PATHOGENESIS OF PRETERM LABOR

Fakhrolmolouk Yassaee

1. Premature activation of the maternal or fetal hypothalamic pituitary-adrenal axis
2. Inflammation and infection
3. Decidual hemorrhage
4. Pathological uterine distention

ACTIVATION OF THE HPA

- stress is a common element activating a series of physiologic adaptive responses in the maternal and fetal compartments. From this perspective, premature activation of the hypothalamic-pituitary-adrenal (HPA) axis can initiate PTB .

- Uteroplacental ischemia is a fetal stressor that can lead to premature fetal HPA activation and has a higher correlation with subsequent PTB than maternal psychosocial stress .

- Premature activation of the maternal or fetal hypothalamic-pituitary-adrenal axis related to stress.
- Exaggerated inflammatory response/infection and/or an altered genital tract microbiome.
- Abruption (decidual hemorrhage)
- Pathologic uterine distention

- In one study, spontaneous PTB ≤35 to 36 weeks of gestation was associated with a four- to sevenfold increased risk of histologic evidence of placental vascular damage, bleeding, fetal vascular disruption, or lack of normal physiologic conversion of maternal spiral arteries .

- In a third study, women whose first pregnancy ended in spontaneous PTB were at increased risk of PTB, preeclampsia, and fetal growth restriction (another disorder characterized by uteroplacental vascular insufficiency) in their second pregnancy compared with women with uncomplicated first pregnancies .

- The earlier the spontaneous PTB occurred, the higher the risk of one of these complications in the second pregnancy.

- The mechanisms by which fetal HPA activation are thought to cause labor, including spontaneous PTB, include:

- Increased placental production and release of corticotropin-releasing hormone (CRH), which appears to program a "placental clock.

- Glucocorticoid induction of the immunophilin cochaperone FK506-binding protein-51 (FKBP51), which binds to the ligand binding site on the progesterone receptor (PR) and glucocorticoid receptor (GR) to inhibit PR- and GR-mediated transcription in decidual cells.

- Increased release of fetal pituitary adrenocorticotropic hormone (ACTH) secretion, which stimulates production of placental estrogenic compounds and prostaglandins that may activate the myometrium and initiate labor .

- Major maternal psychosocial stress can activate the maternal HPA axis and has been associated with a slightly higher rate of PTB . As an example, a prospective cohort study of women with depressive symptoms early in pregnancy found that these women had almost twice the PTB risk of women without such symptoms.

- Placental corticotropin-releasing hormone — CRH appears to play a role in both PTB and term birth. CRH is released by the hypothalamus but, during pregnancy, is also expressed by placental and chorionic trophoblast, amniochorion, and decidual cells.

- CRH also enhances prostaglandin production by amnion, chorion, and decidua . In turn, prostaglandins stimulate CRH release from the placenta , creating a second positive feedback loop for CRH secretion.

- In a normal pregnancy, it is hypothesized that maturation of the fetal HPA axis and development of the fetal zone of the fetal adrenal gland beginning in midgestation cause a physiologic increase in fetal cortisol secretion and enhancing CRH release from the placenta.

- FKBP51 expression in decidual cells — Glucocorticoids enhance FKBP51 expression, which, in turn, inhibits PR- and GR-mediated transcription. Immunohistochemical staining for FKBP51 is elevated in the nuclei of decidual cells from patients with labor compared with prelabor specimens . In culture, overexpression of FKBP51 mRNA decreases PR-DNA binding.

- These findings suggest that maternal and/or fetal stress may enhance FKBP51 expression in decidual cells, leading to functional progesterone withdrawal from reduced reproductive tract PR-mediated transcription.

Interestingly, the presence of the rs1260780 allele, which is associated with significantly enhanced glucocorticoid induction of FKBP51, has been linked to higher risk for major depressive disorders, posttraumatic stress disorders, and suicidality .

INFECTION, INFLAMMATION, AND ALTERED GENITAL TRACT MICROBIOME

- Inflammation is a highly coordinated process set in place to protect the host . When properly controlled, inflammation is beneficial, but when dysregulated, it becomes harmful

- Laboratory and clinical data show a link between spontaneous PTB and the presence of systemic and genitourinary tract pathogens , as well as an altered microbiome .

- In a large retrospective population-based study of 199,093 deliveries, 2.5 percent of patients had asymptomatic bacteriuria, which was independently associated with PTB . Conversely, the diagnosis and treatment of asymptomatic bacteriuria appears to reduce the risk of PTB .

- Both clinical and subclinical chorioamnionitis are much more common in preterm than term deliveries and may account for 50 percent of PTB before 30 weeks of gestation.

- In another study of 759 women who underwent first trimester assessment of their vaginal flora, those with normal vaginal flora had a 75 percent lower risk of delivery before 35 weeks than women with abnormal vaginal flora.

- Absence of lactobacilli and the presence of bacterial vaginosis (BV) were both associated with a twofold increased risk of PTB, while gram positive coccus-associated aerobic vaginitis was associated with a threefold increase in risk of PTB.

- *Lactobacillus* is the predominant flora of the microbial community in normal pregnancy, and the prevalence of a *Lactobacillus*-poor vaginal community state type (CST 4) is inversely correlated with gestational age at delivery .

- In addition, the risk for PTB is more pronounced for women with CST 4 and elevated *Gardnerella* or *Ureaplasma*. However, treatment of BV does not appear to consistently reduce PTB rates in low-risk patients .

- Similarly, periodontal disease and subsequent systemic inflammation may play a role in triggering PTB .

- Bacteria — In addition to inducing an inflammatory response, bacteria may also have a direct role in the pathogenesis of PTB. Some organisms (eg, Pseudomonas, Staphylococcus, Streptococcus, Bacteroides, and Enterobacter) produce proteases, collagenases, and elastases that can degrade the fetal membranes .

DECIDUAL HEMORRHAGE

- Vaginal bleeding from decidual hemorrhage is associated with a high risk of preterm labor and preterm prelabor rupture of membranes (PPROM) . Decidual hemorrhage (placental abruption) originates in damaged decidual blood vessels and presents clinically as vaginal bleeding or retroplacental hematoma formation .

PATHOLOGIC UTERINE DISTENTION

- Multiple gestation, polyhydramnios, and other causes of excessive uterine distention are well described risk factors for PTB. Enhanced stretching of the myometrium induces formation of gap junctions, upregulation of oxytocin receptors, and production of inflammatory cytokines and prostaglandins, and myosin light chain kinase, which are critical events preceding uterine contractions and cervical dilation .

PATHOLOGIC CERVICAL CHANGE

- Cervical insufficiency refers to pathologic dilatation and/or effacement of the uterine cervix unrelated to labor and leading to previable pregnancy loss, as well as PTB.

GENETICS OF PRETERM BIRTH

- PTB demonstrates familial aggregation. Women who were themselves born prematurely have a higher risk of PTB, and the risk of PTB increases by 80 percent in women whose sisters had PTB.


Thank You