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Endocrine Control of Fetal Growth, the Delivery Process, and the Physiology of Childbirth

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Abstract

Childbirth is a complex physiological process characterized by the expulsion of the fetus from the uterus, marked by uterine contractions and cervical changes. The timing of labor is crucial for favorable pregnancy outcomes and is regulated by the neuroendocrine maturation of the fetus. Hormones like estrogen, progesterone, and human placental lactogen play key roles in fetal growth regulation, with fluctuations influencing birth weight and placental development. Progesterone inhibits labor by relaxing the uterus, while estrogen promotes labor by stimulating uterine contractions and cervical changes. The transition from uterine quiescence to active labor involves multiple stages, from myometrial relaxation to enhanced contractility. Labor progresses through phases, starting with quiescence, followed by the onset of rhythmic contractions, active labor, and concluding with involution. Uterine stretching and the role of fetal lung maturation also contribute to labor initiation, as fetal lung surfactant activates macrophages, leading to inflammation and progesterone withdrawal. This process synchronizes labor timing with fetal lung development. In conclusion, labor is influenced by a combination of endocrine and mechanical factors, including prostaglandins, cytokines, and hormones such as oxytocin and CRH. Proper endocrine regulation ensures timely labor, while disruptions in this system, such as premature or prolonged pregnancies, can lead to increased fetal morbidity and mortality.

Introduction

Childbirth refers to a natural physiological process involving the expulsion of the fetus from the uterus. It is characterized by consistent uterine contractions that gradually increase in frequency, strength, and duration, resulting in the gradual thinning and widening of the cervix (Kota et al., 2013; Strauss et al., 2023). Proper timing of labor plays a significant role in achieving favorable pregnancy outcomes. This timing is regulated by the neuroendocrine maturation of the fetus, initiating the childbirth process once the fetus reaches full term and is prepared for life outside the uterus (Petraglia et al., 2023; Strauss et al., 2023).

During normal childbirth, biochemical alterations in the connective tissue of the cervix often occur before uterine contractions, facilitating cervical dilation. These processes eventually lead to the spontaneous rupture of fetal membranes. Research on animals highlights the critical role of fetal endocrine mechanisms in determining the timing of labor. This involves the activation of the fetal hypothalamic-pituitary-adrenal (HPA) axis, triggering an increase in adrenal

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cortisol levels, modifications in the balance of progesterone and estrogen, and the regulation of prostaglandin synthesis within the uterus (Vannuccini et al., 2016; Wilson & Mesiano, 2020; Zagrean, 2020).

In most animal species, the onset of labor is driven by shifts in hormone levels within the maternal and fetal circulatory systems as pregnancy nears its conclusion. In humans, by contrast, labor emerges from an intricate and dynamic biochemical interplay between the fetoplacental unit and the maternal system (Kota et al., 2013). This paper will explore the role of endocrine mechanisms in regulating fetal growth, initiating labor, and the physiological processes of childbirth.

Endocrine Control of Fetal Growth

Throughout pregnancy, the placenta secretes various hormones, including estrogen, progesterone, human chorionic gonadotropin (hCG), growth hormone (GH), and human placental lactogen (hPL), all of which are involved in the regulation of fetal growth. Research conducted on mothers suffering from malnutrition or anemia has shown elevated levels of human placental lactogen, growth hormone, and insulin-like growth factor I (IGF-I) in umbilical cord blood compared to those in healthy pregnant women. Although direct evidence of estrogen and progesterone's role in fetal growth regulation is limited, certain studies have found correlations between the concentrations of these hormones and both birth weight and placental weight (Murphy et al., 2006).

Fetal Insulin

During fetal development, insulin plays a key role in signaling the availability of nutrients. A deficiency in insulin results in reduced fetal growth due to a decline in nutrient transfer to the fetus. Recent research has shown that insulin levels in umbilical cord blood are notably lower in neonates with small gestational age, correlating with birth weight, length, and placental weight. In contrast, insulin levels in maternal serum or amniotic fluid do not show a correlation with birth weight. The use of corticosteroids by the mother temporarily boosts insulin levels. Additionally, increased insulin production is linked to enhanced fetal growth. In cases of maternal hyperglycemia, the fetus responds by ramping up insulin production, a factor contributing to the observed increase in growth and macrosomia in diabetic pregnancies (Murphy et al., 2006).

Placental Growth Hormone (PGH)

Human placental growth hormone is produced by a variant of the growth hormone gene located on chromosome 17. It is expressed in the placenta's syncytiotrophoblast and extravillous cytotrophoblast (EVCT) layers. PGH is detectable in the fetal environment, including in the umbilical cord blood and amniotic fluid. Its levels rise steadily in the maternal circulation from the 5th to 7th week of pregnancy until full term, gradually replacing the pulsatile secretion of pituitary growth hormone between the 15th and 20th weeks of gestation (Velegrakis, Sfakiotaki, & Sifakis, 2017). PGH is vital in regulating maternal insulin-like growth factor I (IGF-I) and stimulates gluconeogenesis, lipolysis, and anabolism in maternal tissues, influencing fetal growth and placental development. A study by Pedersen et al. found that higher maternal PGH levels were associated with increased fetal growth during the first trimester. The results suggest that PGH contributes to fetal growth regulation early in pregnancy (Velegrakis et al., 2017). During pregnancy, placental growth hormone (GH) variants are released into the maternal circulation, inhibiting pituitary GH. In fetal growth restriction, circulating GH and placental mRNA decrease, but insulin-like growth factor (IGF) plays a more dominant role in fetal growth regulation (Murphy et al., 2006).

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Human Placental Lactogen

Syncytiotrophoblasts synthesize placental lactogen and release it into the maternal circulation, where it plays a role in increasing IGF-I levels. This hormone aids in early embryonic growth by triggering the production of other hormones like insulin and IGF-I. Studies indicate that placental lactogen fails to enhance the development of human fetal fibroblasts and myoblasts in the presence of IGF-I antibodies. As pregnancy progresses, fetal serum concentrations of IGF-I, IGF-II, and IGFBP-3 rise markedly, with IGF-I experiencing the highest level of growth (Murphy et al., 2006).

Glucocorticoids

Glucocorticoids are crucial for fetal organ maturation, especially during late pregnancy when cortisol levels rise. Studies in sheep demonstrate that administering ACTH, cortisol, or dexamethasone accelerates adrenal and lung development. These hormones also support the maturation of other organs, including the liver and kidneys, and stimulate surfactant production in human fetal lungs. Betamethasone given to women at risk of preterm labor reduces neonatal respiratory distress and mortality. However, glucocorticoids may suppress IGF-I levels, limiting fetal growth. Observational studies link high-dose glucocorticoids to adverse effects like reduced birth weight and altered fetal heart rates. Despite potential growth restrictions, repeated steroid doses show no additional impact compared to a single dose (Murphy et al., 2006).

Placental 11-HSD2 and Fetal Growth

Placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) is essential for fetal growth, with reduced activity linked to IUGR and lower birth weights. Studies show decreased 11β-HSD2 activity and mRNA levels in IUGR cases, though no gene mutations were found. In asthmatic pregnancies, reduced 11β-HSD2 activity correlates with lower birth weights in female neonates, likely due to post-translational regulation. While some studies suggest a link between 11β-HSD2 activity and birth weight, this correlation is more evident in low-birth-weight cases (Murphy et al., 2006).

Fetal Organ Maturation and Preparation for Extrauterine Life

At birth, the fetus must maintain physiological balance independently of the placenta to survive. Proper timing of fetal maturation and delivery is critical, influenced by glucocorticoids that aid organ development, surfactant production, enzyme regulation, and glycogen storage. Glucocorticoids are essential for lung maturation, reducing respiratory distress in preterm infants. Synthetic glucocorticoids improve survival by enhancing lung development. Cortisol may also stimulate organ maturation but can have harmful effects, which the placental barrier protects against. As pregnancy nears term, this barrier weakens, allowing maternal cortisol to support fetal lung maturation, explaining why glucocorticoid-deficient fetuses often show mature organs at birth (Strauss et al., 2023).

Endocrine Control of Labor

Labor is regulated by hormones that affect uterine contractions and cervical integrity, primarily progesterone and estrogen. Progesterone inhibits labor by relaxing the uterus and closing the cervix, while a decrease in progesterone allows labor to begin. Estrogen, in contrast, stimulates changes in the uterus, cervix, and fetal membranes to promote labor. The balance between progesterone's inhibitory effect and estrogen's stimulating role determines the timing of labor. Labor is triggered when progesterone production decreases, allowing estrogen to enhance uterine contractions, cervical softening, and membrane weakening (Kota et al., 2013; Strauss et al., 2023; Vannuccini et al., 2016).

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Progesterone

Mechanism and Control of Progesterone Cessation

Progesterone (P4) plays a crucial role in the establishment and progression of pregnancy and in initiating labor. It facilitates fetal development by keeping the myometrium relaxed during pregnancy, preventing the activation of the decidua, and promoting maternal immune tolerance. Progesterone receptors (PR) are present throughout P4-target tissues, including the myometrium (Strauss et al., 2023; Vannuccini et al., 2016). The regulation of the birth process involves hormonal interactions that control how progesterone and estrogen affect the myometrial cells. Research indicates that the cessation of progesterone plays a key role in triggering the onset of labor (Strauss et al., 2023). Circulating progesterone (P4) levels in pregnant women remain elevated and continue to rise during labor, with a decrease occurring only after the placenta is expelled (Petraglia et al., 2023).

Fetal cortisol surge activates the P450c17 enzyme in the placenta, converting progesterone to androstenedione, and reducing progesterone secretion. This also increases estrogen production, preparing the uterus and cervix for labor (Strauss et al., 2023). In humans, the shift from a quiescent uterus to contractions during labor is not due to the systemic decrease in progesterone. Both progesterone (P4) and estrogen (E2) increase progressively as pregnancy continues, reaching their peak at labor. P4 maintains uterine quiescence by inhibiting contraction-associated proteins (CAPs) like Cx43, oxytocin receptors (OXTR), prostaglandin receptors (PGFR), PTGS2, and ion channels in the myometrium. Additionally, P4 has anti-inflammatory effects, preventing cytokine production and immune cell migration to the uterus, while inhibiting the pro-inflammatory prostaglandin PGF2a induction in the decidua (Petraglia et al., 2023; Vannuccini et al., 2016; Wilson & Mesiano, 2020; Zagrean, 2020).

Progesterone responsiveness is influenced by the expression and transcriptional activity of progesterone receptors (PR). In humans, the transcription of PR genes is controlled by the isoforms PR-A and PR-B, so the genomic response to progesterone is dependent on the balance between these two. When exposed to progesterone, PR-B shows significant transcriptional activity (Strauss et al., 2023). Functional progesterone cessation occurs through increased PR-B corepressor expression, reduced PR-DNA binding, and progesterone breakdown into inactive forms. Specific microRNAs may alter PR signaling by affecting transcription factor expression. This leads to the loss of PR-B's ability to maintain uterine quiescence during labor (Strauss et al., 2023; Vannuccini et al., 2016; Wilson & Mesiano, 2020). The local mechanism for progesterone cessation during labor involves increased 20α-hydroxysteroid dehydrogenase (20a-HSD) expression in the myometrium, reducing gene transcription that maintains uterine quiescence, and increasing myometrial sensitivity to uterotonic agents. Labor is an inflammatory process in the myometrium, cervix, and decidua, often linked to asymptomatic intrauterine infections and increased prostaglandin production in the fetal membranes due to decidual inflammation (Petraglia et al., 2023).

The Relationship Between Inflammation, Pregnancy, and Progesterone

Pregnancy modifies the maternal immune system to prevent fetal rejection and protect against pathogens. Early pregnancy is marked by pro-inflammatory responses, while mid-pregnancy shifts to anti-inflammatory conditions for fetal development. Full-term labor requires the reactivation of inflammation to initiate birth (Petraglia et al., 2023). Studies show that the physiological inflammation in the uterus during full-term pregnancy is caused by mechanical and endocrine factors, resulting in the release of pro-inflammatory cytokines and chemokines (IL-1β, IL-6, TNFα, CCL2, and CXCL8). These substances, released from various tissues, promote the infiltration of inflammatory cells into the cervix, myometrium, fetal membranes, and amniotic cavity. They activate pro-inflammatory transcription factors like NF-κB and AP-

1, triggering biochemical changes that lead to uterine contractions, labor, and placental expulsion (Petraglia et al., 2023; Vannuccini et al., 2016).

Progesterone helps maintain uterine quiescence by blocking the myometrial response to pro-inflammatory signals through PR-B, inhibiting NF-κB. PR-A counteracts this effect, and labor occurs when factors disrupt PR-A's ability to inhibit PR-B. When the inflammatory load exceeds a threshold, functional progesterone withdrawal, mediated by PR, triggers labor (Strauss et al., 2023). The level of inflammation can be affected by internal factors like uterine wall expansion and fetal growth, as well as external factors such as infections within the uterus and stress experienced by the mother (Petraglia et al., 2023). As pregnancy progresses, the inflammatory load increases, activating protein kinases that phosphorylate PR-A. This reduces the anti-inflammatory effect of progesterone/PR-B, creating a positive feedback loop of inflammation. The inflammation boosts prostaglandin production, which triggers labor by enhancing uterine contractions and softening the cervix (Strauss et al., 2023).

Estrogen

The Activation of Functional Estrogen

Maternal estrogen levels gradually rise during pregnancy due to increased Dehydroepiandrosterone sulfate (DHEA-S) from enhanced fetal Hypothalamic-Pituitary-Adrenal (HPA) axis activity. While the exact role of placental estrogen in labor is unclear, congenital estrogen-related disorders like anencephaly and Congenital Adrenal Hyperplasia (CAH) do not affect labor timing. In CAH, low fetal cortisol boosts Adrenocorticotropic Hormone (ACTH), raising DHEA-S, which converts to estrogen. During labor, estrogen activation is influenced by changes in estrogen receptor (ER) expression. Estrogen receptor alpha (ERα) increases in the myometrium, while estrogen receptor beta (ERβ) remains low. The rise in ERα correlates with higher connexin-43 expression, indicating that ERα mediates estrogen's functional activation, enhancing myometrial response to estrogen (Strauss et al., 2023).

Estrogen regulates uterine contractions by enhancing connexin 43 expression and reducing estrogen receptors in the cervix, promoting cervical maturation. Studies suggest that changes in the E2/E3 balance or an increase in E3 before delivery could trigger labor, with E3 primarily originating from fetal 16-hydroxy-Dehydroepiandrosterone sulfate (16-OH-DHEAS) (Petraglia et al., 2023). Estrogen, a crucial set of female sex hormones, includes estrone (E1), estradiol (E2), estriol (E3), and estetrol (E4). Estradiol is essential for the quick expansion and growth of the uterus during pregnancy, ensuring proper space for fetal growth and development (Petraglia et al., 2023; Zagrean, 2020).

Estradiol (E2) triggers labor by causing biochemical and physical changes. While both E2 and progesterone (P4) are present during pregnancy, P4 suppresses E2 until late pregnancy. Research shows that E2 and its receptor ERα are essential for labor, and as P4 decreases locally and ERΔ regulation is reduced, E2 signaling increases myometrial sensitivity. E2 promotes myometrial activation, including changes in muscle cells, contraction proteins, and ion channels. E2 also stimulates prostaglandin production and cervix maturation. At term, E2 triggers immune cell migration to the uterus and reduces P4's anti-inflammatory effects. Studies show a lower P4:E2 ratio in women delivering at term or prematurely, due to reduced P4 and increased E2. High E2 levels in hepatitis E virus (HEV) infections are linked to increased E2 secretion, low birth weight, and higher fetal mortality from placental dysfunction (Petraglia et al., 2023).

Coordination of Progesterone Withdrawal and Functional Estrogen Activation

Numerous studies have shown that there is a functional relationship between the estrogen receptor (ER) and progesterone receptor (PR) systems. Progesterone weakens the uterine

reaction to estrogen by lowering the levels of ERα expression, while estrogen enhances the uterine response to progesterone by boosting PR-B expression. The amount of ERα expression in the resting myometrium is positively linked to the ratio of PR-A/PR-B expression, meaning that ERα expression in myometrial cells increases as the progesterone response declines. Therefore, progesterone can decrease the uterine response to estrogen by suppressing the expression and/or signaling of ERα in the myometrium (Strauss et al., 2023).

Corticotropin-Releasing Hormone (CRH)

Under normal, non-pregnant circumstances, CRH is a peptide hormone released by the hypothalamus within the hypothalamic-pituitary-adrenal (HPA) axis. It prompts the anterior pituitary gland to secrete adrenocorticotropic hormone (ACTH), which subsequently stimulates the adrenal glands to produce cortisol, a glucocorticoid hormone associated with stress. In pregnancy, CRH from the placenta is created by trophoblasts and was initially identified through radioimmunoassay (RIA) during the early stages of the second trimester (Zagrean, 2020). Placental CRH exerts multifaceted effects, particularly in triggering labor. It operates similarly to a biological clock, counting down from the early stages of pregnancy to indicate the timing of childbirth. Due to this function, it is often referred to as the placental clock (Petraglia et al., 2023; Zagrean, 2020).

Corticotropin-releasing hormone has been studied as an indicator of preterm birth due to its functions in endocrine, autocrine, and paracrine signaling (Wadhwa et al., 1998). Corticotropin-releasing hormone binding protein binds to CRH in circulation, limiting its activity until saturation occurs late in pregnancy as CRH levels rise. CRH acts as a vasodilator in the placenta, regulates myometrial signaling for contraction or relaxation, and stimulates fetal adrenal production of DHEA-S, a precursor for estriol and estradiol synthesis (Smith, 2007). An early rise in CRH was observed in women with recurrent preterm birth compared to those without. This suggests that CRH could serve as a potential marker for identifying a subset of patients with early activation of the placental-fetal adrenal axis (Herrera, Bowman, McIntire, Nelson, & Smith, 2021). Recent studies further support the concept of a biological clock influencing variations in biochemical reaction speeds (Iwata & Vanderhaeghen, 2020; Matsuda et al., 2020; Rayon et al., 2020; Xie et al., 2019). Early placental synthesis and release of CRH may indicate premature activation of the placental-fetal adrenal axis. This acceleration suggests that CRH could help identify a specific subset of women at risk for preterm birth (Herrera et al., 2021).

Several cross-sectional studies have indicated a correlation between elevated CRH levels and preterm birth. This finding led to a prospective study in 1995, introducing the concept of CRH functioning as a placental clock (McLean et al., 1995). CRH levels in maternal plasma rise exponentially throughout pregnancy. After adjusting for gestational age, women who gave birth prematurely exhibited higher CRH levels, whereas those with post-term deliveries had lower concentrations (Herrera et al., 2022). A recent report indicated that women with a history of preterm birth exhibited an early rise in peptide plasma concentrations, suggesting that CRH measurement during the second trimester could help identify those at risk of preterm delivery (Herrera et al., 2021). Additionally, in term pregnancies placental CRH is believed to enhance myometrial contractility by stimulating prostaglandin production in the decidua and fetal membranes, thereby amplifying the contractile effects of prostaglandins and oxytocin on the myometrium (Vannuccini et al., 2016).

Although elevated CRH levels are linked to preterm birth, their predictive value in an unselected population remains low. However, a recent study found that CRH levels were higher in women with recurrent preterm birth compared to those who had a previous preterm birth followed by a term delivery (Herrera et al., 2021). This indicates that CRH identifies a group of women susceptible to preterm birth. In other words, while CRH plays a crucial role in normal

pregnancy physiology, disruptions in its regulation may contribute to a pathological process in some women, leading to preterm birth (Herrera et al., 2022).

Strong evidence suggests that early elevations in plasma CRH are associated with a higher risk of preterm birth. However, the precise threshold at which this risk becomes significant remains undefined. Due to racial and ethnic variations, large-scale data sets are needed for comparative analysis. Additionally, future data collection must follow standardized procedures to ensure consistency. Given the demonstrated reproducibility of results, this would involve an extraction technique followed by radioimmunoassay (Herrera et al., 2021). If the target population can be identified for diagnostic purposes, the next step would be exploring potential therapeutic interventions. A CRH receptor antagonist presents a promising option for preventing preterm birth (Herrera et al., 2022). In sheep, CRH antagonism has been shown to delay delivery significantly (Chan et al., 1998). The development of CRH antagonists for use in human pregnancy appears promising, provided that accurate diagnostic identification is achieved. Beyond CRH, patient-specific genomic profiling may offer additional benefits, as recent studies suggest that RNA profiling could help identify individuals at risk for preterm birth (Camunas-Soler et al., 2022).

CRH appears to have a direct role in controlling the labor process by influencing the contractility of the myometrium. CRH receptors are present in both the myometrium and fetal membranes. Laboratory studies have demonstrated that CRH triggers the release of prostaglandins from the decidua and amnion and enhances the effects of oxytocin and PGF2α on myometrial contractions. For most of the pregnancy, CRH activates adenylate cyclase in the dormant myometrium, leading to an increase in intracellular cAMP levels that promote relaxation. However, as the postpartum period nears, CRH's ability to elevate cAMP decreases, particularly in the postpartum myometrium. This indicates that CRH primarily supports myometrial relaxation during pregnancy, but its effect lessens as labor begins. It remains unknown whether alterations in CRH receptor signaling contribute to the onset of labor (Strauss et al., 2023).

Cortisol reduces CRH production in the hypothalamus through negative feedback within the HPA axis. However, during pregnancy, it enhances CRH production in the placenta via a feedforward mechanism (Zagrean, 2020). The feedforward mechanism is initiated when cortisol produced by the fetal adrenal glands stimulates CRH production in the placenta. This suggests that an external source of CRH, apart from the hypothalamus, plays a crucial role in influencing the fetal-placental unit's activity (Strauss et al., 2023).

Studies on human myometrial tissue show that low CRH levels reduce contractions in term and preterm myometrial strips. Progesterone enhances this effect 3.5-fold. This relaxation, linked to cAMP production, arises from CRH receptor activation via adenylate cyclase. Elevated maternal CRH levels in the early third-trimester correlate with preterm delivery. Monitoring CRH levels indicates higher levels and a steeper rise in preterm cases, while post-term deliveries show consistently lower CRH levels than term deliveries (Zagrean, 2020).

Research indicates that pregnant women experiencing psychosocial stress or distress tend to have elevated levels of ACTH, CRH, and cortisol compared to those who do not face such stressors (McLean & Smith, 2001; Parker & Douglas, 2010). Research suggests that maternal stress and distress can lead to increased CRH levels during pregnancy. Given the significant role of CRH in regulating the timing of childbirth, these stress-related hormonal changes are likely to contribute to a higher risk of preterm labor (Kramer et al., 2009).

Pregnancy introduces additional complexities, including new sources of CRH from gestational tissues and increased psychosocial stress for the mother. Furthermore, pregnancy-related complications may affect the production of gestational CRH and its release into the maternal bloodstream. Findings from two studies that repeatedly measured cortisol and CRH levels in

maternal blood indicated that both biomarkers were elevated in pregnancies that resulted in preterm birth compared to those that reached full-term (Erickson et al., 2001; Sandman et al., 2006). Women experiencing high levels of prenatal anxiety or stress, often accompanied by depressive symptoms, tend to have elevated CRH levels throughout pregnancy (Mancuso et al., 2004). However, prenatal anxiety may also arise from a mother's awareness of pregnancy complications, some of which are associated with increased CRH levels. This complexity makes it challenging to determine the causal relationship between these factors (Chen et al., 2010).

Oxytocin (OT)

A key function of oxytocin is its involvement in stimulating uterine contractions during the process of childbirth (Petraglia et al., 2023). During pregnancy, oxytocin is synthesized by the amnion, chorion, and decidua, promoting the production of prostaglandins. In laboratory studies, oxytocin in human amniotic cells triggers the production of prostaglandin E2 (PGE2), while in human decidual cells, it boosts prostaglandin F2a (PGF2a) levels. This effect occurs through the activation of cytoplasmic phospholipase A2, which releases arachidonic acid (AA) (Strauss et al., 2023; Wilson & Mesiano, 2020; Zagrean, 2020).

Oxytocin, like prostaglandins, regulates uterine contractions during labor. It creates a uterotonic environment, and blocking its action with synthetic antagonists can disrupt labor, reduce contractions in preterm labor, and prolong pregnancy (Strauss et al., 2023). The effect of oxytocin seems to be controlled at the target tissue level through variations in the expression of oxytocin receptors (OXTR) in the myometrium (Strauss et al., 2023; Vannuccini et al., 2016). In humans, the levels and expression of oxytocin receptors (OXTR) in the myometrium and decidua rise progressively, increasing up to 100 times near the end of pregnancy and peaking as labor begins (Petraglia et al., 2023; Strauss et al., 2023; Zagrean, 2020).

Oxytocin is typically not regarded as a key factor in labor initiation since its circulating levels only increase during the expulsive phase. This is supported by studies indicating that oxytocin alone is not always necessary for labor onset or delivery. Furthermore, the effect of oxytocin on the uterus relies on the distribution of its receptors in the myometrium, which changes throughout pregnancy. Notably, only receptors predominantly located in the uterine corpus and fundus are essential for fetal expulsion (Strauss et al., 2023).

Prostaglandin (PG)

Prostaglandins generated by intrauterine tissues play a crucial role in controlling myometrial contractions and facilitating cervical softening (Strauss et al., 2023; Vannuccini et al., 2016). Earlier research has found that: (1) administering PGE2 or PGF2α at any point in human pregnancy triggers uterine contractions, cervical ripening, and labor; (2) blocking PG biosynthesis with aspirin, indomethacin, or specific PTGS2 inhibitors delays labor and prolongs pregnancy; and (3) the production of PGE2 and PGF2α by intrauterine tissues, such as the amnion, chorion, decidua, and myometrium, rises late in pregnancy and is linked to labor initiation (Strauss et al., 2023). PGE2 and PGF2α promote uterine contractions by raising intracellular calcium levels, which enhance contractility via myosin light chain phosphorylation. PGI2, the most prevalent prostaglandin in uterine tissues, especially the myometrium, is believed to relax myometrial muscles by increasing intracellular cAMP concentrations (Petraglia et al., 2023a; Strauss et al., 2023).

The amnion is the primary site of intrauterine PG synthesis, with the chorion contributing to a lesser extent. Both tissues show increased PTGS2 expression at the onset of term and preterm labor. Additionally, PG is produced in the decidua and myometrium, where its levels also rise during labor. In fetal membranes, PTGS2 expression begins to increase in the third trimester and a few weeks before labor starts. These observations suggest that intrauterine PG production

escalates as a driving force of labor rather than as an effect of it (Petraglia et al., 2023; Strauss et al., 2023; Zagrean, 2020).

The diverse actions of PGs across tissue types are attributed to the existence of various receptor species, each associated with distinct intracellular signaling pathways. The specific regulation and distribution of PG receptors in the myometrium and cervix are crucial for the endocrine regulation of pregnancy and labor. Throughout pregnancy, the myometrium expresses receptors for PGE2, PGF2α, PGI2, and thromboxane. PGE2 specifically binds to four receptor subtypes: EP1, EP2, EP3, and EP4. The effects of PG on labor may be influenced by the equilibrium between receptors promoting relaxation and contraction, as well as their specific distribution in the uterus, whether in the fundus or cervix (Petraglia et al., 2023; Strauss et al., 2023; Vannuccini et al., 2016; Zagrean, 2020).

Cytokines

Cytokines are involved in the pathophysiology of preterm labor linked to intraamniotic infection, but they can also contribute to normal labor. Macrophages initially promote uterine calm through anti-inflammatory actions until full term, after which they shift to a pro-inflammatory state to facilitate labor (Gomez-Lopez et al., 2022). Pro-inflammatory mediators such as IL-1, IL-6, and TNF-alpha increase in the maternal bloodstream before spontaneous labor begins. IL-1 beta blocks the expression of progesterone receptors in decidual cells via ERK1/2 activation. Additionally, the fetus may release physical and hormonal signals that trigger macrophage migration to the uterus, leading to cytokine release and the activation of inflammatory transcription factors (Guzeloglu-Kayisli et al., 2015; Unal et al., 2011).

Pregnancy involves three immunological phases regulated by cytokines. The first trimester requires inflammation for trophoblast implantation, while the second phase shifts to an anti-inflammatory state, crucial for maternal-fetal stability and fetal development (Dutta et al., 2024). Proinflammatory cytokines play a vital role in immune defense, protecting against infections and tissue damage. Safeguarding the fetus from infection is essential. Throughout pregnancy, uterine and placental tissue remodeling is necessary to support fetal development (Dutta & Sengupta, 2017; Piccinni et al., 2021). The second gestational immune phase is a stabilizing period, supporting rapid fetal growth and maternal-fetal adaptation. Immune processes promote an anti-inflammatory state, while the placenta facilitates hormone, immune cell, and cytokine exchange. Placental hormones and cytokines help maintain this balance, with exosome regulation influenced by oxygen and glucose levels. Maternal exosomes also stimulate cytokine secretion from endothelial cells (Adam et al., 2017).

Determining whether infection causes or results from preterm delivery is challenging. However, strong evidence links infection and inflammation in gestational tissues to preterm birth. Patients with preterm labor show higher microbial colonization and inflammatory cytokine levels in amniotic fluid than those not in labor. Additionally, intra-amniotic infection or intrauterine inflammation, marked by elevated cytokines and matrix-degrading enzymes as early as mid-trimester, increases the risk of preterm delivery (Agrawal & Hirsch, 2012). Evidence indicates that molecular pathways leading to preterm delivery may be triggered long before preterm labor becomes clinically evident, which may explain why antibiotics are ineffective in treating preterm labor, even in cases of clear infection. Research has explored the presence of infection and inflammation as early as before conception, but antibiotic trials during the preconception period and first trimester have not successfully reduced the risk of preterm birth (van den Broek et al., 2009; Espinoza et al., 2006).

Advancements in molecular biology and genetics have identified potential targets for preterm birth prevention. Inhibiting specific inflammatory pathways, such as the NF-κB pathway, has shown promise in preclinical studies as a strategy to reduce inflammation-related preterm birth (Stanfield et al., 2019). While research on placental microbiota continues, most infections

leading to preterm birth originate from ascending vaginal bacteria. Prevention efforts should focus on identifying risk factors and developing effective treatments. Exploring microbiome-based therapies, such as probiotics or other agents that promote healthy vaginal microbiota, may help prevent pathogenic overgrowth. Additionally, rapid and accurate diagnostic tests for vaginal infections could enable early detection and treatment, reducing the risk of preterm birth (Daskalakis et al., 2023).

There is increasing interest in therapeutic approaches aimed at modulating the inflammatory labor cascade. These strategies focus on inhibiting the production of pro-inflammatory mediators, enhancing anti-inflammatory responses, or administering exogenous anti-inflammatory and pro-resolution mediators to regulate the process (Rinaldi, Hutchinson, Rossi, & Norman, 2011). The use of non-steroidal anti-inflammatory drugs (NSAIDs) to inhibit prostaglandin synthesis has provided early evidence suggesting that anti-inflammatory medications may be effective in delaying preterm birth (Haas et al., 2009; King et al., 2005).

The activation of Toll-like receptor 4 (TLR4) by lipopolysaccharides (LPS) is the most widely used model for studying intrauterine inflammation (IUI), leading to investigations into TLR4 antagonism as a potential therapeutic approach. Research on TLR4–LPS inhibition using a monoclonal anti-TLR4 antibody has demonstrated effectiveness in vivo, showing a reduction in pro-inflammatory mediators such as TNF-α, IL-8, and PGE2 in amniotic fluid (Waldorf, Persing, Novy, Sadowsky, & Gravett, 2008), as well as a decreased incidence of LPS-induced preterm birth .(Li et al., 2010). Cytokine-suppressive anti-inflammatory drugs (CSAIDs) target the NF-κB and p38 MAPK pathways to inhibit cytokine-driven inflammation. They are being studied as a more selective alternative to NSAIDs for preventing inflammation-related preterm birth. Unlike NSAIDs, CSAIDs block inflammatory signaling without disrupting prostanoid homeostasis and may protect the fetus from harmful inflammatory exposure (Ng et al., 2015).

SKF-86002, the first p38 mitogen-activated protein kinase (p38 MAPK) inhibitor studied in human extraplacental membranes, was developed by the Swedish pharmaceutical company Svenska Kullagerfabriken (SKF). It is a potent p38 MAPK inhibitor with weaker effects on cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) (Sullivan, 2002). This discovery led to further research into similar inhibitors that selectively bind to the adenosine triphosphate (ATP) site of p38 MAPK to suppress placental pro-inflammatory cytokine production (Ng et al., 2015). Treatment of LPS-stimulated human fetal membranes with SB202190 reduced the release of IL-6, TNF-α, and prostaglandins (Stinson et al., 2014). To prevent preterm birth, treatments should eliminate pathogens, block cytokine-driven prostaglandin PG and matrix metalloproteinase (MMP) release, delay preterm labor PTL, and reduce fetal inflammatory response syndrome (FIRS) risk. Ultrasound-guided intra-amniotic injection of anti-inflammatory agents offers a targeted approach, enhancing efficacy while minimizing side effects. Slow clearance of certain compounds may further prolong effects, allowing single-dose therapy (Ng et al., 2015).

Trimester-specific serum cytokine profiles serve as a sensitive measure of maternal immune status, illustrating how factors such as maternal BMI, smoking, parity, fetal sex, and birth weight influence immunological development throughout pregnancy. Maternal obesity and smoking were associated with a persistent rise in cytokine levels, likely indicating heightened immune stress. A gradual decline in eotaxin levels across gestation was identified as a consistent marker of normal pregnancy. These findings highlight the dynamic nature of immune regulation during pregnancy and establish a valuable reference for tracking cytokine changes over time. Moreover, the cumulative strain of advancing pregnancy, combined with the physiological preparation for labor, must be acknowledged as a contributing factor to immune stress in late gestation. Serum cytokine profiling provides a reliable and accessible tool for studying pregnancy immunophysiology, offering deeper insights into the intricate immune adaptations that support fetal development and maternal health (Jarmund et al., 2021).

Although the abovementioned mechanisms of cytokine processes in pregnancy and labor provide valuable insights, these explanations are largely experimental and predominantly derived from animal models. Such findings may not fully represent human physiology, limiting their direct applicability. Furthermore, the absence of longitudinal human studies makes it challenging to track the dynamic immunological changes throughout pregnancy and labor. To enhance scientific rigor, future research should focus on long-term human studies and clinical trials, providing more precise and clinically relevant data on cytokine regulation during labor.

The Physiology of Childbirth

The Phases

Childbirth or labor involves a series of processes, including the transition of the myometrium from being inactive to highly contractile, changes in the cervix, and the rupture and thinning of the fetal membranes. These events occur in a coordinated manner and can be separated into different phases, depending on the myometrial contraction activity (Strauss et al., 2023). Labor involves several phases with distinct physiological changes. In phase 0 (quiescence), the myometrium remains relaxed and unresponsive to uterotonic agents, while the cervix is firm. This state is controlled by agents like β-adrenergic agents, PGI2, relaxin, CRH, nitric oxide, and progesterone. During phase 1 (onset of labor), the myometrium begins to contract rhythmically, and the cervix softens in preparation for dilation, with increased expression of contraction-associated proteins, gap junction formation, and changes in ion channels and uterotonic receptors. Intrauterine production of PGE2 and PGF2α also rises. In phase 2 (active labor), the myometrium becomes more responsive to prostaglandins and oxytocin, resulting in coordinated contractions that push the fetus toward the birth canal, while the cervix dilates. Finally, in phase 3 (hemostasis and involution), the myometrium contracts after the expulsion of the placenta and fetal membranes to ensure hemostasis, and the uterus gradually returns to its non-pregnant state, with the cervix closing and firming again (Strauss et al., 2023).

The Role of Uterine Stretching

Uterine stretching is thought to trigger labor, preventing the fetus from growing too large for the pelvic opening. Twin pregnancies tend to be shorter, possibly due to increased uterine stretching. In mice, stretching a non-pregnant uterine horn alters contraction-associated protein (CAP) expression, similar to pregnancy. Progesterone inhibits this CAP gene expression. Uterine myocytes in culture show increased IL-8 expression, which attracts macrophages and neutrophils. As the uterus swells, surpassing a stretch threshold induces CAP and pro-inflammatory gene expression, initiating labor (Strauss et al., 2023).

The Role of Fetal Lung Maturation

Animal studies suggest the fetal lungs play a role in birth. Surfactant protein-A (SP-A), produced by the fetal lung epithelium, enters the amniotic fluid and activates fetal macrophages, which migrate to the myometrium and increase cytokine production, triggering inflammation and progesterone withdrawal. This aligns fetal lung maturation with labor timing. However, no similar system has been found in humans, though some studies suggest SP-A directly affects myometrial cells to boost prostaglandin production and uterine contractility. Fetal membranes express SP-A in response to glucocorticoids, which induces prostaglandin synthesis, potentially synchronizing labor with fetal lung development (Strauss et al., 2023).

Conclusion

Childbirth is a multifaceted physiological event that involves the fetus, placenta, and mother. The endocrine system plays a vital role in regulating the uterine quiescent phase and triggering the onset of labor, which is characterized by heightened uterine contractions and the maturation of the cervix. Several factors influence the timing of labor, including prostaglandins or inflammatory cytokines, which have a direct impact on the contractile mechanisms, and

oxytocin, CRH, or relaxin, which indirectly modify the complementary system mechanisms. The endocrine system's involvement in labor significantly affects perinatal outcomes. Premature birth and prolonged pregnancy, on the other hand, are linked to a higher risk of fetal morbidity and mortality.

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