Review

Maternal-Fetal Medicine®

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Factors of Fetal Origin in the Regulation of Labor Initiation and Preterm Birth

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Abstract

Preterm birth is the leading cause of mortality and morbidity in newborns and children under 5 years-of-age. In order to improve the survival rate and quality of preterm infants, there is critical need to identify the specific mechanisms underlying the initiation of labor. Pregnancy represents a period of constant interactive dialog between mother and fetus. A disturbance in the pattern of maternal-fetal communication can induce physiological or pathological labor. Although a number of studies have investigated the contributions of maternal factors to the initiation of labor, the concept that fetal organ development and maternal adaptation are coordinated has emerged over recent years, thus emphasizing that factors of fetal origin may serve as hormonal signals for the initiation of labor. In this review, we summarize and discuss several specific mechanisms by which factors of fetal origin may influence parturition during term or preterm labor, including the specific regulation of fetal organs, including the lungs and accessory organs during pregnancy. Future research may focus on the specific pathways by which signals from the fetal lungs and other fetal organs interact with the maternal system to initiate eventual labor.

Keywords: Premature birth; Fetal origin factor; Placenta; Fetal membrane; Parturition; Term labor

Introduction

Preterm birth is clinically defined as childbirth prior to 37 weeks of gestation. The most important characteristic of preterm birth is that labor is initiated before the fetus fully matures. Complications caused by preterm birth accounts for approximately 33% of all neonatal deaths,[1] remains the leading cause of mortality and morbidity in newborns and children under 5 years-of-age.[2] Due to organ immaturity, preterm infants have a significantly higher risk of respiratory distress syndrome, necrotizing enterocolitis, and other diseases. Therefore, in order to predict and treat preterm labor effectively, it is necessary to gain an enhanced understanding of the specific mechanisms underlying physiological and pathological birth. The factors involved in the initiation of labor are known to reinforce each other. Pregnancy represents an interactive dialog between the mother and the developing fetus. The timing of delivery is vital as this can support an infant's independent survival outside of the uterus. Therefore, the maternal recognition of key signals from the mature fetus is considered a critical mechanism for normal parturition. In this review, we focus on recently confirmed regulatory pathways of fetus-derived factors that have been shown to be involved in the initiation of labor.

The development and signals of fetal organs

The fetus develops to maturity throughout the progression of pregnancy. In addition, the fetus provides signals to the mother in the form of secreted hormones and cytokines to modulate maternal adaptation and ultimately, the timing of labor.[3] Previous studies suggested that the fetal hypothalamus-pituitary-adrenal (HPA) axis synthesizes and secretes hormones that regulated both the endocrine function of the placenta and the maturation of fetal organs (e.g., the fetal lungs),[4–6] both of which may represent the origin of factors that regulate the initiation of maternal labor.[7]

Signals from the fetal adrenal gland

During human pregnancy, the placental[8] and fetal[9] hypothalamic-derived corticotropin-releasing hormone (CRH) promotes adrenal development in the fetus, thus stimulating the secretion of steroid hormones via the HPA axis. The concentrations of steroid hormones secreted by the fetus vary throughout the period of gestation. In the early and middle stages of pregnancy, the fetal adrenal cortex primarily secretes dehydroepiandrosterone (DHEA).[10] DHEA is important precursor of placental estrogen,[11] a hormone that plays an important role in the maintenance of pregnancy and the initiation of labor. The fetal adrenal glands also secrete small amounts of glucocorticoids at this time, primarily to negatively regulate the fetal pituitary gland. Glucocorticoids are the main adrenocortical hormones secreted by the fetus during the second trimester.[12] Glucocorticoids bind directly with intracellular receptors to activate transcription factors and regulate gene expression. In the chorionic trophoblast, glucocorticoids promote the synthesis of prostaglandins (PGs). Elevated levels of PGs further enhance the activity of 11β-hydroxysteroid dehydrogenase I (11β-HSDI) in the fetal membranes, thus promoting the local synthesis of

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Maternal-Fetal Medicine (2023) 5:4

Received: 7 July 2023 / Accepted: 15 August 2023

First online publication: 13 October 2023

http://dx.doi.org/10.1097/FM9.0000000000000200

cortisol and PGs, and inducing full-term fetal delivery.[13] The synthesis and secretion of placental PGs and the specific mechanisms by which they regulate the initiation of labor and preterm birth will be described in the second part of this review. When the fetus is stimulated by various adverse intrauterine factors, such as hypoxia and inflammation, the HPA axis is activated and the adrenal glands secrete large amounts of cortisol.[14,15] Subsequently, cortisol plays a key role in the in the functional withdrawal of progesterone by down-regulating the expression of 15-PGDH, and increasing the synthesis of PGs to regulate the expression levels and ratio of two progesterone receptors (PRs; PR-A and PR-B) on the myometrium. This process occurs via the protein kinase C (PKC) pathway in response to stimulation by PGs and ultimately induces labor or preterm labor.[16,17]

Signals from the fetal lungs and their regulatory effects

The large amounts of glucocorticoids synthesized and secreted by the fetal adrenal cortex during the second trimester promotes the maturation of the fetal organs and ensures that the fetus can adapt to the extrauterine environment following delivery.[18] These mature organs also secrete relevant factors that act as an inflammatory stimulus to regulate the initiation of labor.[19] Gaining the ability to breathe air is clearly one of the most critical changes for newborns between the intrauterine and extrauterine environments, thus making development of the fetal lungs a significant feature of fetal maturation. Within the uterine environment, the fetus is surrounded by amniotic fluid, which is in direct contact with the fetal alveoli through fetal gulping. Consequently, pulmonary factors secreted by the fetal lungs can directly enter the amniotic fluid. Therefore the amniotic fluid can be used to predict and interpret the stages and physiological status of fetal lung developmental; moreover, analysis of the amniotic fluid could reflect damage incurred by the fetal lungs.[20,21] Related studies suggest that fetal lung-derived pulmonary surfactants, including surfactant proteins A (SP-A) and D (SP-D) can act as signal molecules to induce labor by promoting the secretion of IL-1β by macrophages in the amniotic fluid.[22,23] Previous studies focusing on the upstream regulators of pulmonary surfactants have revealed that the expression levels of lysophosphatidylcholine acyltransferase 1 (Lpcat1), a key enzyme, can regulate the secretion of dipalmitoyl phosphatidylcholine (DPPC) and platelet activating factor (PAF) from the fetal lungs.[24,25] In another study, Gao *et al.*[26] found that wild-type pregnant mice carrying fetuses that were double-deficient in steroid receptor coactivators 1 and 2 (SRC-1 and SRC-2) manifested a dramatic delay in parturition. The lungs of these fetuses were deficient in both SP-A and PAF; these are factors that are normally secreted into the amniotic fluid. These results provide compelling evidence that the fetus initiates parturition by sending signals to the maternal system when its lungs develop the capacity to produce sufficient surfactant lipoproteins to sustain air breathing. More recently, another research group investigated the mechanisms of fetus-derived PAF on human parturition and found that PAF reduces PR-A expression by inducing DNA methylation via the PR-A promoter to subsequently allow RelB/p52 to enter the nucleus and activate a prolabor signaling pathway in the placental cytotrophoblast.[27] These findings suggest that the fetus-derived PAF exerts homologous effects across species through different pathways: in mice, PAF contributes to a drop in progesterone levels by causing maternal luteolysis; while the secretion of PAF from the human fetus causes the functional withdrawal of progesterone by initiating the down-regulation of its receptor in the placenta.

In addition to surfactant-related factors secreted by the fetal lungs, Yu *et al.*[28] showed that the arginase 1 (Arg1) deficiency and the accumulation of L-arginine in the fetal lungs not only induced epithelial cell apoptosis in the fetal lungs to induce abnormal lung development, but also inhibited uterine smooth muscle contraction and delayed the initiation of labor by suppressing myometrial contractile protein expression and the levels of NF-κB phosphorylation. The results of this previous study suggested that Arg1 and its metabolite L-arginine are vital for the development and maturation of the fetal lungs, whereas SP-A and DPPC are more important for preparing the fetus to breathe air after delivery. Collectively, these fetal lung-derived factors may act as comprehensive signals that contribute to the initiation of labor.

In 2019, Ithier *et al.*[29] reported that proteins contained in exosomes within human arterial cord blood were present in higher concentrations when compared exosomes in blood samples from the cord vein, thus suggesting that proteins secreted by the fetus may exert effects on the placenta via the circulation. These authors also identified an abundance of C4b-binding protein alpha (C4BPA) in exosomes from fetal lungs. The mature secretory form of C4BPA can bind to its receptor, CD40, on the surface of placental cytotrophoblast (CTB) cells to promote the entry of RelB/p52 entry into the nucleus to activate the noncanonical NF-κB signal pathway, ultimately inducing the expression of genes related to labor. These lines of evidence suggest that factors derived from the fetal lungs may induce the expression of genes related to the initiation of labor in placental trophoblasts by activating the noncanonical NF-κB signaling pathway and subsequently induce the expression of contraction-associated proteins (CAPs) in the myometrium by activating the canonical NF-κB signal pathway, thus exerting synergistic signaling effects in the initiation of labor (Figure 1).[28,29]

The placenta and fetal membranes as fetal appendages

The placenta and fetal membranes are fetal appendages that are present during maternal gestation. These structures promote adaptive changes during maternal gestation to maintain pregnancy and ensure normal fetal development. In addition, these structures play a regulatory role in the initiation of full-term labor and preterm labor; this occurs via the secretion of hormones, the regulation of immune activation, and tolerance balance at the maternal-fetal interface.

Placental regulation of estrogen and progesterone

As a unique fetal accessory organ during pregnancy, the placenta is not only responsible for the provision of fetal nutrients, gaseous exchange, and the excretion of metabolic waste, it also acts as an important endocrine organ.[30,31] An abundance of growth factors, cytokines, and steroid hormones are involved in the regulation of labor initiation during the progression of pregnancy.[1] During pregnancy, increasing amounts of CRH are synthesized by the human and other primate placentas in response to the mature HPA axis in the fetus. The exponential increase of CRH

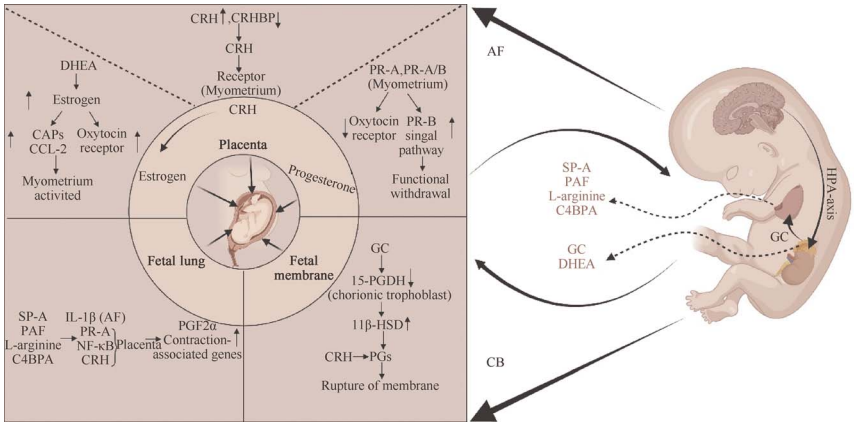

Figure 1. Fetal-derived factors in the regulation of labor initiation. AF: Amniotic fluid; CAPs: cAMP activated proteins; CCL-2: Monocyte chemoattractant protein-1; CB: Cord blood; CRH: Corticotropin-releasing hormone; C4BPA:C4b binding protein alpha; CRHBP: CRH-binding protein; DHEA: Dehydroepiandrosterone; GC: Glucocorticoid; HPA-axis: Hypothalamic-pituitary-adrenal axis; IL-1β: Interleukin-1β; NF-κB: Nuclear factor kappa-B; PAF: Platelet activating factor; PGF2α: Prostaglandin F2α;15-PGDH:15-Hydroxyprostaglandin dehydrogenase;11β-HSD:11β-hydroxysteroid dehydrogenase; PR-A/B: Progesterone receptor A/B; PGs: Prostaglandins; SP-A: Pulmonary surfatcant-associated protein-A.

levels in the maternal plasma is accompanied by a reduction in CRH-binding protein, thus increasing the amount of CRH that can exert regulatory effects during the second trimester.[32] CRH may bind directly to receptors located on myometrial cells to increase myometrial contractility and participate in the regulation of human delivery; in addition, CRH may regulate the synthesis and release of prostaglandins from the fetal membranes.[33,34] Thus, CRH is considered as a biological clock that governs the length of pregnancy in humans and other primates.

In addition to CRH, the placenta also secretes two vital steroid hormones: progesterone and estrogen. Progesterone is secreted by the syncytiotrophoblast during the eighth week of gestation. By the tenth week of gestation, the placenta completely replaces the gestational corpus luteum as the main site of progesterone synthesis. Progesterone maintains the stable state of pregnancy and is an established pregnancy-supporting hormone.[35] Progesterone is known to promote myometrial relaxation and suppress the expression of CAPs, thereby robustly blocking the transformation of the myometrium into the contractile phenotype, thus maintaining pregnancy.[36] Estrogen is predominantly derived from the corpus luteum during early pregnancy and is synthesized by placental aromatase and other enzymes via fetal adrenal-derived dehydroepiandrosterone sulfate (DHEAS) in the form of estriol during late pregnancy. Estrogen antagonizes the effects of progesterone by altering the physiological phenotype of the uterus, increasing uterine excitability, and transforming the uterus into contractile phenotype by altering membrane potential and forming gap junctions between myometrial cells. In addition, estrogen enhances the action of oxytocin in the myometrium, thus stimulating the expression of cervical protein hydrolase which degrades the extracellular matrix to dilate the cervix.[37]

Therefore, it can be inferred that a reduction in progesterone levels (progesterone withdrawal) or an increase in the secretion of estrogen, is the key event that initiates labor in humans.[38] However, no significant reduction of progesterone, or an increase of estrogen, has been observed in maternal blood during the series of events associated with the initiation of labor in humans. It is now generally accepted that during the initiation of human labor, the myometrium mediates the reduced response to placental progesterone and the increased response to estrogen; this implies that both of these changes cause a functional change that mediates the process of labor initiation in humans.[39,40] Structurally, PR-A is the truncated form of PR-B, and lacks 164 N-terminal residues. Functionally, PR-A promotes uterine muscle contraction primarily by up-regulating the inflammatory response and the expression of myometrial connexin43 (CX43), whereas PR-B primarily maintains the resting state of uterine muscle by increasing the expression of inhibitor-κBα (IκBα), a repressor of the nuclear factor-κB (NF-κB) transcription factor, and also by reducing the expression of proinflammatory genes. During gestation, PR-B is the main form of PR, and the initiation of labor is accompanied by an increase in the expression of PR-A and the PR-A/B ratio; this caused by PAF derived from the fetal lungs, at least in part.[41] The functional withdrawal of progesterone precedes an increase in the expression levels of ERα, thus promoting the secretion of monocyte chemoattractant protein-1 (CCL-2) in the myometrium and enhancing the expression of CAPs; these events shift the myometrium from a resting state to an activated state to facilitate the initiation of labor.[42]

Regulation of prostaglandins in the amnion and chorion

As mentioned earlier, the amnion and chorion are also important fetal appendages which synthesize and metabolize PGs.[43] The synthesis of PGs is dynamically regulated by the balance between several synthetic enzymes: prostaglandin endoperoxide H synthases-1 and 2 (PGHS-1 and PGHS-2), cyclooxygenases-1 and 2 (COX-1 and COX-2) and 15-PGDH. It is also important to note that PGs that are synthesized by the amnion do not necessarily reach the receptor site in the myometrium; this is because the chorionic villus tissue between the amnion and the uterus expresses high levels of PGDH, which inactivates PGs before

they reach the myometrium. The concentration PGs exposed to the myometrium ultimately depends on the balance between PGHS-2 and PGDH activity in the chorionic villus. For example, progesterone increases PGHS-2 activity but inhibits PGDH activity, thus increasing the concentration of PGs exposed to the myometrium. However, estrogen, cortisol, CRH, and other immune cytokines may exert the opposite effects, thereby increasing the net exposure of PGs to the myometrium.[44] When the net exposure of PGs in the myometrium reaches a specific threshold, intracellular calcium ions are released, thus stimulating uterine contraction.

In a recent study, Lu *et al.*[45] found that C/EBPδ, a member of the CCAAT/enhancer-binding protein (CEBP) family , increases along with COX-2 and 11β-HSD1 at term and further increases at parturition in the amnion, and that PTGS-2 and HSD11B1 are downstream regulatory genes of C/EBPδ in amniotic fibroblasts. In addition, these authors found that gestational length was prolonged to 20.5 days when embryos developed the Cebpd$^{-/-}$ genotype, thus suggesting that the C/EBPδ pathway may be a potential pharmaceutical target in the amnion for preterm labor.[45]

Regulation of immune activation and tolerance balance at the maternal-fetal interface

The immune microenvironment at the maternal-fetal interface consists of trophoblast cells, decidual stromal cells, and decidual immune cells. Whether the decidua in the immune microenvironment at the maternal-fetal interface plays a role in the initiation of labor and preterm labor has been discussed extensively in recent reviews.[46,47] Here, we focus on the immune cells derived from the fetus and the regulator effects of fetus-derived factors on the immune response at the maternal-fetal interface during the initiation of labor or preterm labor.

Either the fetus itself, or fetal appendages, such as the placenta and the fetal membranes, express paternal histocompatibility antigens and can be regarded as a heterozygous semiallograft that might trigger a rejection reaction by the mother. Consequently, it is important that the mother develops immune tolerance to the fetus and its accessory organs in order to ensure the normal progression of pregnancy. During this period, the developing fetus is also exposed to several immune-stimulatory molecules, including semiallogeneic antigens from maternal cells. Therefore, successful pregnancy relies on a strict balance between maternal/fetal immune activation and immune tolerance to embryonic and maternal-derived antigens; a disturbance in this balance can trigger the physiological or pathological initiation of labor.[48]

Over the last century, studies have suggested that the process of preterm birth is accompanied by activation of the fetal immune response, as evidenced by an increasing number of activated immune cells and factors involved in term and preterm labor.[49,50] However, the exact causal relationship between these factors has yet to be elucidated.[51] Increased levels of IL-6 in the fetal plasma before spontaneous delivery, but not after initiation, suggest the involvement of fetus-derived proinflammatory cytokines in the process of delivery initiation.[52] Over recent years, studies have found that amniotic fluid is rich in a variety of intrinsic immune cells, such as neutrophils, and exerts antimicrobial immune effects in inflammatory preterm births such as chorioamnionitis.[53–55] Whether these cells originate from the maternal or fetal side has yet to be confirmed; however, this provides the basis for future research on the involvement of fetus-derived intrinsic immune cells in the initiation of labor and preterm labor.

When considering adaptive immune cells, T cells are known to play a crucial role in increasing tolerance against self-antigens and are reactive against foreign antigens. Moreover, recent studies have suggested that fetal-derived T cells are involved in the initiation of labor and preterm birth. Frascoli *et al.*[56] reported that the cord blood of preterm infants is characterized by an increased proportion of type 1 T helper phenotype like central memory (CM) T cells (Th1-like CM CD4$^+$ T cells) which produce IFN-γ concomitant with a reduction in the proportion of naive CD4$^+$T cells when compared to infants at term. When isolated from preterm infants, T cells maintain an immune response to maternal antigens when compared to infants at term. In addition, the co-culture of a human myometrial cell line with sorted T cells from cord blood showed that T cells from preterm infants stimulated uterine myometrial contractility via TNF-α and IFN-γ.[56] Gomez-Lopez *et al.*[57] also demonstrated that fetal CD4$^+$ T cell secreted an abundance of IL-2, IL-4, and IL-13 in amniotic fluid during human preterm gestations. Using animal models, the same authors showed that the intra-amniotic administration of activated neonatal CD4$^+$ T cells induced preterm birth in mice, thus demonstrating that fetal T cell activation is implicated in the pathogenesis of idiopathic preterm labor. These lines of evidences suggest that intrinsic and adaptive immune cells of fetal origin, especially T cells, play important roles in labor at both term and preterm birth.

Endogenous substances released by cells in a state of stress or injury are collectively referred to as damage-associated molecular patterns (DAMPs). Sterile inflammation caused by DAMPs is prevalent in normal deliveries and in pregnant women who deliver prematurely with no obvious causative factors and no evidence of infection. The most studied DAMPs include high mobility group box 1 (HMGB1), serum amyloid A1 (SAA1), uric acid, S100 protein, and heat shock protein 70.[58] Gomez-Lopez *et al.*[59] reported a significant increase of HMGB1 in the amniotic fluid of a term labor group, while the intra-amniotic injection of HMGB1 into the mouse amniotic cavity triggered preterm birth, thus suggesting that the HMGB1 signaling pathway may be involved in the process of both full-term labor and preterm labor. In addition, the fetal membrane-derived acute phase response protein SAA1 is known to play a critical role in fetal membrane rupture and labor initiation by promoting the secretion of IL-1β, IL-6, and prostaglandin E2 (PGE2) from amniotic fibroblasts, thus increasing the expression and activity of the extracellular matrix metalloproteinase family, and activating the intracellular autophagy/lysosomal pathway to degrade collagen.[60] However, whether other factors of fetal origin, including SPA, PAF, L-arginine, and C4BPA, as summarized earlier, can also function as DAMPs and directly regulate immune responses at the maternal-fetal interface still needs to be investigated.

In this review, we summarize the influence of fetal-derived factors on the initiation of labor. We focus specifically on the mechanisms by which fetal organs and their accessory organs develop along with the fetus and regulate the initiation of labor and preterm labor under the influence of endocrine hormones and cell-secreted regulators. We also discuss the importance of the specific pathways through which the

fetal lungs secrete substances that are active at the alveolar surface to regulate the initiation of labor, thus providing a more direct theoretical basis for the influence of fetal factors on the initiation of labor. The limitation of this review that there is a lack of further evidence on the specific contribution of other fetal organs to the initiation of term labor and preterm labor in addition to the fetal lungs and placenta, such as the fetal liver and kidneys. This limitation needs to be addressed in future research.

Conclusion

The maternal factors that influence the initiation of labor and preterm labor are relatively well understood. Since the initiation of labor is a physiological phenomenon that occurs as a result of perturbations in maternal-fetal communication, fetal factors must play an important role in this process. Although it is evident that substantial progress has been made identifying the factors of fetal origin that might signal the initiation of labor, the maternal-fetal system is highly complex. Further research is urgently needed to investigate the specific pathways and mechanisms by which these signals of fetal origin can interact with the maternal system to initiate final parturition. These studies will provide new evidence for the specific mechanisms that underlie the regulation of labor and shed new light on the prevention of preterm labor.

Funding

Research in the Gao's laboratory is supported by National Key Research and Development Project 2022YFC2704602 and 2022YFC2704502, National Natural Science Foundation of China 82120108011, Major Project of Shanghai Municipal Education Commission's Scientific Research and Innovation Plan 2021-01-07-00-07-E00144, and Strategic Collaborative Research Program of the Ferring Institute of Reproductive Medicine FIRMA200502.

Conflicts of Interest

None.

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Edited By Yang Pan

How to cite this article: Ding L, Gao L. Factors of Fetal Origin in the Regulation of Labor Initiation and Preterm Birth. Maternal Fetal Med 2023;5(4):238–243. doi: 10.1097/FM9.0000000000000200.