Placental development and physiology

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INTRODUCTION

Placental development is a highly regulated process that is essential for normal fetal growth and development and maintenance of a healthy pregnancy. The placenta fulfills several critical roles as the interface between mother and fetus, including:

- Preventing immune rejection of the fetal allograft
- Transferring oxygen and nutrients from the maternal to the fetal circulation
- Transferring carbon dioxide and wastes from the fetal to the maternal circulation
- Secreting peptide and steroid hormones that regulate both maternal metabolism and fetal growth and development

This topic will discuss placental development and physiology. Gross and histologic placental pathology are reviewed separately. (See "Gross examination of the placenta" and "The placental pathology report".)

EARLY DEVELOPMENT

Implantation and invasion of trophoblast — Development of the placenta, embryo, and fetus is a continuous process that begins at the time of fertilization:

- On days 1 to 3 of post fertilization, the zygote (fertilized ovum) develops within the fallopian tube.

- On day 4, the morula (a solid mass of blastomere cells) enters the uterus.

- On day 5, the morula becomes a blastocyst as fluid accumulates and polarization of the cells occurs. The blastocyst has an outer layer of cells (trophoblast) that will form the placenta and fetal membranes, an inner cell mass at one pole that will form the embryo, and a fluid filled cavity. The inner and outer cell masses multiply and the fluid cavity enlarges until the expanded blastocyst hatches out of the zona shell. Initially it is bathed in uterine secretions that provide oxygen and metabolic substrates; however, these secretions soon become inadequate for support of further development.

- On day 6, within 24 hours of hatching, the blastocyst implants in the decidua, which provides access to substrates (glycogen filled stromal cells) necessary for continued growth. Implantation involves movement of the blastocyst to an optimal location (typically the mid to upper anterior or posterior wall of the uterus), adhesion, and invasion.

- By day 13, as the trophoblast erodes deeper into the decidua, vacuoles form and become confluent to form lacunae. The lacunar space eventually becomes the intervillous space.

- The progenitor cytotrophoblast cell is the stem cell of the placenta. These cells proliferate throughout gestation, differentiating along two pathways to form either villous cytotrophoblast (the inner cell layer) which ultimately becomes syncytiotrophoblast (outer cellular layer) or extravillous cytotrophoblast (EVT) (algorithm 1). Syncytiotrophoblast is a specialized epithelium that has several functions, including transport of gases, nutrients, and waste products and synthesis of peptide and steroid hormones that regulate placental, fetal, and maternal systems. EVT has a proliferative component and an invasive component. There is also a migratory EVT, which is neither invasive nor proliferative; these cells populate the cell islands, septum, chorionic plate, and chorion laeve.

  At four to five weeks of gestation (note change to menstrual dating, ie, dating from the first day of last menstrual period rather than the day of fertilization), EVT erupts in columns with proliferative trophoblast at the base and invasive trophoblast at the distal portion of the column. EVT that invades decidua is called interstitial EVT, whereas EVT that invades and remodels the spiral arteries is called endovascular EVT. Endovascular invasion (intramural or intra-arterial) involves replacement or displacement of vascular smooth muscle and endothelial cells and transforms the narrow spiral arteries into wide uteroplacental arteries (algorithm 1). Anastomoses between the dilated spiral arteries and endometrial veins form maternal sinusoids, which eventually distribute blood into the low resistance vascular network of the lacunar system, thus establishing the uteroplacental circulation.

During invasion, EVT expresses specific proteins defining the stage and role in the differentiation and invasion process. These include integrin cell-extracellular matrix antigens, matrix metalloproteinases (MMPs), signal transduction proteins such as transforming growth factor-beta (TGF-beta), vascular endothelial growth factor (VEGF) and VEGF receptors, and insulin-like growth factor 2.

To invade the decidua and myometrium, the EVT must degrade the extracellular matrix by employing several members of the MMP protease family. The activity of these MMPs is regulated by their tissue inhibitors (TIMPs). TIMP-1, an inhibitor of all MMPs, and TIMP-2 have been found in decidual cells and EVTs. Hepatocyte growth factor (HGF) stimulates trophoblast invasion via the met receptor and induction of MMP-9. The decidua prevents uninhibited EVT invasion by secreting locally acting factors (cytokines, protease inhibitors), which modulate trophoblast invasion.

The trophoblast shell plugs the ends of uteroplacental vessels early in gestation, such that very early in gestation placental tissue develops in a low oxygen environment supported by histiotrophic nutrition [1,2]. Histiotroph is an extracellular material that is produced by endometrial glands in the decidua and accumulates in the space between the maternal and fetal tissues. It is phagocytosed initially by the trophectoderm of the blastocyst, and later by the trophoblast of the placenta or the endoderm of the yolk sac. This environment is thought to protect the developing embryo from oxygen free radical mediated teratogenesis [3].

- Beginning at six to seven weeks of gestation, progressive and gradual disintegration of the plugs allows maternal blood flow into the previously bloodless intervillous space [4], bathing the villous tissue and thereby providing hemotrophic nutrition (ie, the exchange of bloodborne materials between the maternal and fetal circulations) and increasing intraplacental oxygen concentration threefold.

  Oxygen imposes oxidative stress, which is overwhelming in some pregnancies and leads to miscarriage [5-7]. Oxygen is also a major regulator of trophoblast invasion by its effects on expression of the transcription factor hypoxia-inducible factor 1 and TGF-beta-3 (an inhibitor of invasion). Very early in pregnancy when oxygen tension is low, activity of these factors is high, thus promoting trophoblast invasion. As oxygen tension rises, activity of the factors and, in turn, trophoblast invasion decrease. In vitro, low oxygen tension (hypoxia) promotes trophoblast differentiation down the EVT pathway [8].

Villous development

- In week 2 post-fertilization, a layer of syncytiotrophoblast with a core of cytotrophoblast evaginates into the lacunar space to form primary mesenchymal villi. With further

development, the villi acquire an inner core of embryonic mesoderm and become secondary villi.

- By week 3 post-fertilization, the embryonic mesoderm differentiates into blood vessels that subsequently connect to vessels developing in the umbilical cord and embryo, thus forming tertiary villi.

Some villi are anchored to the maternal decidua, others float freely in the lacunae. The embryonic circulation is always separated from maternal decidua and blood by a layer of trophoblast.

Villous cytotrophoblast cells form a continuous layer (the Langhans layer) around first trimester placental villi and donate daughter cells to the overlying continuous syncytium, the syncytiotrophoblast. In late gestation, few villous cytotrophoblast cells are found. At term, the surface area of the syncytiotrophoblast is 12 to 14 m^2. Turnover of syncytiotrophoblast is controlled by the rates of fusion of villous cytotrophoblast and apoptosis. The human endogenous defective retrovirus HERV-W-derived protein syncytin is highly expressed in syncytiotrophoblast and is responsible for cytotrophoblast fusion and syncytialization of trophoblast [9]. Syncytin expression is decreased in preeclamptic pregnancies [10,11].

In pregnancies at high altitude where there is a relative hypoxia or those complicated by maternal anemia, diffusing capacity across the placental surface is maintained by chorangiosis (an increase in volume fraction of fetal capillaries) [12], proliferation of cytotrophoblast cells [13], and decreased mean harmonic thickness of the villous membrane [14].

Vascular development — The proportion of the placenta occupied by blood vessels increases throughout gestation to facilitate nutrient transport. The three stages of human placental vascular development are an initial stage of vasculogenesis followed by branching and then nonbranching angiogenesis. The two umbilical arteries and the vein divide into networks forming the chorionic plate vasculature on the fetal surface of the placenta before diving through the chorionic plate into the stem villi, where they divide many more times in the immature intermediate villi in early pregnancy and mature intermediate villi of late pregnancy. They then terminate in the capillary loops of the terminal villi, which are the functional units of exchange (figure 1).

The terminal villi each contain three to five capillaries, which form capillary loops and occasional sinusoids, perhaps to reduce resistance and slow blood flow in order to maximize time for gas and nutrient exchange. Oxygen also regulates villous vasculogenesis as hypoxia promotes branching angiogenesis [15].

Vascular reactivity — In the absence of autonomic innervation, vascular reactivity in the placenta and umbilical cord is controlled by endocrine, autocrine, and paracrine signaling.

Regional differences in response to various families of mediators are seen throughout the umbilical cord, chorionic plate vessels, and villous vessels. Important mediators include vasoconstrictors, such as the renin-angiotensin system and endothelin, and vasodilators, such as nitric oxide, hydrogen sulfide, and carbon monoxide, as well as histamine, serotonin, prostaglandins, natriuretic peptides, parathyroid hormone, adrenomedullin, urocortin, and corticotropin-releasing hormone. Production and response to many of these factors are altered in pregnancies complicated by diabetes and preeclampsia.

Antithrombotic activity — Thrombosis in the placental vasculature can result in pregnancy loss [16]. To prevent stasis and coagulation of blood in the low velocity intervillous space, the trophoblast actively secretes substances (ADPase, nitric oxide and carbon monoxide) that prevent platelet and leukocyte adhesion and aggregation to the trophoblast surface [17].

The trophoblast surface also has anticoagulant activity. Upon syncytialization, negatively charged phospholipids are expressed on the trophoblast surface, and this potentially may activate the intrinsic pathway of coagulation. Annexin A5, a member of the Ca^{2+}/phospholipid-dependent protein family, has been proposed as a regulator of thrombosis and homeostasis on the villous trophoblast of the placenta by binding to negatively charged phospholipids, where it acts as an anticoagulant that forms a protective barrier over the trophoblast surface [18]. By contrast, antiphospholipid antibodies are thought to oppose the actions of annexin A5 and lead to blood coagulation and thus disrupt normal trophoblast function [19].

Release of microparticles and exosomes — The turnover of villous trophoblast as gestation proceeds releases trophoblast apoptotic material from syncytial knots (approximately 100,000 fragments/day) and generates a variety of placental microparticles (size >100 nm) [20]. The rate of syncytiotrophoblast apoptosis, and hence the amount of microparticles released into maternal blood, increases with advancing gestational age and additionally increases with conditions such as fetal growth restriction [21] or preeclampsia [22]. These placental microparticles can interact with maternal immune and endothelial cells and contribute to systemic inflammation [20]. The release of apoptotic trophoblast material into the maternal circulation also includes cell-free DNA. Changes in the amount of cell-free DNA in the maternal circulation may reflect placental health [23], in addition to its role in noninvasive prenatal diagnosis. (See "Prenatal screening for common aneuploidies using cell-free DNA" and "Cell-free DNA screening for fetal conditions other than the common aneuploidies".)

Placental exosomes are a specific type of extracellular vesicle (size 40 to 120 nm) that are released via exocytosis into maternal plasma. Exosomes contain many signaling molecules including proteins, mRNA, microRNA, and noncoding RNAs that can then be incorporated into target cells by endocytosis. They regulate target cell activity via alteration in translational

activity, angiogenesis, proliferation, metabolism, and apoptosis, thereby functioning as a mechanism for intercellular communication [24]. Placental exosomes can be detected in maternal plasma from as early as 6 weeks of gestation, their number increases with advancing gestation and increases further in pregnancies complicated by diabetes or preeclampsia. In particular, placental exosomes contain members of the chromosome 19 (C19) microRNA cluster which attenuates viral replication in target cells via induction of autophagy, hence providing a mechanism whereby the placenta can increase viral resistance in maternal target cells during pregnancy [25].

Role of imprinted genes — Imprinting refers to the differential expression of genetic material depending on whether it was inherited from the male or female parent. To date, at least 80 imprinted genes have been described in humans. Imprinted genes may have a role in placental development and in the fetal demand for, and the placental supply of, maternal nutrients [26-29]. Gene knockout studies in mice have shown that the function of paternally expressed imprinted genes is to enhance fetal growth, whereas maternally imprinted genes suppress fetal growth.

Role of sexual dimorphism — There appears to be a degree of sexual dimorphism in some pregnancy outcomes, including preterm birth, preeclampsia, preterm prelabor rupture of membranes, and stillbirth [30]. Pregnancies with male fetuses, who grow faster and are usually larger than female fetuses, are associated with higher risk of these adverse outcomes [31]. Sexual dimorphism also affects fetal programming, whereby male and female fetuses exposed to the same intrauterine conditions (eg, maternal obesity or gestational diabetes mellitus) may have different outcomes [32-34].

The underlying physiologic mechanisms likely involve sexual dimorphism in placental function as shown for mitochondrial respiration [35], autophagy markers [36], and placental antioxidant defenses [37] in placentas from pregnant patients with obesity. There is clear sexual dimorphism in gene expression in the human placenta, and immune genes, in particular, are expressed at higher levels in placentas of female versus male fetuses [38].

Maternal inflammatory status (eg, asthma) [39], changes in diet [40], and treatment with n-3 long chain polyunsaturated fatty acids (LCPUFA) [41] also affect placental gene expression in a sex-dependent manner. Aromatase levels in placentas vary depending on fetal sex in both normal pregnancies and those with preeclampsia [42].

ABNORMAL DEVELOPMENT

Preeclampsia and fetal growth restriction — Alterations in trophoblast differentiation occur in various pathophysiological situations and may underlie pregnancy disorders, such as preeclampsia and fetal growth restriction (FGR).

Preeclampsia and FGR are associated with defects in endovascular extravillous trophoblast (EVT) invasion, where some spiral arteries are not invaded at all and some are superficially invaded, leading to lack of the normal physiological adaptation of spiral arteries to pregnancy, reduced blood flow into the intervillous space, and relative hypoxia/ischemia. Interstitial EVT density, however, is not different in pregnancies with preeclampsia. Minimal EVT apoptosis is seen in normal pregnancy, but 15 to 50 percent of cells are apoptotic in preeclampsia, a finding associated with macrophages around spiral arteries [17].

The mechanism for defective invasion may involve defects in protein expression. For example, integrin expression and increased TGF-beta expression appear to play a role in inhibiting trophoblast invasion [43]. In addition, trophoblast from pregnancies with preeclampsia produce less HGF, and anti-HGF antibody blocks HGF-induced invasion [44].

Placenta accreta spectrum — In placenta accreta spectrum (PAS), the anchoring villous tissue is in direct contact with the underlying myometrium and sometimes to the serosa or beyond. Whether this pathology results from lack of decidua, other physical factors (eg, scarring), over-invasiveness of trophoblast, or a combination of these factors, is controversial. The factors that affect the depth of invasion: accreta versus increta versus percreta, are also unclear.

Studies of EVT invasion in PAS are lacking. Conflicting findings have been presented regarding the extent and depth of vascular remodeling by EVT in these pregnancies [45,46]. PAS is associated with increased depth of invasion by both interstitial and endovascular trophoblast, but outer myometrial vessels are not remodeled, suggesting it is not simply the lack of decidua that allows deep myometrial invasion. The strong association of PAS with a history of prior cesarean birth and endometrial curettage suggests a role for uterine scarring. The depth of uterine invasion may be dependent on the depth of the original scar [45] with increta and percreta perhaps more likely to arise from dehiscence of a scar, thus giving cells of the trophoblast columns access to large outer myometrial vessels. However, this explanation would not explain PAS in primigravidas with no history of trauma [46]. A detailed a review of accreta etiopathology is beyond the scope of this topic but is available elsewhere [47].

Gestational trophoblastic disease — Gestational trophoblastic disease (GTD) arises from abnormal proliferation of trophoblast, and is reviewed in detail separately. (See "Gestational trophoblastic disease: Pathology", section on 'Pathogenesis'.)

METABOLIC AND ENDOCRINE FUNCTIONS

The metabolic and endocrine functions of the placenta must be tightly controlled to ensure maintenance of a healthy pregnancy. Although only one-sixth the size of the fetus in late

gestation, the placenta has a metabolic rate sixfold greater, consuming approximately half of oxygen and glucose supplied via the uterine circulation. One-third of the energy generated supports placental hormone synthesis and one-third supports placental transport activity. Alterations in placental metabolism may influence the amount of nutrients reaching the fetus and hence its growth.

Metabolic functions — The placenta is capable of synthesizing glycogen and cholesterol, which are sources of energy for the developing fetus. Additionally, cholesterol is an important precursor in hormone production.

- **Glycogen synthesis –** The placenta synthesizes appreciable amounts of glycogen, which it stores as an energy reserve. The uptake of glucose from the maternal circulation is a rate limiting step in this process, which involves a series of enzymes and regulators. Of particular importance is the enzyme glycogenin, which is coexpressed with the high affinity GLUT-3 transporter in the endothelium, basal decidua, and invading extravillous trophoblast of the human placenta [48].

- **Cholesterol synthesis –** Fetal demands for cholesterol are high. In early pregnancy, maternal cholesterol contributes substantially to this requirement, while in late gestation, the fetus synthesizes cholesterol from placental stores of fatty acids established from maternal body fat accumulation in early pregnancy [49]. Placental cholesterol is an important precursor for placental production of progesterone and estrogens.

- **Protein metabolism –** Placental protein metabolism is largely governed by the demands of fetal growth throughout gestation. At 10 weeks of gestation, placental protein production is approximately 1.5 g per day, but by term rises to 7.5 g daily [50].

- **Lactate –** Lactate, a product of glucose metabolism, is produced in large quantities by the placenta and serves as a fetal substrate. It is efficiently removed from the placenta by L-lactate transporters active on both the microvillus and basal membranes of the syncytiotrophoblast [51].

Endocrine functions — The placenta is not innervated, hence any communication between it, the mother, and the fetus must involve humoral agents. The placenta is an important endocrine organ, releasing hormones into both the fetal and maternal circulations and paracrine and autocrine signaling.

The hormones produced by the placenta can be split into two categories:

- Peptide hormones (human chorionic gonadotropin [hCG], human chorionic somatomammotropin (hCS), cytokines, growth hormone, insulin-like growth factors

[IGFs], corticotropin-releasing hormone [CRH], vascular endothelial growth factor [VEGF], placental growth factor [PlGF], soluble FMS-like tyrosine kinase 1 [sFLT-1])

- Steroid hormones (estrogens, progesterone, and glucocorticoids)

Peptide hormones — The main site of production of the placental hormones is the trophoblast of the chorionic villi.

- **Human chorionic gonadotropin –** hCG is secreted by the syncytiotrophoblast into the maternal blood, where it maintains the endocrine activity of the corpus luteum (ie, synthesis of progesterone) during the early stages of pregnancy. It can be detected in maternal serum as early as day 8 after conception. Levels of hCG rise throughout the early stages of pregnancy and reach their maximum level at week 8 of gestation. By week 13, the level drops dramatically and reaches a low steady state until delivery. By this time, the placenta itself produces enough progesterone to support pregnancy. (See "Clinical manifestations and diagnosis of early pregnancy", section on 'Human chorionic gonadotropin'.)

- **Human chorionic somatomammotropin –** hCS, originally known as human placental lactogen (hPL) is a single chain peptide hormone synthesized by the trophoblast and released into the maternal blood, with increasing levels with advancing gestation (1 g/day at term). The principal action of hCS is to increase the supply of glucose to the fetus by decreasing maternal glucose utilization and mobilizing maternal stores of fatty acids. It does this by creating a state of mild insulin resistance and increasing maternal secretion of insulin.

- **Insulin-like growth factors –** The IGF signaling system plays an important role in normal physiology and fetal growth regulation. There are three ligands, insulin, IGF-1 and IGF-2, at least four receptors and six IGF binding proteins (IGFBPs). The IGF axis is a complex signaling pathway that is a major regulator of fetal and postnatal growth. IGF-2 is the predominant growth factor and acts by binding to the IGF-1 receptor and initiating a signaling cascade that induces cellular proliferation, survival, and growth [52].

- **Corticotropin-releasing hormone –** CRH is a 162 amino acid peptide that is synthesized by syncytiotrophoblast. Glucocorticoids stimulate placental CRH expression (but inhibit hypothalamic CRH), whereas progesterone and estrogen inhibit CRH. CRH concentration in the maternal circulation increases exponentially throughout gestation, but it is bound to a CRH binding protein (CRHBP) secreted by liver, so there is no CRH effect on the maternal pituitary. Concentrations of CRHBP decrease prior to term, so that unbound CRH becomes available, and this is postulated to play a role in the onset of labor.

In patients with idiopathic preterm labor, a more rapid increase in maternal CRH concentration is seen, leading to the hypothesis that placental CRH determines the length of gestation ("placental clock"). CRH secreted into the fetal circulation may drive increased cortisol production, maturation of the fetal lung, and increased surfactant production. CRH and the related protein urocortin are also vasodilators of the fetal-placental circulation [53,54]. (See "Spontaneous preterm birth: Pathogenesis".)

- **Vascular endothelial growth factor, placental growth factor, and soluble FMS-like tyrosine kinase 1** – VEGF is synthesized in villous trophoblast and macrophages, where it is then secreted into the maternal circulation and acts via two receptors, VEGF-R1 (FLT) and VEGF-R2 (KDR), which are found in villous vascular endothelium [55]. The action of VEGF secreted into maternal plasma is negated by binding to a soluble binding protein sFLT-1. Hypoxia stimulates production of both VEGF and sFLT-1 with increased concentrations seen in preeclamptic pregnancy. In the placenta, VEGF acting via FLT-1 and KDR is thought to be involved in branching angiogenesis in early pregnancy.

  PlGF is produced in villous syncytiotrophoblast and the media of large villous vessels and also acts via VEGF-R1 and -R2. PlGF acts via FLT-1 in nonbranching angiogenesis in the last trimester of pregnancy and expression is down-regulated by hypoxia, suggesting that oxygen tension may regulate the balance of VEGF and PlGF and thus, the effects that are seen [56].

  sFLT-1 is produced by syncytiotrophoblast and exerts an antiangiogenic effect by binding to VEGF and PLGF. Synthesis increases exponentially across gestation, and is further increased in patients who develop preeclampsia, where binding to PLGF reduces its bioactivity, thus preventing its vasodilator effect and promoting hypertension [57]. (See "Preeclampsia: Pathogenesis".)

Steroid hormones — The steroid hormones comprise a group of molecules all derived from a common precursor, cholesterol. Steroid hormones are lipophilic molecules, which are protein bound in the bloodstream and can readily cross the bi-lipid membrane of cells. When these hormones bind to their intracellular receptors, the specific complex formed has high affinity for nuclear binding sites. They alter the genetic activity of the cell and thus alter biochemical events.

- **Progesterone** – Progesterone is necessary for the maintenance of a quiescent, noncontractile uterus. The hormone has anti-inflammatory and immunosuppressive functions which protect the conceptus from immunological rejection by the mother. Initially, progesterone is produced by the corpus luteum in order to prepare the endometrium for implantation of the conceptus. At 35 to 47 days post ovulation, the

placenta takes over progesterone production (luteo-placental shift) and the levels are sufficient to solely support the maintenance of pregnancy.

Maternal cholesterol is the substrate for progesterone synthesis and the 3-hydroxysteroid dehydrogenase enzyme (3-HSD) is the rate limiting step. In pregnant people, progesterone concentrations are higher in those over 30 years of age, nulliparous, or nonsmokers and lower in those under age 30 years of age, multiparous, or smokers [58].

- **Estrogens –** Estrogens are secreted by the corpus luteum and the adrenal cortex, as well as the placenta. hCG stimulates the synthesis of estrogen in the placenta, where the syncytiotrophoblast produces it in large quantities. However, the placenta alone is not capable of estrogen production de novo as it cannot hydroxylate C21 steroids at the 17 position.

  The maternal, and primarily the fetal, bloodstreams that perfuse the placenta provide dehydroepiandrosterone sulfate (DHEAS), the substrate for estrone and estradiol, and 16-hydroxy-DHEAS, the substrate for estriol. Large amounts of DHEAS are secreted by the fetal adrenal glands and converted to estrogens in the placenta [59]. Hydrolysis by placental sulfatase yields DHEA and 16-hydroxy-DHEA, which are then acted on by 3-HSD and aromatase to yield estrogens.

  Aromatase is oxygen sensitive, which may account for the low concentration of estrogens in patients with placental insufficiency.

  Placental production of estrogens is higher when the fetus is female and increases in a linear fashion to term [58]. In pregnant people, estrogen concentrations are higher in those under age 30 years or nulliparous and lower in those over age 30 years or multiparous [58].

- **Glucocorticoids –** Glucocorticoids play a crucial role in regulation of organ development and maturation. However, fetal exposure to excessive maternal glucocorticoids may cause growth restriction and can lead to problems, such as hypertension, in later life. Although the placenta does not synthesize glucocorticoids de novo, it regulates fetal exposure to glucocorticoids via the 11-beta-hydroxy-steroid dehydrogenase enzymes, which catalyze reduction (11-beta-HSD1) or oxidation (11-beta-HSD2) of glucocorticoids.

  11-beta-HSD2 is located throughout the syncytiotrophoblast layer where its expression increases with gestational age [60], and it serves to metabolize cortisol to inactive cortisone, thus protecting the fetus against excessive exposure to maternal cortisol. Additionally, a substantial increase in 11-beta-HSD2 is observed around 10 to 12 weeks of gestation when blood flow to the intervillous space is established [61].

An increase in the ratio of 11-beta-HSD2 to 11-beta-HSD1 in placental membranes near term is associated with a switch in placental glucocorticoid metabolism, which may be responsible for the maturation of the fetal hypothalamic-pituitary-adrenal axis [62].

PLACENTAL TRANSFER

The syncytiotrophoblast layer of the placenta is the main site of exchange for nutrients and gases between the maternal bloodstream and the fetus. The efficient transfer of nutrients and solutes across the placenta is essential for normal fetal growth and development.

Mechanisms — There are several mechanisms by which transfer occurs:

Solvent drag — Solvent drag is the movement (bulk flow) of water in which solutes and nutrients are dissolved. Bulk flow has been demonstrated in the perfused human placental cotyledon in response to hydrostatic pressure changes [63].

Simple diffusion — Simple diffusion is the passive transfer of solutes driven by concentration and electrical gradients. All solutes are transferred by diffusion, but the relative contribution is dependent on molecular properties. As an example, lipophilic molecules, such as respiratory gases, are readily exchanged by simple diffusion [64].

Transcellular transfer — This type of transfer utilizes transport proteins in the microvilli or basal membrane of the syncytiotrophoblast. There are three types:

- **Channels –** These proteins form water-filled pores in the plasma membrane through which ions diffuse down an electrochemical gradient. Charged hydrophilic substances, which are insoluble in lipids, can be transported this way. Aquaporins are an example of channels that function in the transport of water and small molecules; they are essential for fetal development [65].

- **Facilitated diffusion –** These transporters are saturable carrier proteins, which are independent of metabolic energy. As an example, glucose is transported by facilitated glucose transporters (GLUT, discussed below).

- **Carrier mediated active transport –** Primary active transport utilizes ATP to move solutes against a gradient, Na^+K^+ATPase and Ca^{2+}ATPase are two examples. Secondary active transport utilizes concentration gradients across the cell that are set by the primary system, Na^+amino acid co-transport and the Ca^{2+}/Na^+ exchanger are examples. Transport ATPases are known to be present in human placenta. These include the Na^+: K^+ pump (Na^+K^+ATPase), which is localized to the microvillous and basal membrane [66], and a high affinity Ca^{2+}ATPase located on the basal membrane [67].

Endocytosis and exocytosis — During endocytosis, material is engulfed in a sample of extracellular fluid to form a fluid filled vesicle following invagination of the cell surface. Exocytosis is the reverse of this process, where vesicles fuse with the cell membrane to release their contents. This process can be receptor mediated: triggered by a specific interaction between the solute and a receptor on the cell membrane.

Transfer of specific substances

Respiratory gas exchange — Both oxygen and carbon dioxide are lipophilic molecules that cross the placenta by simple diffusion. The placental membranes are highly permeable to O_2 and CO_2, thus blood flow is the rate limiting step for exchange of the respiratory gases across this tissue [68]. The partial pressure and the difference between maternal and fetal hemoglobin affinity for O_2 are two important factors that determine rate of exchange.

Glucose transport — Glucose is the primary substrate for fetal oxidative metabolism, thus its efficient transfer across the placenta is essential for normal fetal growth and development. The placenta is not capable of producing appreciable amounts of glucose until late in gestation [69]. Therefore, uptake of maternal glucose is essential for glycogen synthesis.

Members of the GLUT family facilitate glucose transfer; GLUT 1 is the abundant subtype expressed in the human trophoblast [70]. Normal pregnancy is a state of insulin resistance so as to increase glucose availability for the fetus. Insulin resistance is exacerbated in pregnancies complicated by diabetes, where the mother may become hyperglycemic, leading to fetal hyperglycemia. As a result of fetal hyperglycemia, there is increased production of insulin, insulin-like growth factor 1, and leptin, resulting in stimulation of fetoplacental growth [17].

Amino acid transport — The fetus depends on placental transfer of amino acids for protein synthesis for fetal growth. Protein degradation and interconversion to intermediate substrates give rise to synthesis of either glucose or ketone bodies.

The placenta plays a critical role in the delivery of amino acids to the fetus. Transfer involves three steps: uptake from the maternal circulation across the microvillous membrane, transport through the trophoblast cytoplasm, and transport across the basal membrane into the umbilical circulation [71]. Transport systems within the trophoblast can be either sodium-dependent or sodium-independent [72,73], and differ based on their ionic substrates [71]. All amino acids are not transferred equally [74] and transfer can be impaired in pregnancies complicated by fetal growth restriction [75].

Fatty acid transport — Fatty acids are essential for fetal development, both as an energy source and also as a precursor for several important bioactive compounds, such as prostaglandins and thromboxane. The placenta has a considerable capacity for fat uptake

and transport of fatty acids. Transport involves the breakdown of triglycerides (from maternal adipose tissue) to free fatty acids and glycerol and re-esterification with intracellularly generated glycerol phosphate on the fetal side. This conversion is mediated by lipase activity.

Immunoglobulin G transfer — Maternal IgG antibodies are readily transported across the placenta to confer passive immunity to the fetus and newborn. From early in the second trimester the concentration of IgG in fetal blood increases, with most antibodies being acquired in the third trimester. IgG is transported across the syncytiotrophoblast via the Fc receptor, FcRn [76].

Placental transfer of maternal immunoglobulins can also have harmful effects, such as in pregnancies complicated by alloimmunization to red blood cell and platelet antigens, which can cause hemolytic disease of the fetus and newborn (HDFN) and fetal and neonatal alloimmune thrombocytopenia (FNAIT), respectively.

Drugs — Most drugs cross the placenta by simple diffusion; however, any of the mechanisms of placental transfer described above may be involved. Plasma membrane carriers, biotransforming enzymes, and export pumps also play a role [77].

Factors that affect drug transfer include molecular weight, degree of ionization, lipid solubility, protein binding, and fetal and placental blood flow. Nonionized, nonprotein-bound, lipid-soluble drugs with molecular weight below 600 Daltons freely cross the placenta [78]. High molecular weight drugs, such as insulin (6000 Daltons), are not transported in significant amounts.

Calcium and vitamin D — At term, the fetal ionized calcium concentration is significantly higher than the maternal (2.8 versus 2.2 mEq/L) [79]. Calcium is transported from the maternal circulation to the fetal despite the higher concentration of ionized calcium in the fetal circulation; this suggests active transport of calcium across the placenta must occur [80-87]. Maintenance of fetal calcium homeostasis largely depends upon parathyroid hormone-related peptide (PTHrP), which regulates active placental calcium transfer [82,83].

Fetal hypercalcemia inhibits fetal parathyroid hormone (PTH) activity and stimulates fetal calcitonin release. This environment (high calcium, low PTH, high calcitonin) is ideal for skeletal mineralization. Skeletal mineralization occurs in the latter weeks of pregnancy, so most of the 25 to 30 g of calcium present in the term fetus crosses the placenta over a period of a few weeks, peaking at the 35th week. Between the 20th and 35th week of gestation, placental calcium transport increases from 50 to 330 mg per day [88].

The fetus depends on the transfer of maternal 25-hydroxyvitamin D across the placenta; fetal cord blood 25-hydroxyvitamin D concentrations are comparable to, or slightly lower than, maternal 25-hydroxyvitamin D concentrations. Although maternal 1,25-dihydroxyvitamin D

levels rise during pregnancy, the fetal level remains low. It appears that 1,25-dihydroxyvitamin D is prevented from crossing the placenta by the action of a placental 24-hydroxylase, which converts 1,25-dihydroxyvitamin D to 24,25-dihydroxyvitamin D3, a less active metabolite of vitamin D than its precursor [89].

PLACENTAL INFECTION

Overview — Whether the placenta is a sterile environment and the existence and role of the placental microbiome in healthy pregnancies and those with complications, particularly preterm birth, is hotly debated. A review and reanalysis of published data concluded that the mode of delivery and environmental contamination influence the bacterial DNA signal seen in early studies [90].

The placenta generally prevents transfer of maternal bloodborne pathogens to the fetus. Its defenses include 1) syncytiotrophoblast, which lacks intercellular junctions, 2) decidual-trophoblast environment with innate cellular defenses, and 3) physical obstacles, such as a basement membrane [91]. Occasionally, however, these barriers are breached, leading to placental infection and, in turn, possible fetal infection. Some of the organisms capable of placental and fetal infection include Treponema pallidum, Toxoplasma gondii, Listeria monocytogenes, Plasmodium falciparum, and several viruses.

Viral infections — The surge in fetal microcephaly associated with Zika virus has prompted investigation of mechanisms mediating viral transfer across the placental barrier and antiviral defenses. While some viruses appear to be able to infect, replicate, and cross the placenta, others may infect but not replicate or cross, and others do not infect at all. The net result appears to be related to type of virus, gestational age and duration of exposure, and placental cell type infected.

Type I and III interferons are potent antiviral proteins in the placenta. Some viruses can inhibit the type I interferon pathway [92], which not only allows viral replication and infection, but also appears to enhance the proinflammatory placental response to bacterial infection, which may facilitate bacterial infection-induced preterm birth [92,93]. Reduction in placental type I interferon may also underlie the increased mortality and complications seen in pregnant women with bacterial infections [94] and during influenza pandemics [95].

Zika — In vitro, Zika virus and dengue virus can infect all placental cell types from mid or late gestation, including cytotrophoblasts, endothelial cells, fibroblasts, and Hofbauer cells, all of which express Axl, Tyro 3, and TIM-1 viral entry factors [96]. In vivo, however, type III interferons produced by the placenta in late gestation may protect it against Zika virus [97]. However, early in gestation, trophoblast lacks the components necessary for a robust

antiviral response, such that differences in viral infection across gestation may be explained by changes in expression of viral defense genes [98].

SARS-CoV-2 — Data regarding vertical transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the impact on placental function and pathology has been generated at a rapid rate since the start of the pandemic in early 2020. The impact of SARS-CoV-2 on pregnancy is comprehensively overviewed in related content (see "COVID-19: Overview of pregnancy issues"). In brief, the placental barrier appears to largely shield the developing fetus from COVID-19 in utero.

Many studies have examined histopathological changes in the placenta of COVID-19-infected patients with variable observations, including fetal vascular malperfusion, villous edema, and maternal vascular malperfusion. These findings have been reviewed [99-102] and, significantly, gestational age at time of infection appears to be a key determinant of tissue pathology. While a spectrum of pathology findings were seen in placentas of patients with COVID-19 but uninfected neonates, the placentas of infected maternal-fetal dyads showed chronic histiocytic intervillositis, syncytial necrosis, and strongly SARS-CoV-2-positive syncytiotrophoblast [103]. The term SARS-CoV-2 placentitis is used to define the coexistence of three microscopic findings: chronic histiocytic intervillositis, increased fibrin deposition, and trophoblast necrosis, which have been associated with perinatal death after maternal COVID-19, even in uninfected fetuses and newborns [104].

Pregnant patients who are SARS-COV-2-positive may show no evidence of vertical transmission, but they can transfer anti-SARS-CoV-2 antibodies to the fetus, although transmission is less efficient than that of influenza antibodies [105]. Maternal IgG antibodies to SARS-CoV-2 are transferred across the placenta after symptomatic or asymptomatic infection during pregnancy with correlation of cord blood, and maternal antibody concentrations and transfer ratios increased with increasing time between onset of infection and delivery [106].

The COVID-19 mRNA vaccines generate robust immunity in pregnant patients with greater responses than to natural infection, and these antibodies also transfer to the fetus via the placenta [107]. (See "COVID-19: Overview of pregnancy issues".)

SUMMARY AND RECOMMENDATIONS

- **Placental functions –** The placenta attaches the fetus to the uterine wall, functions as an immune barrier that prevents rejection of the semi-allogeneic fetus and directs maternal metabolism to provide nutrients to support fetal growth and development. It is an organ for exchange of oxygen, nutrients, antibodies, and waste products between the mother and fetus. Fetal sex-dependent differences exist that can impact placental

function and pregnancy outcome. (See 'Introduction' above and 'Role of sexual dimorphism' above.)

- **Early cellular development** – The progenitor villous trophoblast cell proliferates throughout gestation, differentiating along two pathways to form either invasive extravillous trophoblast (EVT) or syncytiotrophoblast. Invasive EVT that invades decidua is the interstitial EVT, and EVT that invades and remodels the spiral arteries is the endovascular EVT. The syncytiotrophoblast is a specialized epithelium covering the villous tree and has several functions, such as transport of gases, nutrients, and waste products and synthesis of peptide and steroid hormones that regulate placental, fetal, and maternal systems. (See 'Early development' above.)

- **Vascular development** – Placental vasculature is shown in the figure (figure 1). Defective placentation and inappropriate vascular remodeling underlie many adverse obstetric pathologies, such as preeclampsia, fetal growth restriction, and placenta accreta. (See 'Vascular development' above.)

  The placenta is not innervated; therefore, vascular reactivity is regulated by humoral and autocrine/paracrine factors. (See 'Vascular reactivity' above.)

- **Metabolic and endocrine functions** – The placenta has tremendous metabolic activity, consuming approximately half of oxygen and glucose supplied to the pregnant uterus. Alterations in placental metabolism may impact substrate availability for the fetus. (See 'Metabolic functions' above.)

  The placenta produces peptide (human chorionic gonadotropin, human chorionic somatomammotropin, cytokines, growth hormone, insulin-like growth factors, corticotropin releasing hormone, vascular endothelial growth factor, placental growth factor) and steroid hormones (estrogens, progesterone and glucocorticoids). (See 'Endocrine functions' above.)

- **Mechanisms of placental transfer** – There are several mechanisms by which placental transfer occurs, including solvent drag, simple diffusion, transcellular transfer, and endocytosis/exocytosis. (See 'Placental transfer' above.)

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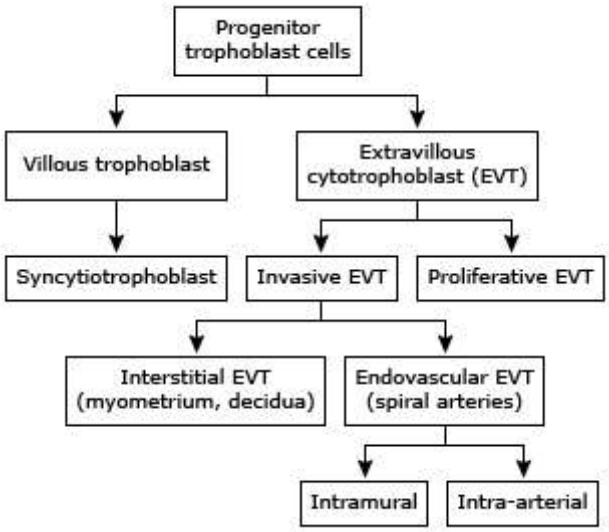
Topic 2284 Version 27.0

GRAPHICS

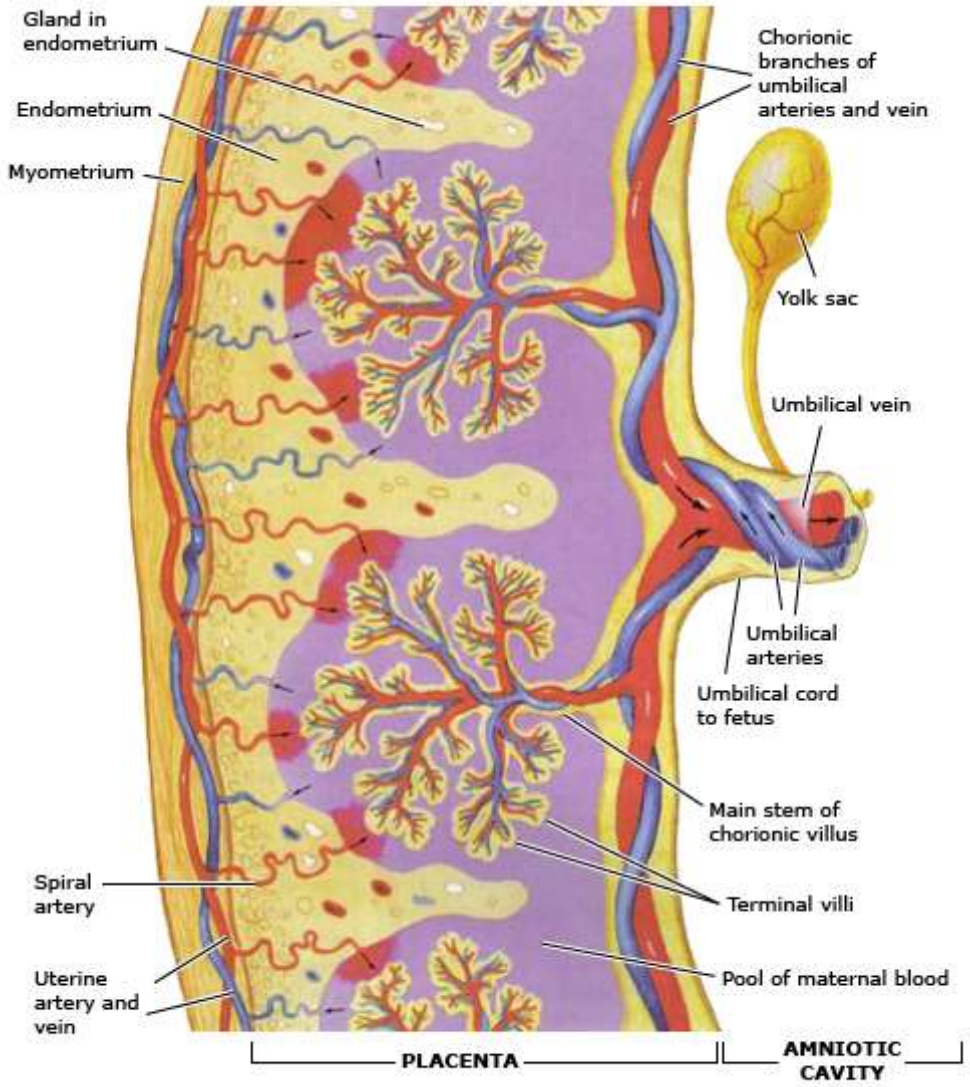
Formation of extravillous trophoblast (EVT)



The interstitial EVT invades decidua and myometrium, where it anchors the conceptus and forms a continuous shell around it at the level of the decidua. Endovascular EVTs are associated with spiral arteries, either within the vessel wall (intramural) or replacing endothelium (intra-arterial). EVTs transform the narrow spiral arteries to wide uteroplacental arteries, which distribute blood into a low resistance vascular network.

Graphic 57887 Version 6.0

Placental vasculature



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