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Pathophysiology of preterm labor with intact membranes

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ABSTRACT

Preterm labor with intact membranes is a major cause of spontaneous preterm birth (sPTB). To prevent sPTB a clear understanding is needed of the hormonal interactions that initiate labor. The steroid hormone progesterone acting via its nuclear progesterone receptors (PRs) in uterine cells is essential for the establishment and maintenance of pregnancy and disruption of PR signaling (i.e., functional progesterone/PR withdrawal) is key trigger for labor. The process of parturition is also associated with inflammation within the uterine tissues and it is now generally accepted that inflammatory stimuli from multiple extrinsic and intrinsic sources induce labor. Recent studies suggest inflammatory stimuli induce labor by affecting PR transcriptional activity in uterine cells to cause functional progesterone/PR withdrawal. Advances in understanding the functional interaction of inflammatory load on the pregnancy uterus and progesterone/PR signaling is opening novel areas of research and may lead to rational therapeutic strategies to effectively prevent sPTB.

Introduction

Preterm labor with intact membranes—defined as regular uterine contractions and cervical dilation prior to the 37th week of gestation—is a leading cause of spontaneous preterm birth (sPTB). In the United States, preterm birth is a major healthcare and socioeconomic problem that affects 10–15% of pregnancies and causes 70–80% of perinatal mortality and morbidity.[1] To prevent preterm birth a clear understanding is needed of the physiology that initiates the process of human parturition. To this end, understanding the hormonal interactions that control the contractile state (quiescent or laboring) of the pregnant uterus to initiate the process of parturition is pivotal. This review builds on the concept, first proposed by George Corner in the 1930s[2,3] and later refined by Arpad Csapo[4,5] in the 1950s, that the process and timing of parturition are controlled by the net effect of progesterone that promotes uterine quiescence to maintain pregnancy, balanced against factors that oppose the actions of progesterone to promote labor and trigger parturition. More recently it has become clear that inflammation within the gestational tissues (myometrium, cervix, decidua, and fetal membranes) is a key trigger for parturition, and that it does so by opposing the relaxatory actions of progesterone and inducing progesterone withdrawal. The etiology of preterm labor with intact membranes can therefore be considered in the context of the

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functional interaction between pro-labor/pro-inflammatory influences on the pregnant uterus and how those factors affect the pro-pregnancy actions of progesterone.

Maintenance of pregnancy

The fetal development program requires time and therefore the uterus must be conducive to pregnancy for a specific gestation period. The optimum human gestation period is 37–42 weeks (referred to as term), with a singleton pregnancy gestating for an average of 40 weeks.[6,7] Thus, mechanisms that promote uterine quiescence are crucial for the success of pregnancy. For this to occur the muscular wall of the uterus, the myometrium, is maintained in a relaxed state and grows (mainly by cellular hypertrophy) in coordination with the growing conceptus; the cervix is maintained in a closed, rigid state to minimize the size of the uterine outlet, and the decidua (the specialized endometrium of pregnancy) that is in direct physical contact with fetal cells, is maintained in an immunologically dormant state to prevent rejection of the allogeneic fetal tissue. This pro-pregnancy uterine phenotype is primarily induced by the steroid hormone progesterone.

As its name implies progesterone is a "pro-gestation" hormone. In all viviparous species examined to date, it is essential for the establishment and maintenance of pregnancy.[8] Early studies of progesterone led to the progesterone block hypothesis, which posits that progesterone maintains pregnancy by actively promoting uterine quiescence and blocking the onset of labor. The implication of this model is that uterine quiescence is not a default phenotype but instead is actively induced by progesterone, and that removal of progesterone leads to the laboring phenotype and uterine emptying. This is indeed the case as it is now clear from studies in multiple species that removal of progesterone or disruption of its actions induces labor and delivery at all stages of pregnancy.

Progesterone promotes uterine quiescence by affecting the myometrium, cervix, and decidua. In the myometrium, progesterone inhibits contractility by increasing the resting membrane potential and inhibiting responsiveness of myometrial cells to hormones that induce contraction [e.g., oxytocin, prostaglandin (PG)$F_{2\alpha}$]. It also decreases the expression of genes that code for gap junction proteins that connect myometrial cells and allow for action potential propagation and synchronous contractions.[9–13] Progesterone maintains cervical integrity by inhibiting collagen breakdown via increased expression of tissue inhibitor of metalloproteinase, which in turn inhibits matrix metalloproteinases in the cervical stroma.[14–16] It also inhibits expression of the hyaluron synthase 2 gene, which decreases production of hyaluronidase thereby preventing water absorption and collage dissolution in the rigid cervix.[17] In the decidua, progesterone exerts anti-inflammatory actions to prevent an immune reaction to the adjacent fetal tissue and to prevent inflammation-induced weakening of the amnion membrane.[18,19] Anti-inflammatory actions of progesterone also occur in the myometrium and cervix.[20–24]

Effects of progesterone on the pregnant uterus are mediated primarily by its interaction with the nuclear progesterone receptor (PR) isoforms, PR-A and PR-B, expressed by myometrial, cervical, and decidual cells.[25,26] The importance of PR-mediated signaling for the maintenance of human pregnancy is reflected by the fact that administration of PR antagonists at any stage of pregnancy induces labor.[27–30] Disruption of PR signaling increases myometrial contractility and excitability, promotes cervical ECM degradation leading to cervical softening and dilation and increases inflammatory activity in the decidua. Thus, the progesterone block to labor and parturition operates through progesterone/PR-mediated mechanisms in uterine cells, and inhibition or disruption of PR activity alone is sufficient to induce parturition.

Induction of labor

The cornerstone of the progesterone block hypothesis is that removal of progesterone triggers parturition. Indeed, it is now well-established in multiple species, including humans, that progesterone withdrawal–either systemically or functionally (e.g., by modulation of PR signaling)—induces labor at all stages of pregnancy.[8] Thus, elucidation of the hormonal interactions that control progesterone withdrawal is key to unraveling the hormonal control of parturition. Importantly, progesterone withdrawal is the likely terminal convergence point for factors that cause preterm labor leading to preterm birth.

In most species term parturition is initiated by a systemic decrease in maternal progesterone levels. This does not occur in women. Instead, maternal progesterone levels remain elevated until delivery of the placenta.[31] Although this suggests that human parturition is not induced by progesterone withdrawal, as described above, clinical studies with PR antagonists such as mifepristone show that inhibition/modulation of PR signaling alone induces labor at all stages of pregnancy. This led to the hypothesis that human parturition is triggered by a functional progesterone withdrawal, whereby PR signaling in progesterone target cells in the uterus is altered to remove the PR-mediated progesterone block to labor.[32,33]

Studies in human myometrial cells and term myometrium have revealed several possible mechanisms for functional progesterone withdrawal. These include (1) activation of PR-A-mediated inhibition of PR-B transcriptional activity[22,23,25,33,34]; (2) decreased PR co-activator levels in myometrial cells which decreases PR transcriptional activity[35]; (3) inhibition of PR transcriptional activity by the NFκB transcription factor complex which is increased in association with the onset of labor in myometrium and in response to pro-inflammatory/pro-labor stimuli[20,36–38]; and (4) generation of unliganded PRs by conversion of progesterone to a metabolite with lower affinity for the PR ligand binding pocket.[13,39,40]

The PR-A/PR-B hypothesis is based on observations in multiple cells types, including human myometrial cells, that PR-A inhibits the transcriptional activity of PR-B.[41] This effect is referred to as trans-repression and decreases net progesterone responsiveness, especially when PR-A abundance exceeds that of PR-B (i.e., PR-A/PR-B > 1). Indeed, PR-A represses the transcriptional activity of PR-B in myometrial cells as the PR-A/PR-B ratio increases,[22,25,42] and the onset of labor at term is associated with increased PR-A abundance in