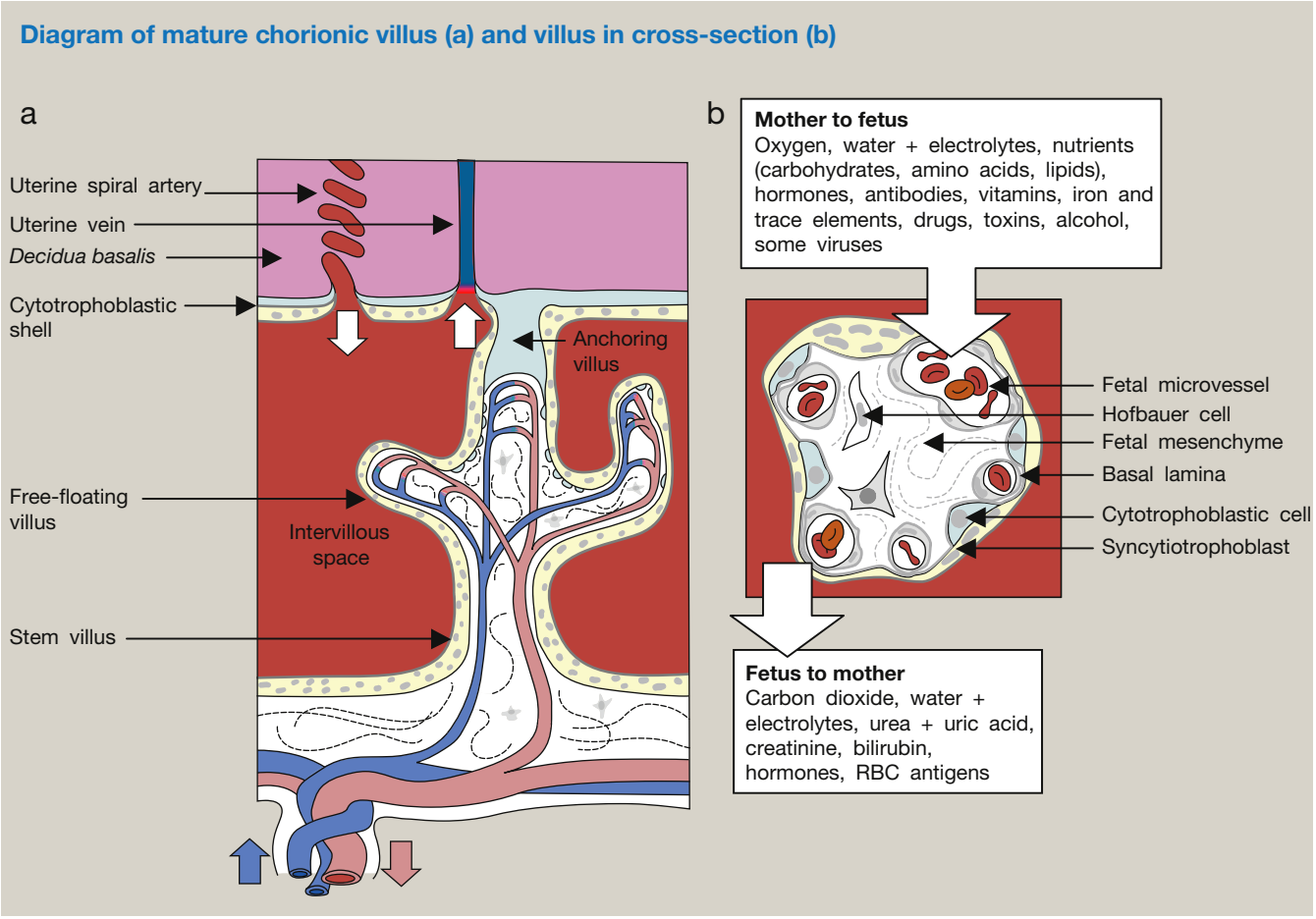
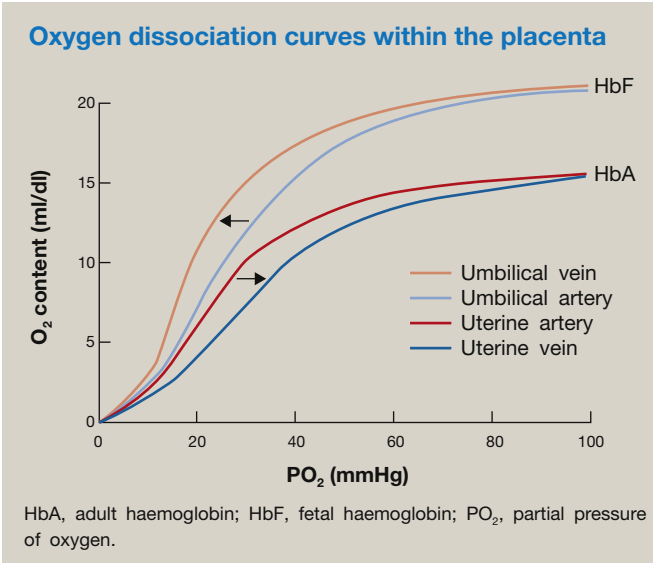


Figure 1



HbA, adult haemoglobin; HbF, fetal haemoglobin; PO_2, partial pressure of oxygen.

Figure 2

combines with water to form carbonic acid, which then dissociates into protons and bicarbonate ions:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

(only 30% of carbon dioxide combines with haemoglobin and 10% remains in physical solution). The fetal microcirculation has a high partial pressure of carbon dioxide (PCO_2) and a relatively low pH (44 mmHg and 7.33 in the umbilical artery) compared with the uterine artery (28 mmHg and 7.45). Protons and bicarbonate ions will diffuse along concentration gradients from the fetal microcirculation to the intervillous space, lowering the pH and causing oxygen to dissociate from the maternal HbA. With the removal of protons, the pH will simultaneously increase within the fetal microvessels, facilitating uptake of oxygen by HbF. This double Bohr effect means that the oxygen dissociation curves for HbA and HbF move apart (Figure 2)

- a double Haldane effect (i.e. the increased ability of deoxyhaemoglobin to accept protons and carry carbon dioxide). As maternal blood unloads oxygen, its deoxygenated HbA accepts protons with greater avidity, shifting the above equation to the right, and facilitating the formation of carboxyhaemoglobin. The uptake of oxygen by HbF simultaneously reduces its capacity to accept protons, allowing them to combine with bicarbonate ions and so shifting the equation to the left.

Nutrient uptake by the placenta

The fetus obtains the nutrients required to support its growth from the maternal blood via the placenta — principally glucose,

amino acids, fatty acids, vitamins and minerals. Nutrient transport is influenced by concentration gradients as well as placental blood flow and metabolism.[3]

Glucose

Transport of glucose occurs by facilitated diffusion along a concentration gradient across the placenta from mother to fetus. The process is mediated by the GLUT family of transporters, principally the GLUT-1 isoform, which occurs within the maternal ('microvillous') and fetal ('basal') membranes of the syncytiotrophoblast.[4] The latter site is populated less densely and GLUT-1 at this locale acts as a rate-limiting step. Other isoforms occur variably at different times of gestation.

Amino acids

The high rate of protein synthesis needed for growth and development means that fetal concentrations of amino acids are generally higher than the maternal, and some 15–20 specific active transport mechanisms have been identified in the microvillous or basal syncytiotrophoblast membranes.[3,5] These mechanisms include Na^+-dependent as well as Na^+/Cl^--dependent, cationic and glycoprotein-associated amino acid transporters.[6] The transporters may be inhibited by alcohol or nicotine.

Fatty acids

Essential fatty acids are a vital component of membranes and are a requirement for cellular growth and metabolism. Maternal lipoproteins may be taken up by the placenta directly via specific lipoprotein receptors or scavenger receptors, or fatty acids may be generated by placental lipase activity, especially lipoprotein lipase in the microvillous membrane. The free fatty acids (FFA) that are produced diffuse across the membrane, although unesterified fatty acid uptake is probably mediated by fatty acid-binding proteins ($FABP_{pm}$), fatty acid translocase and fatty acid transport proteins (FATP) by a mechanism that remains unclear.[7] Within the syncytial cytoplasm, FABP-bound FFA may be esterified, β-oxidized or transported to the fetal vasculature by FATP or diffusion.

Calcium

The fetus accumulates 25–30 g of calcium over the course of a pregnancy to mineralize the skeleton (particularly during the third trimester) as well as to contribute to many cellular functions, including cellular growth, neurotransmitter release and signal transduction. Various reverse transcriptase polymerase chain reaction (RT-PCR) and blocking studies point to (especially L-type) voltage-gated calcium channel and transient receptor potential channels as candidates for actively transporting calcium channels in the syncytiotrophoblast membranes.[8]

Iron

Ferritins and transferrins have evolved, respectively, to store and transport iron – vital elements in many cellular processes, but also a catalyst for the production of harmful reactive oxygen species. Diferric transferrin binds to a receptor on the microvillous syncytiotrophoblast membrane and the complex is internalized into acidic vesicles.[9] Subsequent transport to the fetal vasculature probably involves a divalent metal transporter-1, iron-regulated transporter-1 and copper oxidase (hephaestin).

Fluid regulation by the placenta

Water derived from the maternal circulation via the placenta moves between the fetal body compartments, the placenta and the amniotic fluid.[10] Resorption of amniotic fluid occurs by fetal swallowing, but also more directly across the amnion to the fetal circulation (the intramembranous pathway). Movement of water across the placental syncytiotrophoblast is probably driven by a combination of osmotic and hydrostatic forces, possibly regulated by the expression of aquaporin water channels in the plasma membranes.

Elimination of waste metabolites by the placenta

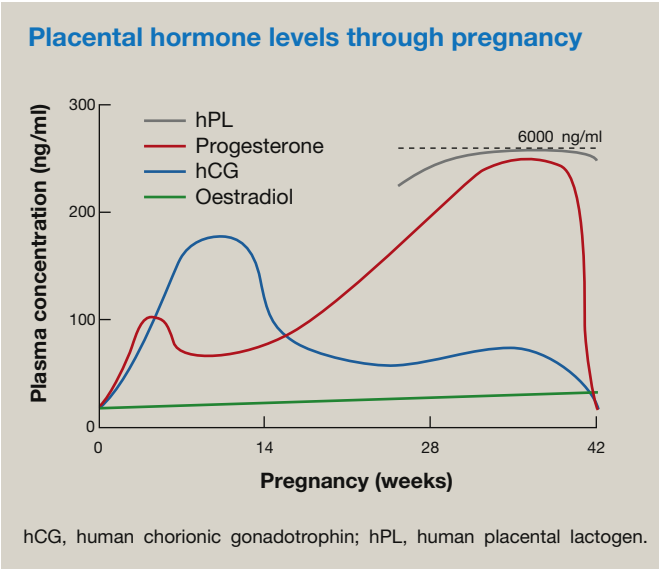
Excretion of carbon dioxide is discussed above. Toxic ammonia from purine and amino acid catabolism is converted into uric acid and urea, both of which diffuse passively across the syncytiotrophoblast.

Bilirubin is a breakdown product of normal haem catabolism and its unconjugated form is also believed to cross the placenta by passive diffusion, although there is some evidence that carrier-mediated transport may occur at both the microvillous and the basal membranes.[11]

Hormonal action of the placenta

The placenta functions as an endocrine organ. It secretes both peptide and steroid hormones, which act to maintain pregnancy and prepare for parturition and lactation. The two main peptide hormones secreted by the placenta are human chorionic gonadotrophin (hCG; produced by the syncytiotrophoblast) and human placental lactogen (hPL), also known as human chorionic somatomammotropin (Figure 3). hCG is luteotrophic, prolonging the life of the corpus luteum, and hence maintaining progesterone secretion to prevent shedding of the endometrium. After 6–8 weeks the placenta takes over the production of progesterone and continues to secrete smaller amounts of hCG.

hPL is also produced by the syncytiotrophoblast. It acts to promote the growth of breast tissue in preparation for lactation



hCG, human chorionic gonadotrophin; hPL, human placental lactogen.

Figure 3

and also has metabolic effects by antagonizing maternal glucose use and enhancing fat mobilization.

The major steroids secreted by the placenta are oestrogens (principally oestradiol) and progesterone. Progesterone maintains the endometrium, reduces myometrial activity and suppresses maternal immunological responses to fetal antigens. It acts as a precursor for steroid production by the fetal adrenal glands. Production of oestrogens involves the use of androgenic substrates from the mother and fetus ('the maternofetoplacental unit'). Dehydroepiandrosterone (DHEA) is produced by the fetal adrenal gland and is converted to 16-hydroxy-DHEA in the fetal liver. Active aromatase enzymes in the placenta then convert these precursors into oestradiol and oestrone.

Drug transport across the placenta

Many drugs are able to cross the placenta and can have a harmful effect on the fetus at any time during pregnancy. Drugs administered during the first trimester may produce congenital malformations. Those given in later trimesters may cause problems that affect the growth or functional development of the fetus or may even be toxic to fetal tissue.

Small hydrophobic compounds are rapidly transported from mother to fetus by flow-limited passive diffusion. Hydrophilic drugs diffuse more slowly. Their diffusion is membrane limited but may still pose a threat to the fetus (e.g. transport of teratogenic substances). Some commonly encountered drugs are briefly mentioned below, but careful consideration of both risk and benefit should always be given when prescribing in pregnancy.

Anaesthetic agents

During parturition, anaesthetic agents are often administered. Inhaled substances such as nitrous oxide are lipid soluble and pass rapidly from mother to fetus, and a similar situation is seen with respect to some induction agents. Thiopental can reach levels in the fetus approaching those of the mother only 1 minute after injection. Etomidate is less lipophilic and crosses the placenta more slowly. Muscle relaxants such as suxamethonium are highly ionized and do not pass across the placenta easily. Anticholinergic agents such as atropine may cross the placenta easily, but those with a more polar structure (e.g. glycopyrrolate) do not pass across so readily. Many anticholinesterase agents are quaternary ammonium compounds (e.g. neostigmine and edrophonium) and due to their polar nature do not quickly pass across the placenta. Vasopressor agents such as ephedrine and phenylephrine pass across the placenta easily. Opioids may be highly lipophilic (e.g. morphine) and can rapidly cross the placenta, with levels in the fetus approaching those in the mother. However, some agents such as fentanyl show higher albumin binding in plasma, which reduces their relative lipophilicity and consequently their transit across the placenta.

Anticoagulants

Oral anticoagulants are teratogenic. Warfarin can readily cross the placenta and cause fetal malformation, although stopping warfarin before the sixth week of gestation has been shown to dramatically reduce this risk. Heparin does not readily cross the placenta and has a shorter half-life, making it more suitable for use in pregnancy.

Angiotensin-converting enzyme inhibitors

Most angiotensin-converting enzyme inhibitors are contraindicated in pregnancy. They are known to affect fetal and neonatal blood pressure and control of renal function.

Anti-epileptics

It should be considered whether the benefit of treatment outweighs the risk to the fetus. It has been reported that the risk of teratogenicity is greater if more than one drug is used. Also, because of the significant risk posed to the fetus, it is recommended that folic acid is taken throughout the pregnancy.

Non-steroidal anti-inflammatory drugs

These agents may need to be prescribed for their tocolytic effect. They can readily cross the placenta. It has been reported that with regular use there is a risk of closure of the fetal ductus arteriosus (*in utero*) and possibly the development of persistent pulmonary hypertension of the newborn. There are also implications of a delayed onset and increased duration of labour.

Corticosteroids

Corticosteroids vary in their ability to cross the placenta. Some, such as betamethasone and dexamethasone, will cross easily, whereas 88% of prednisolone is inactivated as it crosses the placenta. The major concerns regarding prolonged or repeated administration in pregnancy are that fetal adrenal suppression may occur and that there is an increased risk of intrauterine growth restriction. Glucocorticoids are used to promote fetal lung maturity when preterm birth is implicated, and it is therefore important that these agents can rapidly pass across the placenta when administered. ◆

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