Placental physiology

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Introduction

The embryo implants into the endometrium (decidua), and it rapidly progresses into a sphere enveloping the amniotic cavity with a local thickening, the placenta. The placenta is a vital organ that gradually forms during the first three months of pregnancy. It is a temporary organ whose genetic characteristics are identical to those of the fetus. The several layers that form this organ (parenchyma, chorion, amnion, and umbilical cord) need to develop normally to allow proper function during pregnancy.

Anatomy and blood flow

The placenta develops from the blastocyst shortly after implantation. Due to hormonal changes in the mother (e.g. increase in luteinising hormone), degrading enzymes released, autocrine growth factors (e.g. human chorionic gonadotropin [hCG]), and insulin growth factor (IGF), the blastocyst further invades the endometrium. Gastrulation (reorganisation into a multilayered and multidimensional structure) now takes place.

At term, the human placenta is a villus haemomonochorial structure, the maternal blood is in direct contact with the fetal villus, which is composed of a single layer of trophoblasts (monochorial). Abnormal proliferation of trophoblasts results in gestational trophoblastic disease.

Within 11 days of fertilisation, the trophoblast forms two layers, the cytotrophoblast and the syncytiotrophoblast (STB), containing lacunar lakes. The lacunae enlarge with the trophoblasts forming villi, which consist of the vascularised core of the cytotrophoblast covered by the STB. The maternal spiral arteries are eroded by the trophoblast, which then flows directly into the intervillous space.

The functional unit of the placenta is known as the uteroplacental unit. This unit contains fetal and maternal components that are arranged in a specific manner to allow maternal and fetal blood to come into close proximity to each other, without mixing. The fetal side of the placenta forms the chorionic plate while the maternal side forms the basal plate. The area between these two plates is known as the intervillous space.

Uterine blood flow (UBF) comes from the uterine arteries with minor contributions from the ovarian arteries. Maternal blood travels through the spiral arteries and reaches the intervillous space where it pools, surrounded by villi that contain fetal capillaries. These capillaries will receive deoxygenated blood from the fetus via two umbilical arteries. Maternal-fetal exchange of nutrients, respiratory gases, fetal waste, and other substances takes place at the terminal villi. Maternal blood then returns to the maternal circulation through the uterine veins, and oxygenated blood travels to the fetus via the umbilical vein (Figure 1).

In a term pregnancy, the uterus receives 500–900 ml/min or 10% of the maternal cardiac output (compared to 50–100 ml/min in the non-pregnant uterus). The majority of this (80–90%) supplies the placenta while the rest goes to the myometrium and non-placental endometrium. To accommodate this increase in blood flow, the spiral arteries of the uterus undergo growth and remodelling. The replacement of the tunica media in these vessels results in optimal vasodilation, resulting in uterine arterial
pressure (UAP) being dependent on maternal blood pressure and cardiac output.

The uterine vasculature still maintains intrinsic responsiveness to α-adrenergic agents and possibly β-adrenergic agents, thus affecting uterine vascular resistance (UVR) so that UBF is determined as follows: 5

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\text{Uterine blood flow (UBF)} = \frac{\text{uterine arterial pressure (UAP)} - \text{uterine venous pressure (UVP)}}{\text{uterine vascular resistance (UVR)}}
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Utterine perfusion pressure (UPP) = UAP - UVP

Subsequently, during pregnancy, three major factors decrease UBF: systemic hypotension, uterine vasoconstriction, and uterine contractions. Hypovolemia, aortocaval compression, and sympathetic blockade caused by neuraxial anaesthesia can cause maternal hypotension. Aortocaval compression, certain drugs (e.g. oxytocin), uterine contractions, or skeletal hypertonia (e.g. seizures, Valsalva) can cause an increase in UVP resulting in a decrease in UBF. UVR can be increased by the stress-induced release of endogenous catecholamine, vasopressin release secondary to hypovolemia, exogenous vasopressors (e.g. phentolamine, epinephrine, and a high dose of local anaesthetics), and compression of the endometrial spiral arterioles during contractions. Clinical studies have shown phentolamine and metaraminol are effective in treating pregnant women and are associated with less fetal acidosis compared to ephedrine. 5 Hypertensive disorders are associated with decreased UBF due to generalised vasoconstriction. 4

Function

The placenta has numerous responsibilities with the terminal villi acting as a functional unit allowing the maternal-fetal exchange of gases and nutrients. Oxygen, water and electrolytes, hormones, and nutrients are provided by maternal blood, while the fetus excretes water, urea, hormones, carbon dioxide, and other waste products. The maternal and fetal blood do not mix, instead, blood flow moderates the passive or active transport of products between the vasculature. 6

Gas exchange

Fetal respiratory movements can be seen as early as 11 weeks. There is no gaseous exchange, instead oxygenation and elimination of carbon dioxide take place by simple diffusion across the fetal membrane. The oxygen supply to the fetus is at 8 ml/kg/min and is achieved by a cord blood flow of 165–330 ml/min.

The rate of diffusion of a gas is dependent on its lipid solubility and size. Because of the differences in solubility, carbon dioxide diffuses across the lipid membrane 20 times faster than oxygen, and several other factors affect the movement of respiratory gases between maternal and fetal circulation. Critical to this process is the concentration gradient between fetal and maternal blood: structural differences in maternal and fetal haemoglobin and their oxygen dissociation curves, the double Bohr effect, and the double Haldane effect. 7,8 The fetus compensates for low PO2 by having a higher haematocrit (Hb 15–17 g/dl) and a left-shifted oxygen dissociated curve with HbF having a greater affinity for oxygen. Consequently, the average oxygen content of fetal blood is greater than maternal blood. 7

Metabolic transfer

Nutrients are obtained from maternal blood. Glucose, the principal source of energy for the fetus, is transferred by transport proteins (seven GLUT isoforms have been identified) through the process of facilitated diffusion and converted into glucose-6-phosphate or glycogen. An increased expression of GLUT-1 has been seen in pregestational diabetes mellitus. 9 Triglycerides and fatty acids are transported directly from the mother in early pregnancy, while other lipids required for growth and development are produced in the fetus. Cholesterol is an important precursor for progesterone and oestrogen. Amino acids, which are higher in fetal blood than in maternal blood, are transferred by active transport involving an enzymatic process (ATPase). Protein synthesis is initially 1 g/day and becomes 7.5 g/day at term. 10

Water and electrolytes

Various aquaporin isotypes form specific water channels that allow rapid transcellular movement of water in response to osmotic and hydrostatic pressure gradients. 11 This movement will be altered when the mother receives hypo- or hypertonic intravenous fluid. 11 Sodium, potassium, and chloride cross the fetal membrane via simple diffusion, while calcium, phosphorus, and iron cross by active transport. 6

Endocrine

The placenta releases placental growth factor to prepare the maternal body for cardiovascular adaption. This factor also promotes fetal development and maturity. Human chorionic somatomammotropin (HCS), or human placental lactogen (HPL), promotes breast development and changes the maternal metabolism to decrease the woman's insulin sensitivity, thus allowing more glucose to be available for the fetus. 5 In the fetal circulation, HPL modulates embryonic development, regulates intermediary metabolism, and stimulates the production of insulin-like growth factor, insulin and adrenocortical hormones, and pulmonary surfactant. 5

There is a slow movement of the following hormones across the placenta: insulin, steroids from the adrenals, thyroid, and chorionic gonadotropin/placental lactogen. This results in their concentration being lower than in maternal plasma. Parathormone and calcitonin do not cross the placenta. The placenta also has multiple enzymatic functions including the production of diame oxide, which inactivates circulatory pressor amines, oxytocinase, which neutralises oxytocin, and phospholipase A2, which synthesises arachidonic acid. 12

Immunological

Antibodies and antigens in immunological quantities can cross the placenta in both directions. The placenta can also metabolise

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numerous substances and protect against microbes. Essential role players in the protection of the fetus include macrophages in the stroma of the chorionic villi and STBs. In addition, leucocytes can be found in the decidua of the endometrium. 6

**Anticoagulant**

The STB takes on vascular characteristics such as the presence of von Willebrand factor (vWF), CD31 makers, adhesion molecules, and coagulation components. Thrombosis of the placental vasculature would be devastating, subsequently, there needs to be an efficient mechanism for fast activation and localised regulation of coagulation. Procoagulant (e.g. tissue factor and plasminogen activator inhibitors) and anticoagulant (e.g. tissue factor pathway inhibitor, thrombomodulin, nitric oxide, ADPase, carbon monoxide, a membrane glycoprotein that activates protein C, and annexin V) components are present on the placental vascular endothelial cells and STB. Reduced annexin V has been associated with the presence of antiphospholipid antibodies. Activation of coagulation may be a favoured process as seen by the elevation of fibrin deposits in pathological states. 13

**Placental drug transfer**

Several factors affect drug transfer across the placenta and can be summarised as physical or pharmacological. Physical factors include placental surface area, placental thickness, pH of maternal and fetal blood, placental metabolism, UBF, and the presence of placental drug transporters. Pharmacological factors are the molecular weight of the drug, lipid solubility, pKa, protein binding, and concentration gradient across the placenta. 8 The mechanisms of drug transfer are discussed below.

**Diffusion**

Small, nonpolar and uncharged particles can cross the lipid bilayer via simple diffusion (passes directly across the lipid membrane or through channel proteins). Fick’s law of diffusion determines this movement and it can be used to calculate the amount of oxygen and carbon dioxide that passes directly through the lipid bilayer.

Net flux (amount transported) = diffusing capacity of membrane (DM) × (P1 - P2)

Where diffusing capacity = A (solubility) / T (√MW)

(P1 - P2) is the pressure gradient over a membrane where P1 is maternal and P2 is fetal, A is the surface area of the membrane, T is the thickness of the membrane, and √MW is the square root of the molecular weight of the particle.

Therefore, charged or large molecules will have a slower passage through the membrane. Carrier proteins in the lipid bilayer increase the rate of diffusion by creating channels for these particles to travel (facilitated diffusion). Hormones will regulate whether the channels are open or closed. Glucose is transported by facilitated diffusion. 14

**Osmotic and hydrostatic pressure (bulk flow)**

Water is a polarised molecule and its passage is driven by osmosis and hydrostatic pressure, it is carried by aquaporins in the placental membrane. 11 This bulk flow drags along dissolved solutes.

**Active transport**

Active transport is similar to facilitated diffusion, except that cellular energy is used to move the molecules against the concentration gradient. When ATP is hydrolysed for energy, this is called direct active transport (e.g. Na/K ATPase pump, amino acids, calcium, and phosphate). 2

**Vesicular transport**

Large macromolecules cross from maternal to fetal circulation through pinocytosis, which is a form of energy-requiring vesicular transport. The cell membrane forms a vesicle by surrounding the macromolecule. This vesicle then fuses with another cellular membrane releasing the macromolecule. Immunoglobulins and iron are examples of products transferred through this process. 5

**Breaks**

The placenta is not an impenetrable structure and occasionally fetal and maternal blood may mix. This Rh sensitisation occurs usually at delivery. 7

**References**


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