Review

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Mechanisms of Immune Tolerance and Inflammation via Gonadal Steroid Hormones in Preterm Birth

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Abstract

In 2019, preterm births (PTB) accounted for approximately 0.66 million deaths globally. PTB is also associated with a significantly higher risk of mortality and long-term complications for newborns. Long-term studies associated several factors, including disruption of immune tolerance and inflammation, with PTB. However, the pathogenesis of PTB remains unclear. Gonadal steroid hormones are critical for pregnancy maintenance and regulation of immune and inflammatory responses. However, it is not clear how unbalanced gonadal steroid hormones, such as imbalanced estrogen/androgen or estrogen/progesterone contribute to PTB. In this review, we discuss how gonadal steroid hormones mediate dysfunction in immune tolerance and inflammatory responses, which are known to promote the occurrence of PTB, and provide insight into PTB prediction.

Keywords: Gonadal steroid hormones; Immunity tolerance; Inflammation; Premature birth

Introduction

Preterm births (PTB) is a common pregnant complication and associated with an increased risk of neonatal mortality, morbidity, and long-term complications in preterm infants under the age of five.[1] Many factors can cause PTB, including reduced immune tolerance and increased inflammation.[2] During pregnancy, the maternal immune system undergoes major adaptive changes to avoid rejection of fetus and to protect the mother and the baby from infection. During pregnancy, the immune system can be proinflammatory or anti-inflammatory, depending on the gestational stage,[3] which is associated with gonadal hormones regulation. Gonadal hormones have been recognized as regulators of immune tolerance and inflammation, which is related to pregnancy outcomes, including the risk of PTB.[4] However, it is not clear how gonadal hormones imbalances contribute to PTB. In this review, we discuss how gonadal steroid hormones contribute to the dysregulation of immune tolerance and inflammation, and their effects on PTB.

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Mechanisms of progesterone-mediated immune tolerance and inflammation in PTB

Progesterone levels in PTB

Progesterone is secreted by the corpus luteum in the early stages of pregnancy, and then by the placenta from the 12th week of pregnancy. Progesterone maintains pregnancy by inducing decidual quiescence, myometrial relaxation, and cervical closure. These processes integrate pregnancy synchronization and an uterine clock to ensure timely and safe delivery.[5] The parturition of all viviparous species studied so far, is easily affected by progesterone withdrawal and is regarded as a factor of parturition-triggering mechanism.[6] Therefore, progesterone withdrawal can be described as a reactor, similar to the reminder function of an alarm clock. Progesterone withdrawal triggers spontaneous abortion and local inflammation in maternal tissue, which changes from a state of quiescence to a state of labor, such as fetal membrane weakening, myometrial contractions, and cervical softening.[5] In humans, progesterone levels are much higher during pregnancy and remain high until the placenta is delivered. However, progesterone levels do not change significantly during late pregnancy. Progesterone levels have been reported to be higher in cases of iatrogenic PTB than that in the group of the term birth at 9 to 14 weeks and 28 to 32 weeks.[7] In addition, lower concentrations of serum progesterone at 4–10 weeks of gestation are not associated with a shortened gestation period or higher risk of PTB.[8] It should be noted that iatrogenic preterm labor, preterm premature rupture of membranes (pPROM), and spontaneous premature birth (sPTB) have different etiologies, and that their hormone levels may also differ. International Federation of Gynecology and Obstetrics (FIGO) indicated that progesterone can be used to prevent PTB.[9] Studies indicate that the onset of delivery is only associated with reduced progesterone activity in myometrium.[10] We speculate that when PTB is associated with the sudden progesterone withdrawal, it affects various biological samples, such as serum, amniotic fluid, and gestational tissues differently. However, more clinical data, such as from large cohort studies of PTB-associated systematic changes in progesterone levels, are needed to test this possibility.

Progesterone acts by interacting with progesterone receptors (PRs). Progesterone signaling may be regulated at the receptor level through downregulation of PR expression, changes in the relative expression of PR isoforms, and changes in the estrogen/progesterone ratio.[11] Several immune cell types express PRs, including macrophages, mast cells, lymphocytes, eosinophils, and dendritic cells (DCs).[12] Notably, there are sex differences in the expression of PRs. For instance, in female rats, a higher number of immature bone marrow-derived DCs express PR protein compared with males, but this difference was not present at the transcriptional level.[13] It has been reported that progesterone can stabilize myometrial activity throughout pregnancy via intracellular receptor–regulated mechanisms. The single-copy human PR gene uses separate promoter and translational start sites to produce two distinct isoforms, designated PR-A (94 kD) and PR-B (116 kD), which only differ by the presence of an additional 165 amino acids in the amino terminus of PR-B.[14] The isoforms have different functions, with PR-B functioning as an activator of progesterone-responsive genes, while PR-A functions as a modulator or repressor of PR-B function.[15] At parturition, the rise in PR-A expression promotes labor by inhibiting the anti-inflammatory actions of PR-B and stimulating pro-inflammatory gene expression in response to progesterone.[16] Moreover, changes in the PR ratios, rather than individual receptor fluctuations, are thought to affect progesterone signaling in the placenta.[17] However, further research is needed to determine how the levels of progesterone and its receptors might contribute to preterm birth.

Mechanisms of progesterone-mediated immune tolerance in PTB

Progesterone is a critical inhibitor of maternal immune response to the fetus. Evidence suggests that major histocompatibility complex class I-G (HLA-G) regulates maternal immune tolerance to the fetus. Progesterone regulates uterine by decidual natural killer (dNK) cells and promotes the expression of HLA-G gene, which is the ligand for inhibitory and activating receptors presented on dNK cell membranes.[18] Very small levels of HLA-G are detectable in decidual stromal cell cultures, and its levels are significantly elevated by treatment with interferon (IFN)-γ, and a combination of progesterone and cyclic adenosine monophosphate (cAMP).[19] HLA-G expression is characterized by time- and dose-dependence, with peak concentrations being detected in cell lysates and culture supernatants at 4–5 and 24 hours after progesterone stimulation JEG-3 choriocarcinoma cells and human cytotrophoblasts in vitro.[20] In addition, cultured primary cytotrophoblasts, JEG-3 choriocarcinoma cells, and mesenchymal stem cells derived from human adipose tissue, bone marrow and decidua express high levels of HLA-G after progesterone stimulation.[20,21] Importantly, progesterone enhances HLA-G expression, probably via PR activity, which binds progesterone response elements in the HLA-G promoter region.[19,22] This suggests that PTB may be caused by progesterone regulating the expression of HLA-G and unable to maintain maternal-fetal immune tolerance.

During the occurrence of PTB, various types of immune cells might be conducive to the maintenance of immune tolerance. Progesterone inhibits innate immune responses, such as by suppressing the activity of dNK cells and macrophages.[23] During pregnancy, high progesterone levels may suppress T-helper type 1 (Th1) cell immune responses, while promoting T-helper type 2 (Th2) cell immune responses.[24] Additionally, studies have shown a relationship between the decreased numbers of regulatory T cells (Treg) and the abnormal expression of Treg's master regulator, FoxP3, during PTB.[25] Progesterone can promote T cell differentiation into Treg lymphocytes and has been shown to increase the number of Tregs.[26] Treg dysfunction/deficits may only be the effectors in a small proportion of PTBs.[27] Progesterone has been suggested to inhibit innate immune responses by suppressing NF-κB activation and upregulating the expression of suppressor of cytokine signaling 1.[28] Studies indicate that placental extracellular vesicles (EVs) may modulate immune regulation rather than promote inflammation. Mouse embryo EVs are reported to carry progesterone-induced blocking factor, which adheres to the surface of $CD4^+$ and $CD8^+$ peripheral T cells, inducing interleukin 10 (IL-10) production.[29] This effect was abrogated by pretreating the EVs with an anti–progesterone-induced blocking factor antibody.[29] Progesterone therapy has been proposed as a potential therapeutic strategy for preventing PTB by attenuating the proinflammatory response caused by T-cell activation at the cervix and the maternal-fetal interface.[30] It is possible that progesterone activity is blocked in preterm patients, resulting in immune cell changes, including the enhancement of innate immune cell activity, an imbalance in Th1/Th2 ratios, and a reduction in regulatory T-cell levels.

Mechanisms of progesterone-mediated inflammation in PTB

In vitro and in vivo studies indicate that progesterone suppresses uterine contractility, affects cervix remodeling in preparation for birth, and activates the amnion through inflammation. Progesterone is reported to exert anti-inflammatory effects and to inhibit the expression of the proinflammatory cytokines, IL-1 and IL-8.[31] Progesterone also suppresses NF-κB signaling, nitric oxide production, and *Tnfα* mRNA expression in murine macrophages.[22,32–34] Progesterone stimulation promotes the expression of toll-like receptor (TLR) 2, TLR-5, and nucleotide-binding oligomerization domain containing 2 (NOD2). However, it did not affect the expression of the TLR4 and NOD1 genes, alone or in combination with TLR/NOD-like receptor (NLR) agonists, but it suppressed the expression of IL-1β and IL-8, which are upregulated by TLR2, TLR5, and NOD2 agonists.[35] Progesterone is reported to suppress the expression of the proapoptotic factors, Bax and Bid, which are induced by stimulation with proinflammatory cytokines (TNF-α, IL-18, and IL-1β) and thrombin.[35] These reports indicate that progesterone is closely involved in inflammatory responses during pregnancy. With regard to maternal inflammation triggers, it has been shown that progesterone suppresses the expression of monocyte chemotaxis protein 1, which contributes to monocyte recruitment into the myometrium. Monocytes differentiate into macrophages as a result of macrophages producing more cytokines, metalloproteinases (MMPs), and prostaglandins, which regulate the inflammation in the tissue microenvironment.[36] MMP-8 and MMP-9 are involved in extracellular matrix collagen and glycosaminoglycan degradation, which promotes cervical maturation.[37,38] The static tension of uterine muscles is maintained by reducing the production of prostaglandin, which encodes a component of the oxytocin and prostaglandin receptors expressed in the myometrium.[31,39] Progesterone

induces myometrial quiescence by inhibiting the expression of contraction-associated proteins (e.g., Cox-2) and inflammatory cytokines (e.g., IL-1, and C-C motif chemokine ligand 2 (CCL2)).[16,40] Progesterone participates in the control of cervical maturation by regulating extracellular matrix metabolism.[41] With regard to fetal inflammation, the effects of progesterone on the decidua and chorion include inhibition of basal- and TNF-α–induced apoptosis, which protects cells from calcium-induced cell death and reduces the expression/activity of cytokine-induced MMP.[42] Furthermore, exosomes/EVs might regulate infection- and stress-induced inflammatory signaling between the fetus and mother.

It is increasingly acknowledged that an abnormal maternal immune system can cause PTB via premature activation of inflammatory pathways.[43] Progesterone protects from pPROM via anti-inflammatory and antithrombogenic effects on term human fetal amniotic membrane cells.[35] RU486, a progesterone antagonist, is reported to cause PTB in mice, probably through elevated levels of decidual prostaglandin E2 (PGE2) and IL-6.[44] The concentrations of IL-6, IL-21, and TNF-α, as well as PR-A expression by CD19+ B cells, have been identified as maternal plasma markers of sPTB and their levels are higher in PTB patients than in term delivery cases. PTB has been associated with the activation of inflammatory pathways, which induces PR-A expression in CD19+ B cells, which may cause inflammation-mediated disruption of maternal–fetal tolerance and PTB.[45] Recent research has confirmed that progestin therapy may prevent PTB and neonatal adverse outcomes by weakening T cell activation-induced proinflammatory reactions at the cervix and the maternal-fetal interface.[30] Indeed, progesterone administration through the vagina has been shown to reduce the risk of PTB, although its mechanism is not fully established.

Mechanisms of estrogen-mediated immune tolerance and inflammation in PTB

Estrogen levels during PTB

Estrogen is mainly synthesized by the corpus luteum in early pregnancy and then by the placenta after the 9th week of pregnancy. Estrogen levels gradually increase with advancing gestational age. Estrogen modulates placental development as well as the trophoblast cells invasion, proliferation, and differentiation of placental cells.[46] The primary form of estrogen, estrone, is sequentially converted into estradiol (E2), which is then transported into the fetal circulation and absorbed by the liver, where it is converted into estriol (E3).[47] E3 then enters maternal circulation and is cleared through the maternal urinary system.[48] Although E2 is regarded as one of the most important estrogens during reproductive years, its metabolite, E3, is the primary pregnancy-associated estrogen and its concentration increases significantly in late pregnancy. It has been reported that fetal cortisol promotes placental 17-hydroxylase activity, thereby decreasing the secretion of progesterone and increasing estrogen production, which reverses estrogen/progesterone proportions and increases prostaglandin production, ultimately triggering labor.[49] However, serum progesterone levels do not fall as labor approaches, indicating that estrogen might modulate labor, but this is poorly studied.[50]

Some studies have reported estrogen as an indicator of preterm maturity, which is characterized by an early interruption of placental estrogen and progesterone supply, resulting in a 100-fold decrease in the plasma levels of estrogen and progesterone in preterm infants.[51,52] Premature delivery has been associated with markedly higher plasma and amniotic fluid E2 concentrations when compared with full-term delivery.[53] However, it is reported that plasma E2 and progesterone levels cannot accurately predict PTB.[54] Thus, to better understand their roles in PTB, further research is needed to determine the levels of estrogen and progesterone in maternal serum and amniotic fluid.

Mechanisms of estrogen-mediated immune tolerance in PTB

HLA-G levels have been reported to be negatively associated with E2 levels.[55] Elevated estrogen/progesterone ratio might trigger labor, suggesting that increased E2 levels might result in the downregulation of HLA-G and the failure to establish good immune tolerance, which needs further evidence to confirm. E2 influences adaptive immune responses by regulating the functional activity of innate immune cells. Moreover, stimulation with E2 can improve the cytotoxicity of dNK cells and production of IFN-γ in vitro, while reducing the expression of surface activation markers on dNK cells and the secretion of granzyme B and fas ligand.[56,57] In vitro studies have shown that E2 promotes the differentiation of bone marrow precursor cells into functional CD11c$^+$ DCs, as well as the synthesis of chemokines, including IL8 and CCL2 by immature DCs,[58,59] but downregulates antiviral responses, including via the production of IFN-α and CXCL10.[60] E2 also promote cellular and humoral immune responses.[61] Generally, low E2 concentrations enhance Th1 responses and cellular immunity, whereas high concentrations of E2 promote Th2 responses and humoral immunity.[61] In contrast, pro- and anti-inflammatory responses change in pregnancy. In late pregnancy, anti-inflammatory responses are more dominant and are associated with elevated E2 and progesterone concentrations, which inhibit Th1 immune responses and promote Th2 immune responses.[12] E2 interaction with the estrogen receptor (ER) triggers IFN-γ expression by binding to the estrogen response elements in the promoter region of the IFN-γ gene in lymphoid cells.[62] The number of regulatory T cells increases during the follicular phase of the human menstrual cycle, as well as during proestrus and estrus in mice.[63] High E2 concentrations can suppress the expression of IL-17 in mouse Th17 cells.[64]

Estrogen, specifically E2, has an important role in many "classic" estrogen effects in reproductive and nonreproductive tissues. ERs are expressed by various lymphoid tissue cells, such as lymphocytes, macrophages, and DCs.[12] The two subtypes of ERs (ERα and ERβ), as well as G-protein coupled ERs, are expressed at different levels in various immune cell subtypes. ERα is upregulated in T cells, whereas ERβ is highly expressed in B cells.[65] The effect of estrogen on immune function depends on the estrogen level (that is, the physiological or pregnancy dose) and the type, density, and distribution of ERs. E2 regulates the differentiation of DCs primarily through ERα, and not ERβ.[66,67] In addition, bone marrow–derived suppressor cells (MDSCs) are a heterologous population of immature immune cells that regulate crosstalk between E2 and progesterone, with balanced Th1/Th2 cytokine production. As a prerequisite for a successful pregnancy, increases in MDSCs and monocyte MDSCs

correlate positively with umbilical cord serum E2 levels.[68] The high levels of ERα in placental tissue suggest that E2 might mediate the accumulation of monocyte MDSCs in PTB infants.[69] These observations indicate that abnormal estrogen levels can impact maternal and fetal immune tolerance by influencing the levels of HLA-G and immune cells, thereby promoting labor and triggering PTB. However, further investigation of these interactions between cells and pathways may reveal the precise mechanism involved.

Mechanisms of estrogen-mediated inflammation in PTB

Studies indicate that estrogen has a dual-enhancing effect (proinflammatory or anti-inflammatory) on macrophages and monocytes. Low levels of estrogen enhance the production of proinflammatory cytokines (IL-1, IL-6, and TNF-α), Th1 responses, and cellular immunity, whereas high levels of estrogen inhibit proinflammatory cytokine production, and promote Th2 responses and humoral immunity.[12] Additionally, E2 promotes the expression of pattern recognition receptors by peritoneal macrophages.[70] Additionally, E2 enhances the production of IFN-γ by $CD11c^{+}$ DCs and the synthesis of proinflammatory cytokines, including IL-1 and TNF-α, in ovariectomized mice.[71] Low doses of E2 promote the activity of mitogen-activated protein kinase (MAPK) and T-bet, as well as the production of IFN-γ in T cells, and this effect is reversed by ER antagonists.[72,73] In vitro exposure of immature DCs to E2 increased the production of the IL8 and CCL2, but suppressed antiviral responses and the production of IFN-α and CXCL10.[59] Furthermore, elevated levels of circulating E2 and increased Erα activity also enhanced proinflammatory reactions.[74–76] These observations suggest that E2 is associated with inflammation.

Intra-amniotic infections can also cause PTB and pPROM via inflammation.[42] The NF-κB pathway is associated with both PTB and pPROM despite differences in their inflammatory responses.[77] Additionally, analyses of fetal murine brain tissue revealed that increased levels of inflammatory cytokines were accompanied by an upregulation of estrogen receptor 1 and estrogen receptor 2 transcripts, although their protein levels were reduced.[78] The pathogenesis of PTB involves a hormone regulatory sub-network that includes the follicle-stimulating hormone estrogen, progesterone, and luteinizing hormone, and their functions. Increased ER activity contributes to the proinflammatory cascade, causing parturition. Additionally, ER activation promotes labor by increasing the transcription of genes that encode uterine contraction-associated proteins, such as oxytocin and cyclooxygenase-2(COX-2).[77] Levels of estrogen is critical for its pro-inflammatory or anti-inflammatory effects during pregnancy. In the absence of PTB caused by inflammatory responses with known causes, abnormal changes in estrogen levels during pregnancy may trigger the onset of PTB by disturbing the inflammatory balance.

Mechanisms of androgen-mediated immune tolerance and inflammation in PTB

Androgen levels in PTB

It is widely speculated that androgens are synthetic precursors of estrogen in the placenta.[79,80] Dehydroepiandrosterone sulfate (DHEAS) is secreted by the fetal adrenal gland, and to a lesser extent by the maternal adrenal gland. DHEAS is metabolized into androstenedione (A4) and testosterone and then converted into estrone.[81] Compared with the nonpregnant period, serum A4 levels significantly increase between 37 and 42 weeks of pregnancy. However, throughout pregnancy, the levels of maternal circulating DHEAS drop to approximately 50% of the levels detected in the nonpregnant period.[82] It is reported that testosterone levels significantly increase from the first three months of pregnancy, and increased further at second and third trimester.[83,84] Therefore, the physiological increase in androgen levels in maternal circulation may be crucial for a successful full-term pregnancy.[85] DHEAS, as a precursor for testosterone synthesis, is also crucial during pregnancy. Moreover, androgens might inhibit delivery by suppressing uterine muscle contraction, and structural cervical abnormalities are associated with an increased risk of PTB.[85] When compared with women with female fetuses, those with male fetuses exhibit a higher risk of PTB, which has been attributed to higher androgen levels in the fetal compartment, and higher testosterone levels are associated with a greater risk of PTB.[86] However, sufficient evidence of a causal correlation between PTB and higher androgen concentrations in the fetal compartment is lacking. Higher maternal age is a risk factor for PTB and is negatively correlated with androgen levels in pregnant women.[87] These observations indirectly suggest that androgens might inhibit delivery by suppressing the uterine muscle contraction. Abnormal increase in androgen levels during pregnancy can increase insulin resistance and cause diabetes, thereby indirectly increasing the risk of PTB.[85,88,89] Polycystic ovary syndrome (PCOS) patients with hyperandrogenemia have an increased risk of PTB. Furthermore, testosterone levels in premature infants are reported to be higher at birth and to decline more slowly before term compared with neonates born at term. However, the levels of dihydrotestosterone (DHT) and the activity of the classical androgen biosynthetic pathway were much lower in preterm infants compared with neonates born at term.[90] Another recent study found that in premature offspring, exon-1 of the androgen receptor (AR) has more duplications in the coding sequence of the ligand activation domain.[91] Currently, few studies have investigated the role of androgens in PTB, although previous studies have speculated that prematurity may be associated with elevated androgen levels. Therefore, further research is needed to determine the role of androgens before delivery.

Mechanisms of androgen-mediated immune tolerance in PTB

Serum HLA-G levels are reported to be lower in women with PCOS than in healthy subjects. The patients with PCOS are associated with insulin resistance, oxidative stress, and ovarian hyperandrogenism.[92] Additionally, studies have demonstrated that the expression of Treg's main transcription factor, Foxp3, by human T cells, is increased upon stimulation with DHT in vitro, and increased Treg numbers in males when compared with adult females.[93,94] Hence, androgens may influence the number of T cells in vivo, in the early stages of life. It has recently been reported that in the adipose tissue of adult men, CD3+, CD8+, and CD4+ T cells correlate negatively with serum testosterone levels.[95] Microarray analysis has revealed that the levels of proinflammatory genes, such as IFN, IL-12

receptor-β 2, LTβ, and GNLY are higher in T cells from adult females, whereas the levels of IL-10, IL-5, and IL-17A are higher in T cells from adult males.[96] It has also been shown that in females, androgens can directly induce the conversion of peripheral blood T cells into Tregs.[97,98] Furthermore, testosterone has been associated with immunosuppression during infectious diseases, autoimmune diseases, and cancer.[99]

Previous study showed that human thymocytes express ARs.[100] Most innate and adaptive immune cells express ARs, indicating that androgens are directly involved in the regulation of the development and function of immune cells.[100] Indeed, in humans and mice, several innate immune cells, including monocytes, macrophages, innate lymphoid cell progenitors, and mast cells, express ARs.[101–103] Moreover, adaptive immunity cell types, such as CD8+, CD4+, and splenic CD4+ CD25+ T cells express ARs.[101,102,104] CD4+ and CD8+ T cells also express the membrane androgen receptor (mAR).[105] Notably, linkage analysis has shown that in premature infants, the exon 1 of AR has more sequence repeats in the site that encodes the domain involved in ligand activation.[91] However, research on the role of androgens in PTB, as well as their roles in the regulation of immune tolerance at the fetal–maternal interface is limited.

Mechanisms of androgen-mediated inflammation in PTB

Past studies have shown that inflammation imbalance (anti-inflammatory or pro-inflammatory) during pregnancy is frequently associated with adverse pregnancy outcomes. Importantly, androgens may have an impact on inflammation in mothers, but no comprehensive studies have been conducted so far. Reduced serum levels of IL-1β and TNF have been observed in hypogonadal men, and increases in IL-10 have been observed after hormone replacement therapy. It is reported that upon stimulation with TLR8/9 ligands, peripheral blood mononuclear cell (PBMCs) from healthy adult males secrete much higher amounts of IL-10 than PBMCs from females. However, after stimulation with TLR7, PBMCs from males produced lower levels of IFN-α than those from females.[106] DHEA downregulates the expression and secretion of IFN-γ in a dose- and time-dependent manner.[107] Moreover, high androgen levels in women with PCOS were associated with decidualization and placental enation. Moreover, DHT enhanced decidualization in non-PCOS endometrial stromal cells.[108] Studies have shown that pregnant women with PCOS have much higher androgen levels than healthy pregnant women and that this was accompanied by a 6% higher risk of PTB.[109] However, PCOS is associated with increases in the levels of various inflammatory mediators, which may cause PTB. Thus, excessive androgen levels may not be the only driver of PTB in these women.[110] Both experiments and observations made in pregnant PCOS patients imply that abnormal androgen levels affect the balance of inflammation. It is reported that optimal in vivo decidualization requires intracrine androgen signaling, which confirms that during decidualization, androgens mainly influence the development of the vascular system by

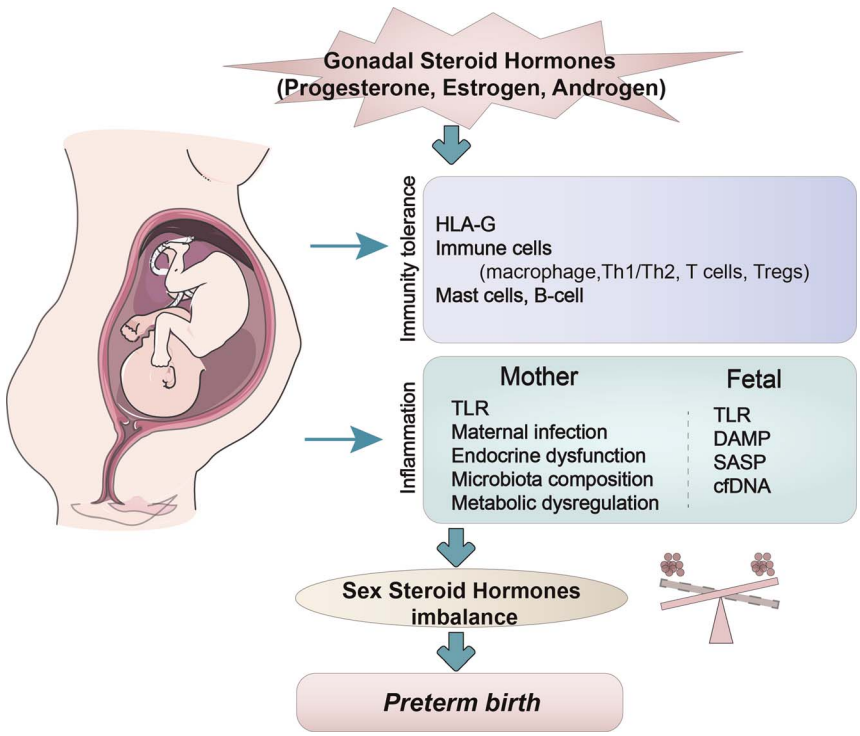

Figure 1. Schematic representation of the mechanism by which gonadal steroid hormones influence immune tolerance and inflammation during preterm birth. Abnormal levels of the three gonadal steroid hormones (progesterone, estrogen, and androgen) during pregnancy may lead to preterm birth due to their effects on immune tolerance and inflammation. These hormones can affect the activity of HLA-G and immune cells, and can cause maternal and fetal inflammation, both of which can contribute to preterm birth. HLA-G: Human leucocyte antigen-G; TLR: Toll-like receptors; DAMP: Damage-associated molecular pattern; SASP: Senescence-associated secretory phenotype; cfDNA: Cell-free DNA.

regulating the vascular endothelial growth factor (VEGF) pathway.[111] Although no studies have investigated androgen-dependent regulation of inflammation during PTB, the inflammatory responses they mediate and the abnormal decidualization reported in other studies, indicate that they may be involved in the occurrence of PTB.

Prospective

Future research directions include the following: (1) investigations into the mechanisms that regulate gonadal hormone production and maturation. These hormones are trafficked between the placenta and the fetus and require synthesis enzymes for inner change. Gonadal hormone synthesis is mainly catalyzed by cytochrome P-450 (CYP) enzymes and members of the hydroxylation family, such as hydroxysteroid dehydrogenase (HSD). The CYP family of enzymes mainly catalyze the synthesis of gonadal hormones via substrate hydroxylation and cleavage, while the reduction and oxidation of gonadal hormones are executed by the HSD family of enzymes.[112] Because imbalances in enzyme levels can cause imbalances in hormone levels, this may contribute to PTB through the disruption of immune tolerance or inflammation. Indeed, it is reported that the repression of the enzyme, 11β-HSD-1, might be a promising therapeutic target for preventing PTB.[113] However, few studies have investigated this research area. (2) Investigations into the connections between gonadal hormones, the timing of delivery, and how these may vary depending on fetal gender and time of hormone measurement could provide insight into the prevention of premature birth. Swedish national data suggests that male fetuses are more likely to experience PTB.[114] Hormone levels were also found to differ between trimesters. Future research should investigate the mechanism underlying differences in delivery timing in male vs female fetuses. More clinical data are needed, which may require large study cohorts to systematically detect changes in various hormones during PTB. (3) PTB occurrence may depend on more than one hormonal effect, and imbalances in the proportions of different hormones should be evaluated in future studies. Although the role of exosomes (fetal and maternal) in the occurrence of PTB has also been explored, further research is needed to determine whether hormone imbalances influence the release of exosomes and their contents. Moreover, future research should determine the following: (1) whether fetal inflammation caused by hormonal imbalance during maternal inflammation is associated with PTB, (2) whether maternal spill-over of inflammatory cytokines caused by hormonal imbalance has consequences, and (3) whether PTB is caused by fetal inflammation, maternal inflammation, or both.

Conclusion

Gonadal steroid hormones, including progesterone, estrogen, and androgens, influence the success of pregnancies, and disruptions in their levels can cause adverse pregnancy outcomes, including PTB. Progesterone, estrogen, and androgen may contribute to PTB progression by influencing immune tolerance and driving an imbalance between pro- and anti-inflammatory factors (as shown in Fig. 1). However, it should be noted that many effects of steroid hormones on immune cells may not be direct, but might occur through uterine cells, which can produce cytokines and other factors that regulate immune cell function. Moreover, enzymes associated with the synthesis of gonadal steroid hormones also have important roles in the regulation of hormone levels. Although the role of gonadal steroids in the occurrence of PTB is poorly studied, and the specific mechanisms of action are unclear, emerging evidence suggests that they have important roles in the process.

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Author Contributions

All authors contributed to conceptualization. Yongmei Shen and Yaqi Li did the writing original draft preparation. Jiasong Cao and Wen Li did the writing—review and editing. Qimei Lin and Jianxi Wang did the supervision and language polish. Zhuo Wei did the project administration. Yongmei Shen did the funding acquisition. Ying Chang did the resources and project design. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

None.

Editor Note

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