Review

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OPEN

Expression of Key Steroidogenic Enzymes in Human Placenta and Associated Adverse Pregnancy Outcomes

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Abstract

Steroid hormones, including progestagens, estrogens, androgens, corticosteroids, and their precursor cholesterol, perform essential functions in the successful establishment and maintenance of pregnancy and normal fetal development. As the core endocrine organ at the prenatal stage, the human placenta is involved in the biosynthesis, metabolism, and delivery of steroid hormones. Steroidogenic pathways are tightly regulated by placenta-intrinsic cytochrome P450 and hydroxysteroid dehydrogenase. However, the relationship between placental steroidogenic enzyme expression and adverse pregnancy outcomes is controversial. In this review, we summarize the possible upstream regulatory mechanisms of placental steroidogenic enzymes in physiologic and pathophysiologic states. We also describe the human placental barrier model and examine the potential of single-cell sequencing for evaluating the primary functions and cellular origin of steroidogenic enzymes. Finally, we examine the existing evidence for the association between placental steroidogenic enzyme dysregulation and adverse pregnancy outcomes.

Keywords: Placenta; Steroidogenic enzymes; Maternal-fetal outcomes; Cytochrome P450; Hydroxysteroid dehydrogenase

Introduction

The placenta is a species-specific multifunctional organ that allows communication between the mother and fetus. It is mainly involved in nutrient transport, excretion of fetal metabolic waste, gas exchange, and secretion of multiple steroid hormones (SHs) that regulate maternal metabolism and fetal growth and development, prevent maternal allogeneic rejection of the fetus, and ensure optimal fetal growth. The structure and function of the placenta can adapt to various external pressures, but failure to adapt can lead to fetal growth restriction (FGR), preterm birth (PTB), or disease development and may even directly threaten the survival of the fetus.[1,2] Placental abnormalities have also been implicated in maternal diseases, such as pre-eclampsia (PE).[3] The placenta is the main endocrine organ for the biosynthesis, metabolism, and transport of SHs during pregnancy, including sex steroids such as progestins, estrogens, androgens, and corticosteroids (glucocorticoids (GCs) and mineralocorticoids).[4] Progesterone (P4) and estrogen are mainly derived from multinucleated syncytiotrophoblasts (STBs) during pregnancy and are involved in embryo implantation, endometrial decidualization and establishment of receptivity, immune tolerance, placental development and angiogenesis, and other vital processes affecting fetal development and pregnancy outcome. Corticosteroids and androgens are mainly synthesized by fetal organs (adrenal cortex and liver),[5] are transferred between the placenta and fetus, and rely on complementary enzyme activities for mutual transformation.[6] Other types of intrinsic placental cells such as extravillous trophoblasts (EVTs) also synthesize placental (p)SHs and participate in maternal tissue and uterine spiral artery remodeling by regulating cell migration and invasion.

The synthesis and secretion of pSHs are tightly regulated by enzymes expressed in placental cells; dysregulation of the upstream molecular signaling pathways can lead to serious adverse outcomes. The human placenta has all enzyme systems necessary for the production of SHs, including cytochrome P450 (CYP), which catalyzes the hydroxylation and cleavage of SH substrates, and hydroxysteroid dehydrogenase (HSD), whose isomers modulate SH reduction and oxidation. The activities of the two enzyme systems are distinct but complementary. However, placental steroidogenic enzyme expression and its effects on maternal-fetal physiology, including adverse pregnancy outcomes, are not fully understood.

In this review, we summarize the current knowledge regarding the expression and regulation of key human placental steroidogenic enzymes under various pathophysiologic conditions, as well as changes in their expression and synthesis products due to maternal diseases and exogenous

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factors. We also describe adverse maternal and fetal outcomes related to these changes. Lastly, the regulatory mechanisms and signaling pathways associated with dysregulated expression or activity of placental steroidogenic enzymes and their contribution to adverse pregnancy outcomes are discussed. We also refer to findings from the isolated human placental tissue culture system. Finally, we address open questions and directions for future research.

pSHs in the human placental barrier model

The human placenta is formed after blastocyst localization, adhesion, and invasion of trophoblasts into the deep decidua. It is located at the interface of maternal and fetal circulation and participates in the biosynthesis and metabolism of SHs as well as regulation of and material exchange between maternal and fetal compartments. After implantation, the trophoblast has differentiated into two layers: cytotrophoblasts (CTBs) and STBs. Mononuclear CTBs proliferate throughout pregnancy and differentiate into STBs and EVTs, which participate in villus formation.[7] CTBs form a continuous layer below STBs in early pregnancy; as pregnancy progresses, their shape changes from cubic to flat and the cells proliferate and fuse with STBs to support their growth and regeneration.[8] The villous core is a fetal blood vessel composed of placental-fetal endothelial cells (pFECs), macrophages, and mesenchymal cells embedded in an acellular matrix. STBs are specialized epithelial cells that exhibit characteristics of polarized membranes. The cell membrane on the maternal surface serves as the tip of the microchorion to directly contact the maternal blood, and the basal plasma membrane on the fetal surface contacts fetal capillaries in the villi. These membranes are the most critical barriers for the transport of gases, nutrients, metabolic waste products, and hormones and the synthesis of pSHs that regulate the placenta, fetus, and maternal systems.[9] After passing through STBs, biologically active molecules must pass through pFECs to enter the fetal circulation. Thus, STBs and pFECs actively regulate the uptake, metabolism, and transfer/exchange of these molecules, while extracellular noncellular structures act as filters and storage sites.[10] EVTs are present in cell islands, placental septum, chorionic plate, and smooth chorionic membrane; proliferative EVTs protrude from the basal membrane in a columnar shape. Infiltrating EVTs located at the distal end of the column further differentiate into interstitial EVTs that invade the decidua and intravascular EVTs that participate in spiral artery remodeling. The two cell types eventually replace vascular smooth muscle and endothelial cells. The maternal blood sinus formed by the anastomosis of the enlarged spiral artery and endometrial vein distributes blood to the low-resistance vascular network in the lacunar system, thereby establishing uteroplacental circulation.

The mature placenta is a disc-like structure composed of the dense chorion of the fetus, maternal basal decidua, and interstitial space filled with maternal blood. Placental villi are bathed in maternal blood, and villi cells form a barrier to prevent maternal and fetal blood from directly contacting the fetus. Villi cells and STBs are the primary sites of SH biosynthesis, metabolism, and transportation and secrete hormones into the maternal blood that influence maternal physiology. Various hormones enter the fetal circulation to ensure the normal development and programming of the fetus.[7] The placenta also provides an enzyme barrier for the conversion of cortisol to cortisone to protect the fetus from the adverse effects of high cortisol levels in the maternal circulation.[11] As pregnancy proceeds, the anatomy and transcriptome of the placenta change significantly to ensure proper placental function. Hormones play an important role in determining the placental phenotype in fetal and maternal circulation.[12,13] Accordingly, the expression of steroidogenic enzymes involved in the biosynthesis, transfer, or metabolism of SHs in the placenta changes over the course of pregnancy. As the structure of the placenta is species-specific, there is no perfect animal model of the human placenta, and care must be taken when extrapolating data from nonhuman mammalian species; only higher primates, such as baboons and monkeys, have a placental structure and pSH regulation comparable with humans.[14] The advantages and limitations of animal models of the human placenta have been reviewed elsewhere.[15]

Placental CYPs

Adverse pregnancy outcomes seriously affect the health of pregnant women and their fetuses and have been linked to aberrant expression of CYPs (Table 1).

CYP11A1

CYP11A1 expression

CYP11A1, also known as P450c11 or P450 side-chain cleavage enzyme, has monooxygenase activity in the placenta and is only expressed in the inner mitochondrial membrane of STBs where it transfers maternal cholesterol to the inner mitochondrial membrane to be cleaved into the precursor of pregnenolone (PREG), an SH. This process is the first and rate-limiting step in SH synthesis. CYP11A1 is also a metabolic enzyme for other sterols, including 7-dehydrocholesterol to 7-dehydropregnenolone and hydroxylates the side chain of vitamin D.[33] From 6 to 8 weeks of pregnancy until full term, placental CYP11A1 protein expression remains constant as the concentration of human chorionic gonadotropin (hCG) decreases, with the result that STBs gradually become the primary source of the P4 precursor PREG.[16] The two splice variants of CYP11A1 encode distinct homologous isomers; however, because the minor isoform lacks a mitochondria-targeting peptide, the subcellular localization of the isomers remains unclear.

Transcriptional regulation of CYP11A1

Tissue-specific expression of CYP11A1 in the placenta is tightly regulated by two activators (transcriptional regulating protein of 132 kDa (TReP-132) and long terminal repeat-binding protein 1B (LBP-1B)) and two repressors (LBP-9 and LBP-32) that bind to the proximal region (–155/–131) of the *CYP11A1* gene promoter. As the promoter also contains GATA-binding elements, the distal region (–475/–447) can be combined with cyclic (c)AMP-response element binding protein 1 and GATA-binding protein 2 to achieve a maximum level of transcription. These regulatory proteins are expressed by STBs in early pregnancy, but there are no regulators of CYP11A1 besides steroidogenic factor 1 in other tissues.[34] Heart and neural crest derivatives expressed 1 was shown to induce the methylation of the *CYP11A1* promoter by binding to AlkB homolog 1, histone H2A dioxygenase (ALKBH1), and inhibiting its transcription in JEG-3 cells.[35] Hedgehog signaling promoted *CYP11A1* expression by activating GLI family zinc finger 3 in JEG-3 and BeWo cells.[36] General control nonderepressible

Table 1

Placental CYPs associated with adverse pregnancy outcomes.

Enzyme	Regulation	Sample type	Outcome	Ref.
CYP11A1	Upregulated	Trophoblasts (H)	PE	16
		Placenta (R)	PE	17
		Trophoblasts (H)	PE	18
	Downregulated	HTR-8/SVneo cells	Impaired fetal growth and placental angiogenesis, weight loss	19
		Placenta (R)	Increased preterm birth risk	20
		Cytotrophoblasts (H)	FGR	21
		JEG-3 cells	FGR	22
		Placenta (M)	FGR	23
		Trophectoderm cells	Embryo implantation failure	17
		Placenta (H)	PE	24
	Overexpressed	BeWo cells	PE-like symptoms	25
CYP17A1	Downregulated	Placenta (R)	FGR	26
CYP19A1	Downregulated	JEG-3 cells	Impaired fetal brain and genital development	27
		JEG-3 cells	Endocrine disorders of fetal placental units	28
		JEG-3 cells, Placenta (H)	PE	29
		Placenta (M)	PE like symptoms	30
		Maternal plasma	Female fetal FGR	31
	Decreased activity	Placenta (H)	Virilization in PORD patients (46, XX)	32

CYP: Cytochrome P450; FGR: Fetal growth restriction; H: Human; M: Mouse; PE: Pre-eclampsia; PORD: Cytochrome P450 oxidoreductase deficiency; R: Rat.

2–mediated mitochondrial stress is another important mechanism leading to the downregulation of placental *CYP11A1* expression.[37] Conversely, calcitriol treatment increased *CYP11A1* transcript level in primary cultures of human placental cells, although protein expression was not significantly altered.[19] Prenatal exposure to environmental toxins can adversely affect placental *CYP11A1* expression. Low-dose bisphenol A inhibited *CYP11A1* expression by activating the extracellular-regulated protein kinase (ERK) signaling pathway in JEG-3 cells.[38] In a study of pregnant rats treated with cocaine, *CYP11A1* expression was decreased along with maternal serum PREG and P4 levels.[20] Pentachlorobenzene significantly inhibited CYP11A1 expression and P4 secretion in placental explants.[39] Cadmium is an environmental toxin related to FGR; excessive cadmium caused by smoking reduced *CYP11A1* expression and P4 synthesis in human trophoblasts.[21] Cadmium was shown to downregulate *CYP11A1* expression by activating mitochondrial autophagy regulated by protein kinase R–like endoplasmic reticulum kinase signaling. Conversely, melatonin relieved cadmium-induced downregulation of *CYP11A1* expression and decreased P4 synthesis by inhibiting reactive oxygen species-mediated GCN2/ATF4/BNIP3-dependent mitochondrial autophagy in JEG-3 cells.[22,23]

CYP11A1-associated adverse pregnancy outcomes

Aberrant *CYP11A1* expression in the placenta has been linked to embryo implantation failure, placental development disorder, FGR, and PE. Cadmium exposure may damage placental vascular development and reduce the weight of fetal liver and lungs by downregulating *CYP11A1*.[37] A study using next-generation sequencing to detect dysfunctional blastocysts found that decreased expression of *CYP11A1* was a cause of embryo implantation failure.[17] Meanwhile, *CYP11A1* expression level was significantly higher in PE compared with normal placenta of humans and rats, which is in line with the observed increase in PREG level.[18,24] *CYP11A1* overexpression suppressed trophoblast proliferation and induced HTR8/SVneo cell apoptosis by activating caspase-3. Similarly, increased placental *CYP11A1* expression resulted in the production of lipid peroxides, which may contribute to the pathogenesis of PE.[40] Overactivation of autophagy induced by *CYP11A1* overexpression in trophoblasts induced PE-like symptoms in a rat model, which is thought to be related to placental developmental disorders.[25]

CYP17A1

CYP17A1 expression

CYP17A1 (or P450c17) protein is present in the endoplasmic reticulum of CTBs and STBs[41] and is a dual-function enzyme that catalyzes the two critical steps of PREG synthesis. CYP17A1 converts PREG into 17α-hydroxypregnenolone (17α-OHP4REG) and then dehydroepiandrosterone (DHEA) or converts P4 into 17α-OHP4 and then androstenedione. It also produces androgens by breaking the C17–C20 bond through its 17,20-lyase activity. The expression and functional activity of placental CYP17A1 are controversial. Early studies suggested that the placenta could not synthesize androgens de novo because of an absence of CYP17A1 expression and activity and that placental estrogen production mainly depended on the fetus and only to a small extent on maternal androgen precursors, especially DHEA-sulfate. However, recent evidence indicates that CYP17A1 is expressed in STBs and is upregulated at full term, although its expression is still significantly lower than that of 3β-HSD1, CYP19A1, CYP11A1, and 17β-HSD3.[19,42] This is supported by the observation that the concentration of human plasma 17α-OHP4 was increased at term.[43] 17α-OHP4 is marker for CYP17A1 activity and was shown to be upregulated throughout pregnancy, especially after 30 weeks. However, the level declined sharply after delivery in parallel with an increase in P4 and a decrease in estradiol (E2) level.[44] In a rodent model, CYP17A1 expression gradually increased during pregnancy, reached a peak on day

18, and decreased before delivery.[45] These results indicate that placental CYP17A1 is an important source of androgen precursors in tissues and promotes estrogen synthesis.[46] Considering placental weight, blood flow, and SH precursors, 20% to 30% of estrogen produced during pregnancy is estimated to arise from PREG conversion by placenta CYP17A1.[47]

Transcriptional regulation of CYP17A1

There have been few studies on the regulation of *CYP17A1* expression in the placenta. Using primary trophoblasts and JEG-3 cells treated with the protein kinase A (PKA) pathway agonist forskolin and inhibitor H89, it was found that 17α-OHP4 synthesized by CYP17A1 was regulated by cAMP/PKA signaling.[48] A study investigating the endocrine-disrupting potential of commonly used azole antifungal drugs showed that clotrimazole, miconazole, ketoconazole, and fluconazole treatment led to the accumulation of P4 and cortisol and suppression of androgens and estrogens in H295R cells, which was thought to be related to inhibition of CYP17A1 lyase activity.[49] It is expected that with continuous improvements in highly sensitive detection technologies, placental CYP17A1 expression and its regulatory mechanisms will be elucidated.

CYP17A1-associated adverse pregnancy outcomes

Aberrant CYP17A1 expression has been linked to independent pseudohermaphroditism and transsexualism. A study evaluating human placental CYP17A1 expression at different gestational ages found that *CYP17A1* mRNA level was higher in full term compared with early preterm placenta, although only the protein levels differed significantly.[41] Downregulation of placental CYP17A1 was found to be associated with zearalenone-induced FGR in rats,[26] although another study showed that there was no difference in *CYP17A1* expression between normal and PE placenta.[50]

CYP19A1

CYP19A1 expression

CYP19A1 (also known as P450AROM) is an aromatase that is present in the endoplasmic reticulum and catalyzes the final step in estrogen biosynthesis. 3β-HSD1 catalyzes the conversion of DHEA to androstenedione, which is further converted to estrone by CYP19A1. CYP19A1 can also convert testosterone (T) to E2, but CYP19A1 has a higher affinity for androstenedione.[51,52] STBs formed by the fusion of CTBs express CYP19A1 and become highly active endocrine glands. After 2-month pregnancy, the placenta has completed the conversion of estrogen-producing units; *CYP19A1* mRNA and protein levels were shown to be significantly upregulated with increasing gestational age.[41]

Transcriptional regulation of CYP19A1

Under normal physiologic conditions, increased placental estrogen synthesis involves activation of the *CYP19A1* promoter I.1. Placental corticotropin-releasing hormone regulates glucose transporter expression and stimulates E2 production by upregulating steroid sulfatase, CYP19A1, and 17β-HSD1 expression in trophoblasts.[53] The micro (mi)RNAs miR-19b and miR-106a regulated by c-Myc directly target CYP19A1 to inhibit the differentiation of human trophoblasts. Compared with normal matched placenta, these miRNAs were highly expressed in the PE placenta whereas *CYP19A1* expression was decreased.[54] CYP19A1 overexpression in a 20% O_2 environment induced the differentiation of CTBs into STBs, while the redox-sensitive transcription factor nuclear factor erythroid 2–related factor 2 promoted phenotypic differentiation by inducing *CYP19A1* expression and increasing placental differentiation-related transcription factors CCAAT/enhancer binding protein β and peroxisome proliferator-activated receptor γ expression.[55] Human placental aromatase has multiple phosphorylation sites, and its activity is regulated by phosphorylation and posttranslational modification of the Y361 residue at the reductase coupling interface.[56] Heart and neural crest derivatives expressed protein 1 ectopically expressed in trophoblasts inhibited *CYP19A1* transcription by directly binding to the NNTCTG sequence in the promoter, leading to placental cell apoptosis and inflammation; a phosphoproteomics analysis found that activation of the phosphatidyl inositol 3-kinase/protein kinase B (PI3K/AKT) signaling pathway may play an important role in these processes.[35] Acetaminophen decreased CYP19A1 protein expression in JEG-3 cells in a dose-dependent manner.[27] Corticotropin-releasing hormone and hCG jointly promoted *CYP19A1* expression by activating the cAMP/PKA pathway and inducing the expression of the transcription factor specificity protein 1 in trophoblast cultures.[57] Aflatoxin B1 inhibited CYP19A1 expression in JEG-3 cells, and it was suggested that long-term exposure could cause endocrine disorders of fetal placental units.[28] Similarly, the fungicides tebuconazole, triadimefon, vinazoline, and tributyltin inhibited *CYP19A1* expression in JEG-3 cells through competitive or noncompetitive inhibition.[58] Bisphenol A significantly reduced E2 level in JEG-3 cells in a dose-dependent manner, which was accompanied by a decrease in CYP19A1 protein level although the specific regulatory mechanism remains unclear.[59]

CYP19A1-associated adverse pregnancy outcomes

CYP19A1 expression and function are reduced during pregnancy in PE placenta.[29] Downregulation of placental *CYP19A1* expression was accompanied by sex hormone imbalance in PE patients. Animal experiments showed that low *CYP19A1* expression induced by ischemia and hypoxia induced PE-like symptoms in pregnant mice via PI3K/AKT signaling pathway activation.[30] Studies of FGR indicated that compared with the control group, the FGR placenta had lower maternal plasma E2 concentration and increased CYP19A1 level.[31] Polycystic ovary syndrome (PCOS) is a common endocrine and metabolic disease characterized by clinical or biochemical manifestations of androgen hypertrophy that affects approximately 5% to 10% of women of childbearing age. Compared with normal placenta, PCOS placenta tissue showed decreased CYP19A1 activity and increased androstenedione and T concentrations.[60] Placental biosynthesis of androgens plays a role in fetal virilization. CYP oxidoreductase deficiency (PORD) caused by mutations in POR is a steroid metabolism disorder characterized by abnormal sexual development. Inhibition of placental CYP19A1 activity was shown to be the leading cause of virilization in 46, XX PORD patients, suggesting that steroid production is perturbed in FGR pregnancies.[32]

Placental HSDs

HSD known to be involved in adverse pregnancy outcomes are shown in Table 2.

Table 2

Placental HSDs associated with adverse pregnancy outcomes.

Enzyme	Regulation	Sample type	Outcome	Ref.
3β-HSD1	Downregulated	Placenta (H)	PE	50
		JEG-3 cells	Impaired fetal brain/genital development	27
	Upregulated	Placenta (H)	Fetal reproductive toxicity	61
		Placenta (H)	Disrupt fetal reproductive development	62
11β-HSD	Methylation (HSD11B1)	Placenta (H)	Large for gestational age	63
	Polymorphisms (HSD11B1)	Placenta (H)	Increased risk of PIH and PE	64
	Downregulated (11β-HSD2)	Placenta (H)	FGR/low birth weight/PTB/unfavorable cardiometabolism	65
		Placenta (R)	PE	66
		Trophoblasts (H) and JEG-3 cells	Increased placental impairment/FGR	67
17β-HSD	Upregulated (17β-HSD1)	Placenta (H)	Disruption of fetal reproductive development	62
	Upregulated (17β-HSD2)	Placenta (R)	Reduced placenta and fetus weight, abnormal glucose and lipid metabolism	68
	Decreased activity (17β-HSD3)	Placenta (H)	Male pseudohermaphroditism	69

FGR: Fetal growth restriction; HSD: Hydroxysteroid dehydrogenase; H: Human; PE: Pre-eclampsia; PIH: Pregnancy-induced hypertension; PTB: Preterm birth; R: Rat.

3β-HSD

3β-HSD expression

There are two subtypes of 3β-HSD.[70] 3β-HSD1 encoded by *HSD3B1* catalyzes the oxidation and conversion of delta (5)-ene-3-β-hydroxysteroid precursors into delta-4-ketosteroids to produce all types of SH, and 3β-HSD2 encoded by *HSD3B2* is a bifunctional enzyme that catalyzes the oxidative conversion of delta(5)-ene-3-β-hydroxysteroids and ketosteroids. PREG is converted to P4 by 3β-HSD1 in the endoplasmic reticulum.[71] 3β-HSD1 is only expressed in STBs, whereas 3β-HSD2 is mainly expressed in the adrenal glands and gonads.[72] In addition to PREG, human 3β-HSD1 also uses 17α-OHP4 and DHEA as substrates.[73]

Transcriptional regulation of 3β-HSD

GATA2 and transcription enhancer factor 5 regulate the expression of 3β-HSD1. Both CYP11A1 and 3β-HSD1 are required for the production of P4. Heart- and neural crest derivatives-expressed protein 1 binds to the human antigen R (HuR) protein and induces the destabilization of *HuR* and *3β-HSD1* transcripts by promoting their interaction, resulting in the failure of 3β-HSD1 protein translation in JEG-3 cells.[35] cAMP and the PKC agonist phorbol 12-myristate 13-acetate increased the *3β-HSD1* mRNA level in JEG-3 cells, indicating that PKA and PKC signaling pathways regulate 3β-HSD1 expression in placental cells.[74] Exposure to the DNA methylation inhibitor 5-Aza-CdR caused an approximately 40-fold increase in 3β-HSD1 expression in BeWo cells, suggesting epigenetic control of *3β-HSD1* expression.[75] Prenatal exposure to fine particulate matter (<2.5 μm, PM2.5), the primary air pollutant, increases the risk of adverse pregnancy outcomes by decreasing P4 secretion and 3β-HSD1 and CYP11A1 mRNA and protein expression.[76] The fungicide tributyltin, insecticide methoxychlor, and its metabolite hydroxychloroquine suppress P4 production and inhibit 3β-HSD1.[58,71] In contrast, ochratoxin A-induced 3β-HSD1 expression, leading to increased P4 production.[77]

3β-HSD–associated adverse pregnancy outcomes

A prospective cohort study examining the effect of prenatal triclosan exposure on fetal reproductive hormone levels found that a decrease in placental 3β-HSD1 concentration was related to increased umbilical cord blood T concentration, which was potentially associated with fetal reproductive toxicity.[61,62] 3β-HSD is essential for placental P4 synthesis: exposure to placental cadmium decreased 3β-HSD1 expression in JEG-3 cells and is associated with FGR.[23] Increased 3β-HSD1 activity was detected in PCOS placental tissue, which may increase androgen production during pregnancy.[60] Insulin and insulin growth factor 1 were shown to enhance the activity of 3β-HSD1. Meanwhile, insulin resistance and hyperinsulinemia were significantly associated with the occurrence of gestational diabetes and PE.[78] Further studies are needed to clarify the expression and activity of 3β-HSD1 in these diseases.

11β-HSD

11β-HSD expression

11β-HSD is a microsomal enzyme encoded by the *HSD11B* gene that catalyzes the conversion of inert undecanone product (cortisone) into active cortisol or its reverse reaction, thereby regulating GC production and entry into the SH receptor signaling pathway. There are two subtypes of *HSD11B* in humans, *HSD11B1* (11β-HSD1) and *HSD11B2* (11β-HSD2), that depend on reduced nicotinamide adenine dinucleotide phosphate (NADPH) and nicotinamide adenine dinucleotide (NAD+), respectively. 11β-HSD1 acts as a reductase in the conversion of NADPH-dependent cortisone to cortisol, producing active cortisol and amplifying GC. In contrast, 11β-HSD2 is an oxidase that converts cortisol into the inactive 11-keto metabolite cortisone. Circulating cortisol levels increase as pregnancy progresses, peaking in the third trimester, suggesting that the conversion of cortisone to cortisol is increased in placental tissues.[65,79,80] 11β-HSD1 and GC receptor (GR) are widely expressed in the decidual interstitium and epithelium, whereas 11β-HSD2 expression is mainly limited to the decidual epithelium. 11β-HSD1 is only present in fetal blood vessels in the interstitial core of villous tissue. *HSD11B1* mRNA is detected in CTBs and STBs, whereas 11β-HSD2 is mainly expressed in STBs. Although it has been speculated that the cortisol regeneration function of 11β-HSD1 is a fine-tuning mechanism to control fetal placental cortisol levels, its expression and substrate affinity are lower than those of 11β-HSD2 and it lacks the capacity for cortisol release.[42]

Transcriptional regulation of 11β-HSD

Corticotropin-releasing hormone and cortisol play an important role in *11β-HSD2* expression mediated by hCG in trophoblasts.[57,81] However, this conversion of cortisol is incomplete and a small amount remains unmetabolized. Residual GC is transported out of the cell through the energy-dependent drug efflux pump ATP-binding cassette subfamily B member 1 (ABCB1) located in STBs, thereby preserving the placental GC barrier.[82] GC drugs (dexamethasone and betamethasone) were shown to induce *ABCB1* expression in CTBs.[83] It was suggested that 11β-HSD2 and ABCB1 cooperate to minimize the exposure of the fetus and placenta to maternal cortisol. 11β-HSD2 activity is controlled by multiple mechanisms including transcriptional control, posttranscriptional modulation of *HSD11B2* transcript half-life, epigenetic regulation via methylation of genomic DNA, and direct inhibition of enzymatic activity.[84] Nicotine inhibited 11β-HSD2 expression in BeWo cells in a concentration-dependent manner (0.1–10 μM), which may be related to nicotine-induced abnormal *HSD11B2* promoter histone modification and inhibited its expression through the nicotinic acetylcholine receptor/ERK/ETS like 1 protein/early growth response 1 signaling pathway.[85] Lipopolysaccharide exposure significantly decreased *HSD11B2* expression by inhibiting peroxisome proliferator-activated receptor γ expression in mouse and human placenta.[86] Lipoxin A4 is an endogenous dual anti-inflammatory and proinflammatory mediator that inhibited corticosterone production in experimental PE rats by antagonizing the effects of GC on *11β-HSD2* expression.[66] Melatonin treatment antagonized cadmium-activated GC/GR signaling by blocking protein kinase R–like endoplasmic reticulum kinase signaling, resulting in the upregulation of vascular endothelial growth factor A and 11β-HSD2 protein expression in JEG-3 cells.[67]

11β-HSD–associated adverse pregnancy outcomes

Placental 11β-HSD2 is the main barrier to the transfer of cortisol between the mother and fetus and acts by inactivating GC in maternal circulation, thereby protecting cells from the growth-inhibitory and/or proapoptotic effects of cortisol.[11] Excessive GC exposure caused by aberrant 11β-HSD expression has been linked to various pregnancy complications.[87] The expression pattern of 11β-HSD1 suggests that the mother needs a higher cortisol concentration than the fetus during the first trimester of pregnancy. Excessive exposure of the fetus to GC decreases fetal birth weight and has adverse effects on development. A significant correlation has been reported between the methylation of a single CpG site in the *HSD11B1* promoter and gestational age.[63] *11β-HSD1* is involved in metabolic syndrome and its dysregulation has been observed in PE and FGR. Interestingly, preliminary clinical data indicates that *HSD11B1* gene polymorphisms increased the risk of pregnancy-induced hypertension and PE.[64] Whether tissue-specific dysregulation of *11β-HSD1*—especially in the placenta—is associated with gestational diabetes remains to be confirmed in humans.[88] Placental *HSD11B2* mutations can cause GC overdose syndrome and hypertension, but whether it can serve as a gestational hypertension biomarker remains unclear. Functional impairment or downregulation of placental 11β-HSD2 can lead to low birth weight and FGR, especially in the first 12 months.[89] A prospective birth cohort study reported that lower placental 11β-HSD2 expression caused by high GC levels was significantly associated with insulin resistance in infancy,[90] and an association was demonstrated between decreased 11β-HSD2 activity and the occurrence of PE and PTB.[65]

17β-HSD

17β-HSD expression

17β-HSD, also known as 17-ketosteroid reductase, catalyzes the reversible conversion of 17-keto and 17β-hydroxyl groups in androgens and estrogen (including androstenedione, DHEA, and E2). The direction of the reaction depends on the substrate. The 17β-HSD family comprises several isozymes (17β-HSD1, 17β-HSD2, 17β-HSD3, 17β-HSD5, 17β-HSD7, etc). 17β-HSD1 has reductase activity and catalyzes the stereospecific reduction of estrone to the more active E2, which is promoted by NADPH.[91] 17β-HSD2 has oxidase activity and catalyzes the conversion of E2, T, and dihydrotestosterone to the less active forms 17-ketone, estrone, androstenedione, and 5α-androstanedione, respectively.[92] The expression profile of 17β-HSD2 changes over the course of pregnancy; it is mainly expressed in giant cells at the interface between the chorio-placenta and decidua and functional tissues during pregnancy, but the precise subcellular localization is unclear.[68] Although 17β-HSD1 has been detected in STBs in the 4th week of pregnancy, 17β-HSD2 is expressed in pFECs only after the 12th week. 17β-HSD2 is thought to prevent the excessive entry of active estrogen into the fetal circulation by catalyzing the inactivation of E2 into estrone in pFECs.[93] 17β-HSD3 preferentially uses NADP as a cofactor, catalyzes the conversion of androstenedione to T, and is mainly expressed in the testis and trophoblasts; its location in the placenta is not known. Meanwhile, 17β-HSD5 protein and HSD17B7 mRNA expression have been reported in the human placenta.[94]

Transcriptional regulation of 17β-HSD and associated adverse pregnancy outcomes

Most studies to date on 17β-HSD have been descriptive, and little is known of its role in adverse pregnancy outcomes. A study on the relationship between prenatal exposure to environmental pollutants and fetal reproductive development found that polyfluoroalkyl substances may disrupt fetal reproductive development by altering the expression of 3β-HSD1 and 17β-HSD1 in the placenta; these associations were more pronounced in females than in males.[62] 17β-HSD2–mediated excess of maternal androgen reduced the weight of the placenta and fetus, increased pSH production, and had long-term adverse effects on glucose and lipid metabolism in female offspring.[68] Posttranscriptional regulation-related miR-22 was shown to be upregulated in the PE placenta and induced the upregulation of 17β-HSD3, although the underlying mechanism has yet to be elucidated.[95] *HSD17B3* mutation reduced 17β-HSD3 enzymatic activity and the conversion of androstenedione to T. 17β-HSD3 deficiency is thought to be a rare cause of male pseudohermaphroditism with gynecomastia and 46 XY sexual development disorders.[69]

Summary and outlook

The placenta has the ability to program the fetus during pregnancy, and any damage will indirectly cause permanent changes to the structure and function of fetal tissues and organs, leading to a variety of adult diseases in the offspring,

which is the basis of the placental origin of chronic diseases theory.[96] The tightly controlled expression of placental steroidogenic enzymes, including CYPs and HSDs, is essential for converting human placental cholesterol to active pSHs including P4, estrogen, androgen, and GC that can affect fetal outcome through paracrine and autocrine functions. However, because of ethical issues and limited availability of samples that are also highly heterogeneous, investigating the impact of placental steroidogenic enzymes on fetal outcomes in humans remains challenging. Microarray analyses have revealed significant differences in gene expression patterns between primary placental cells and immortalized trophoblast lines, such as BeWo, JEG-3, and Jar.[97] In addition, research on human placental steroidogenic enzymes using rodents or other model organisms is hampered by interspecies differences in placental enzyme type, expression, and regulation. Thus, there is much that remains to be elucidated with regard to the mechanisms regulating the expression of placental steroidogenic enzymes.

To more intuitively demonstrate differences and associations between activation of genes or signaling pathways that regulate the expression of steroidogenic enzymes in the placenta and adverse pregnancy outcomes, we summarized the key upstream regulatory steroidogenic enzyme genes/protein implicated in PTB, PE, and FGR. We used the GeneMANIA prediction server to construct a molecular interaction network with CYPs and HSDs at the core and analyzed their relationships, including coexpression, colocalization, genetic and physical interactions, predictive associations, and shared protein domains to identify the key upstream regulatory molecules (SDC Fig. 1A, http://links.lww.com/MFM/A23). We then conducted a Kyoto Encyclopedia of Genes and Genomes pathway analysis to visualize the critical upstream signaling pathways regulating steroidogenic enzyme expression in the human placenta in adverse pregnancy outcomes (SDC Fig. 1B, http://links.lww.com/MFM/A23).

Human placental explants or primary CTBs—especially the separation and perfusion of the placenta, placental villi tissue explant culture technology, and the maternal-fetal interface on a chip model to simulate the entire placental barrier—are useful in vitro models for studying the expression and activity of human placental steroidogenic enzymes.[98] Single-cell sequencing has become a powerful tool for further analyzing the cell type composition and transcriptional activity of the placenta and its compartments during normal and pathologic parturition[99,100] and is currently being used to study the heterogeneity between various placental cell types in normal and diseased placentas and molecular interactions within placental cell populations. This approach may more readily capture the temporal and spatial transcriptional signatures of steroid synthases in different cell types of the placenta and can clarify the complex roles of SHs in the regulation of fetal growth and adaptation of maternal physiology to pregnancy. In the future, single-cell sequencing could be used to characterize differences in placental steroidogenic enzyme expression and location at different gestational ages and in pregnancy complications, such as PTB and PE, which could provide insight into the association between pSHs and adverse pregnancy outcomes and may be useful for establishing models to investigate the interdependence of transplacental transport and cell function. It is worth noting that in addition to pregnancy-related diseases, exogenous factors, such as a high-fat diet, environmental toxins, and smoking, contribute to the abnormal expression of placental steroidogenic enzymes, but their long-term effects on the mother and fetus are largely unknown. Exploring the mechanisms regulating the expression of pSH-producing enzymes requires the use of placental explant/organoid (or placenta-on-a-chip) or knockout models combined with analysis of clinical samples. At the same time, high-quality prospective cohort studies are needed to determine the correlation between the dysregulation of pSH-producing enzymes and adverse pregnancy outcomes.

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Conflicts of Interest

None.

Editor Note

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