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A Review Article of Corticotrophin-Releasing Hormone and Preterm Birth: A Placental Clock

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ABSTRACT

Preterm Birth is one of the main causes of infant mortality and morbidity worldwide. An estimated 15 million preterm births are birthed each year. Preterm Birth is not a single disease but a complex syndrome. The placenta's production of Corticotrophin-Releasing Hormone (CRH) is one theory for Preterm Birth. The peptide hormone CRH, which levels rise exponentially during pregnancy, has been linked to preterm Birth due to its endocrine, autocrine, and paracrine functions. It has been suggested that CRH functions as a component of the placental clock, with preterm Birth occurring when the placental clock is activated too early. In this review article, we will discuss Preterm Birth and the role of CRH in Preterm Birth.

Keywords: Preterm Birth, Corticotrophin-Releasing Hormone (CRH), Placental clock

INTRODUCTION

Preterm Birth (PTB) is a clinical diagnosis characterized by present uterine contractions, increasing effacement, and cervix dilation before 37 weeks of gestation. An estimated 15 million preterm births are birthed each year. Preterm Birth is the main cause of infant mortality and morbidity in developed countries. Early neonatal morbidity caused by preterm births includes respiratory distress syndrome, necrotizing enterocolitis, infections, apnea, hypoglycemia, seizures, and jaundice. Cohort research in French found that neurological prognosis and survival rate improve as gestational age increases. In contrast to those born at 32 weeks, who have a 98% chance of survival and only a 4% risk of cerebral palsy at age two and an 8% risk of neurodevelopmental delay, children born at 25 weeks have a 40% risk of death and approximately 45% of the survivors are expected to have a moderate-to-severe handicap.[(1),(2),(3)]

Long-term research has demonstrated the adverse effects of preterm Birth on life after delivery, particularly cardiovascular and neurological health. A more comprehensive understanding of the pathophysiological pathways by which preterm birth increases is important to improve the prediction and prevention of preterm delivery. Concerning the contribution of corticotrophin-releasing hormone (CRH) as a potential pathogenic cause of preterm Birth. [(4)] In this review article, we will discuss Preterm Birth and the role of Corticotrophin-Releasing Hormone synthesized by the placenta in the incidence of preterm Birth.

DISCUSSION

PRETERM BIRTH

Three scenarios might result in clinical Preterm Birth: spontaneous preterm labor, spontaneous preterm prelabor rupture of membrane and delivery due to a maternal or fetal indication. According to the American College of Obstetricians and Gynecologists, preterm births between 34 and 36 completed weeks are considered late preterm, and those occurring before 34 weeks are considered early preterm. Extremely

preterm Birth is defined by the World Health Organization as occurring before 28 completed weeks, very preterm Birth occurs between 28 and 32 completed weeks, and late preterm Birth occurs between 32 and 37 completed weeks. Because morbidity depends on gestational age, these definitions attempt to indicate the level of prematurity. [(4),(5)]

Temperature instability, respiratory distress, apnea, hypoglycemia, seizures, jaundice, kernicterus, feeding issues, and periventricular leukomalacia are among the short-term morbidities of late preterm births. Late preterm Birth has been linked to longer-term changes in behavior, cognition, and motor abilities. Extremely preterm births have higher morbidity rates, including major behavioral sequelae, interventricular hemorrhage with associated mild to severe neurodevelopmental impairment, and significant respiratory distress. Preterm babies account for 66% of newborn mortality in the US. Preterm Birth appears to be a syndrome rather than a specific pathway or illness. That is to say, multiple pathologic causes of Preterm Birth may or may not have common pathways with parturition at term. Increased myometrial contractility, cervical remodelling, and membrane rupture are required for parturition at term. Progesterone's effects, which inhibit the release of proinflammatory cytokines including interleukin-1 [IL-1], IL-6, and IL-8 and protest the nuclear factor-B (NF-B) pathway, favor myometrial quiescence for the majority of gestation. [(4),(5),(6),(7)]

Multiple mechanisms reduce the progesterone effect in pregnancy. The progesterone receptor subtype B mediates progesterone activity in pregnancy. Subtype B in the myometrium suppresses the expression of contraction-related proteins and activates the transcription factor zinc finger E-box-binding homeobox 1 (ZEB1), suppressing the expression of both progesterone-metabolizing enzymes and contraction-related proteins (e.g., 20 alpha-hydroxysteroid dehydrogenases). Progesterone receptor A is phosphorylated in response to an inflammatory signal at term, which counteracts the effect of the B subtype and induces a functional progesterone withdrawal. Progesterone action is decreasing at term, although active estrogen receptor one production is growing while plasma estriol concentrations are rising. The myometrial changes caused by estrogens, in turn, stimulate cervical ripening and contractions. Recent transcriptome analysis indicates that the myometrial changes in progesterone receptors, progesterone metabolism, and estrogen action are downstream from increases in the transcription factor NF-B, which may be stimulated by a rise of CRH concentrations as CRH has been demonstrated to stimulate NF-B activity in the brain. [(4),(8)]

In preterm labor, when the mechanisms of premature uterine activation, cervical remodeling, and membrane rupture may differ, this new understanding of term labor gives a crucial framework. Changes in the extracellular matrix's structure and mechanical properties cause cervical remodeling for dilation. Cervical softening, a progesterone-dominant pregnancy phase, involves replacing fibrillar collagen with strong cross-links with collagen with weak cross-links. The postpartum repair of the cervix is influenced by the inflow of tissue monocytes into the cervix and the activation of proinflammatory and tissue repair macrophages, which occurs due to the loss of progesterone function in late pregnancy during the cervical ripening period. Cervical dilation necessary for parturition is influenced by changes in progesterone receptor isoforms and an increase in progesterone metabolism in late pregnancy, similar to the myometrium. Membrane rupture is caused by the dynamic interactions between the decidua and inflammatory cytokines (such as tumor necrosis factor- and IL-1) or thrombin activation (decidual bleeding/abruption) in combination with altered activity of matrix metalloproteases and tissue inhibitors of

matrix metalloproteases, increased granulocyte-macrophage colony-stimulating factor activity, dissolution of cellular cement like fibronectin, and apoptosis. NF-B has been highlighted as a target for new tocolytics, and these modifications may be downstream from the activation of NF-B. Pathologic interference with these three processes can occur at the maternal, uterine, placental, decidual, and/or cervical levels and through various pathways, including stress, infection, vascular diseases, and/or altered immunological tolerance. Most likely, there is also a role for genetic and environmental factors. [(4),(9)]

Unplanned premature delivery has been causally associated with several mechanisms, including intra-amniotic infection. Bacteria can enter the amniotic cavity through ascending infections, transplacental passages, retrograde fallopian tube seeding, or invasive treatments. (e.g., amniocentesis). The most common way of entry is through an ascending infection, where pathogens that colonize the cervix, decidua, and membranes may eventually enter the amniotic sac. Most studies define intra-amniotic infection as individuals with a positive amniotic fluid culture for a pathologic microorganism rather than "clinical chorioamnionitis," or the clinical condition caused by bacterial invasion of the amniotic cavity. According to these criteria, an infectious agent is colonized in 25% to 40% of all preterm Birth, though culture techniques may have a bearing on this percentage. It is believed that the innate immune system contributes to the infection mechanism that results in preterm delivery by activating pattern recognition receptors, which then set off an inflammatory cascade, promoting the creation of prostaglandins and matrix-degrading enzymes. [(4),(10)]

Markers for Preterm Birth Risk

Preterm Birth is currently predicted mostly using a summative clinical picture based on a patient's risk factors. However, many testing and monitoring techniques, including uterine monitoring, fetal fibronectin measurement, phosphorylated insulin-like growth factor-binding protein 1 measurement, and placental alpha microglobulin measurement, have been suggested as markers for the risk of preterm Birth. However, no test can reliably identify a woman's preterm birth risk. There are several known risk factors. The most crucial factor is still previous preterm births. However, only 10% of preterm births are predicted by preceding preterm deliveries. Pregnancy factors such as threatened abortion, fetal abnormalities, multifetal gestation, polyhydramnios, low cervical length, and short or long interpregnancy interval are known to increase the chance of preterm Birth. Lifestyle (tobacco and illegal drug use, prepregnancy body mass index), genetic, infectious (mycoplasma, bacterial vaginosis), and periodontal disease are additional risk factors for preterm Birth. No one test can predict every preterm Birth, but a test like the CRH test may be created to focus on a particular etiology.[(4),(11),(12)]

Preterm Birth Prevention

Vaginal progesterone, intramuscular progesterone, and cervical cerclage are the three treatments the Society for Maternal-Fetal Medicine and American College of Obstetricians, and Gynecologists recommend for the prevention of preterm Birth. Women with a singleton gestation and a short cervix (less than 25 mm) are advised to use vaginal progesterone; those with a singleton gestation and a history of premature Birth may consider either intramuscular progesterone or vaginal progesterone. [(13),(14)]

For the subset of women diagnosed with cervical dysfunction consistent with cervical insufficiency, a short cervix (25 mm), and a prior history of Preterm Birth, cervical cerclage is a treatment. Due to the possibility of cerclage treatment, serial cervical length assessment is advised for women with a singleton gestation and a history of premature Birth. Additionally, reducing established risk factors for preterm delivery (such as smoking, using illegal

drugs, and being underweight before getting pregnant) can help lower the likelihood of premature Birth. The next phase is to go beyond progesterone. Alternative pathologic routes need to be found, justifications for identifying populations at risk of Preterm Birth based on pathology need to be developed, and new preventative methods must be created. CRH is one of these pathways. [13),(14),(15),(16)]

CORTICOTROPHIN-RELEASING HORMONE (CRH)

The anterior pituitary adrenocorticotropin (ACTH) secretion is controlled by the 41 amino acid peptide hormone CRH, which is generated in the hypothalamus. CRH is identified in human circulation outside of pregnancy. The maternal circulation, the amniotic fluid, and the fetal circulation exponentially grow during pregnancy due to the placental production of CRH. A unique circulating binding protein for CRH is known as CRH-BP. The saturated binding protein dimerizes and is eliminated when CRH levels are high in late gestation, increasing free, physiologically active CRH that may help to initiate parturition. [(4),(15)] Pregnancy in humans causes an exponential rise in placental CRH production. Additionally expressed in the hypothalamus, the single-copy CRH gene is a crucial regulator of the stress response and is subject to the negative feedback control of glucocorticoids. Contrarily, the placental expression of CRH is subject to positive feedback from glucocorticoids and cyclic adenosine monophosphate (cAMP), resulting in an exponential rise in expression throughout gestation. [(16),(17)]

The human CRH gene promoter presents a consensus CRE, a caudal-type homeobox response element (CDXRE), and two cAMP response elements (CRE). Additionally, the CRH promoter contains a negative glucocorticoid response element (nGRE), which glucocorticoids use to inhibit the production of CRH in the hypothalamus. The CRH promoter also possesses an NF-B2 enhancer site, and chromatin immunoprecipitation research revealed that this enhancer is linked to RelB and P52 in trophoblast. These two molecules are involved in the non-canonical pathway that can be increased in the placenta and myometrium during Preterm Birth. Glucocorticoids and progesterone both boost and diminish this enhancer's interaction with RelB and P52. In primary trophoblast culture, glucocorticoids have also been found to increase CRH expression by acetylating H3K9 histone, whereas cAMP increases CRH messenger RNA (mRNA) expression by increasing histone-3, lysine-4 trimethylation (H3K4me3), and histone-4 acetylation (acH4). After the fifth week of gestation, the CRH mRNA increases in the placenta in normal pregnancy. [(4), (16),(17)]

Effects of CRH Downstream in Pregnancy

As a result of the pituitary receptor becoming desensitized to CRH in late pregnancy, the stimulatory effects of CRH on the generation of ACTH, -endorphin, and cortisol in the maternal pituitary are reduced. CRH makes uterotonic substances like oxytocin and prostaglandin E2 more effective in the myometrium. (PGE2). There appears to be a change in isoforms as parturition approaches, which lowers the pathways activated by cAMP signaling that promote relaxation and increase contractility. CRH promotes the production of prostaglandins (PGE2 and PGF2) in the membranes and amniotic compartment, which aids in uterine contractions and cervical ripening. Furthermore, prostaglandins promote additional CRH release, resulting in a positive feedback loop in the placenta. CRH causes peripheral blood monocular cells to produce more IL-6 in maternal circulation. In parturition and infection, these cells are noticeably more prevalent and move to the placenta and cervix. Another positive feedback loop is the formation of placental CRH, which is increased by IL-6 and IL-1 together. By the middle of the third trimester, CRH promotes

ACTH in the fetal pituitary, increasing the production of cortisol and dehydroepiandrosterone sulfate (DHEA-S) in the fetal circulation. [(4),(18)]

Additionally, CRH increases the fetal adrenals' ability to produce cortisol. Increased markers of fetal lung maturity at Birth in women with greater CRH levels show that cortisol, in turn, directly impacts fetal lung maturity. Contrary to the hypothalamus, fetal cortisol feeds to the placenta positively, encouraging higher placental CRH synthesis. In the fetal zone of the fetal adrenal, the hormone CRH directly promotes the formation of DHEA-S. Following 16 hydroxylations in the fetal liver, fetal DHEA-S serves as the main substrate for the formation of estriol in the placenta. Then estriol is released into the mother's bloodstream, which might stimulate labor by acting on the fetal membranes, cervix, and myometrium. The positive feedback loop between DHEA-S and CRH production is similar to that of cortisol. By way of a different CRE in the CRH promoter, it has been demonstrated that estrogen and progesterone regulate the production of placental CRH. Up to parturition, CRH is gradually amplified by the numerous positive feedback loops in the body. [(18),(19)]

PRETERM BIRTH AND CORTICOTROPHIN-RELEASING HORMONE (CRH)

High CRH concentrations have been linked to preterm Birth in many cross-sectional studies, and it has been reported. McLean et al. carried out prospective research in 1995 and proposed the concept of CRH as a placental clock. CRH levels in the maternal plasma were observed to rise dramatically throughout the pregnancy. Compared to women who gave Birth at term, preterm births had greater CRH levels than post-term births, even after controlling for gestational age. These abnormalities became visible as early as 16 to 18 weeks of gestation. In the three populations, there were no variations in the concentrations of CRH-BP in the females. Based on these findings, CRH was hypothesized as a placental clock; earlier elevated CRH levels that were adequate to saturate CRH-BP in the maternal bloodstream may have resulted in enhanced bioavailable CRH capable of starting parturition. Preterm Birth can be predicted by looking at processes that are thought to start before the mid-trimester and proceed at a rate that can be estimated from observing CRH levels. According to a recent study, CRH was higher in women who had repeated preterm births than in women who had a prior preterm birth and a subsequent term pregnancy. [(20),(21)]

This shows that CRH identifies a population more likely to give birth prematurely. In other words, CRH has a definite role in healthy pregnancy physiology, which can be changed to create a pathophysiologic process in a subset of women that leads to premature Birth. Preterm pre-labour rupture of membranes with chorioamnionitis has been associated with higher placental CRH, which suggests that stress-related pathways involved in infectious processes are responsible for placental CRH activation. However, preterm Birth does not always happen. In twin gestations, CRH is increased to more than three times that of a singleton gestation. Additionally, the presence of fetal growth restriction, pregnancy-induced hypertension, and gestational diabetes is associated with elevated levels of CRH, and many indicated preterm births. Since stimulation of these stress-related pathways can affect early brain development, CRH elevation may be a compensatory strategy brought on by these pathways irrespective of infection status. [(4), (20),(21)]

CONCLUSION

Preterm Birth is still a major concern for public health everywhere. Prematurity must be prevented, its consequences on preterm neonates must be minimized, and both require evidence-based strategies. This clinical state's multiple etiology and contributing elements must be

acknowledged for a complete understanding of preterm delivery. CRH produced by the placenta is one possible pathogenic mechanism leading to preterm delivery. The measurement of CRH for clinical prediction is still difficult since a precise cut-off point for use has not been determined, despite substantial evidence for its physiological plausibility and relationship with preterm Birth.

Declaration by Authors

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