Preventing premature birth by exploiting anti-inflammatory actions of progesterone

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Premature birth is a major word-wide socioeconomic problem that causes the majority of neonatal morbidity and mortality. The burden of prematurity can be significantly reduced by prolonging pregnancy (*i.e.* preventing preterm birth) and/or optimizing the intrauterine environment to minimize hostile intrauterine inflammation. The process and timing of parturition involve hormonal cross-talk between the mother and fetus, and paracrine interactions at the maternal-fetal interface that are dominated by pro-inflammatory/pro-labor stimuli that induce labor by promoting tissue-level inflammation in the uterine effector tissues (myometrium, cervix and decidua). We refer to this as the inflammatory load on the pregnancy uterus and propose that it represent the net effect of multiple intrinsic (*e.g.* fetal maturation) and extrinsic (*e.g.* intrauterine infection) pro-inflammatory stimuli.

Progesterone is essential for the establishment and maintenance of pregnancy. For most of pregnancy progesterone blocks parturition by anti-inflammatory actions mediated by the nuclear progesterone receptor (PR) isoforms, PR-A and PR-B. Thus, progesterone *via* the PRs promotes uterine quiescence by inhibiting responsiveness of uterine cells to inflammatory load stimuli. Human parturition is triggered by the functional withdrawal of PR-mediated anti-inflammatory actions that leads to the tissue-level inflammation that transforms the uterus to the labor state. Functional withdrawal of PR anti-inflammatory activity involves post-translational modifications of the PR, mainly site-specific serine phosphorylation of PR-A. We have found that labor at term is associated with a significant increase in the abundance of PR-A phosphorylated at serine residues 344 and 345 (pSer344/5-PRA) in myometrium. This phosphorylation induces the trans-repressive activity of PR-A in myometrial cells such that it inhibits anti-inflammatory activity mediated by PR-B. Interestingly, we found that the generation of pSer344/5-PRA in term myometrium is ligand dependent and induced by pro-inflammatory stimuli. Our data suggest that pro-inflammatory stimuli trigger human parturition by inducing pSer344/5-PRA which inhibits progesterone/PR-B-mediated anti-inflammatory activity leading to uterine tissue-level inflammation. Thus, we propose that for most of pregnancy progesterone *via* PR-B inhibits the response of uterine effector cells (mainly myometrial and cervical cells) to inflammatory load stimuli. However, an inflammatory load threshold exists above which inflammatory stimuli induce the generation of pSer344/5-PRA leading to inhibition of PR-B-mediated anti-inflammatory activity. This suggest that the timing of human parturition is determined by the inflammatory load trajectory and when it reaches the inflammatory load threshold. Based on this model we propose that inhibition of PR-A phosphorylation will increase the threshold by preventing PR-A-mediated functional progesterone withdrawal. This will promote the anti-inflammatory actions of progesterone that would prevent intrauterine inflammation to favor fetal/neonatal wellness and prevent inflammation-induced parturition. We have recently found that PR-A phosphorylation in human myometrial cells can be controlled by non-steroidal selective PR modulators (SPRMs). Some of our SPRM compounds exert strong PR-mediated anti-inflammatory activity but fail to induce the generation of pSer344/5-PRA in human myometrial cells. This represents a novel approach for the prevention of preterm birth and promotion of fetal wellness by preventing PR-A-mediated functional progesterone withdrawal to exploit the natural anti-inflammatory actions of progesterone.