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Prematurity and the puzzle of progesterone resistance

Yasushi Hirota, Jeeyeon Cha, and Sudhansu K Dey

Division of Reproductive Sciences, Perinatal Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA

Sudhansu K Dey: sk.dey@cchmc.org

Parturition is a complex and involved process. Within the protected confines of the mother, the fetus grows rapidly for 37–42 weeks until the right combination of signals, stemming from both endocrine and mechanical stimulation, induces parturition, culminating in birth. Aberrations in these signals may lead to prematurity or stillbirth.

Globally, nearly 13 million premature births and more than 3 million stillbirths occur each year¹. Prematurity is a direct cause of 30% of all neonatal deaths, totaling more than 1 million annually, and often leads to developmental delays and serious long-term disabilities in those who survive. Many factors have been debated as causes of preterm birth (Fig. 1). Despite numerous clinical efforts to decrease the incidence of preterm birth, the major underlying mechanism of preterm labor remains unclear, as does the reason for the high incidence of preterm birth.

Progesterone (P₄), known as the 'hormone of pregnancy,' is crucial for pregnancy success, as it supports embryo implantation and subsequent pregnancy maintenance. P₄ fulfills these responsibilities by modulating uterine cell-specific proliferation and differentiation through differential gene expression in a manner dependent on the stage of pregnancy, such as implantation, decidualization (proliferation and differentiation of uterine stromal cells surrounding the implanting embryo) and placentation. Primary functions of P₄ are to modulate the actions of estrogen; prepare the uterine lining for implantation and pregnancy maintenance; and, during pregnancy until parturition, confer quiescence of the uterine myometrium, the muscular layer of the uterine wall that contracts during labor.

Given all of these functions, there has been a great deal of interest in examining whether P₄ might have an effect on preterm delivery. Several recent clinical trials have tested P₄ or its analogs for this condition.

A randomized control study published in *The New England Journal of Medicine* shows that P₄ treatment (administered nightly between 24 and 34 weeks gestation) reduces the frequency of preterm delivery (to 19.2% versus 34.4%) before 34 weeks of gestation in women with short cervical length, a trait previously determined to be a risk factor for preterm birth². The findings dovetail with another study showing that treatment with 17 α -hydroxyprogesterone caproate (17-OH-PC) reduces the incidence of preterm birth in women with a history of preterm birth³, which, in and of itself, increases the risk of preterm labor by 2.5-fold⁴. The women who responded to P₄ supplementation were perhaps P₄ resistant, meaning they had reduced uterine responsiveness to endogenous P₄. These positive findings suggest that P₄ resistance can be overcome by supplementation with P₄ or its analogs.

Although the treatment clearly had some effect in these trials, many women did not respond. Moreover, two additional studies suggest that neither P_4 nor 17-OH-PC reduces premature birth in women with a different risk factor for preterm birth: twin pregnancy^{5,6}.

These contrasting clinical findings show that we still have much to learn about how parturition proceeds mechanistically. The differing sensitivities to P_4 supplementation depending on the risk factor suggests that there may be more than one pathway leading to preterm labor. Why do some women not respond to treatment? What is the difference between singleton and twin pregnancies that allows one to respond to P_4 treatment but not the other—is preterm labor in twin pregnancy activated by heightened distension of the uterine muscle, or by more severe P_4 resistance? And what causes P_4 resistance? Although the outlines of the process of parturition have become clearer, many supporting details remain missing.

Given the differences in reproductive systems between species, improved animal models that better mimic conditions surrounding human parturition are crucial for moving the field forward. Only through a better mechanistic understanding of parturition can we learn how to more effectively intervene and prevent premature birth.

In pregnant women, P_4 increases through-out pregnancy and remains high during labor and delivery. In humans, the main source of P_4 is the ovary in the first trimester, but shifts to the placenta in later stages of pregnancy. By contrast, in rodents the ovary is the major source of P_4 throughout pregnancy. During pregnancy, parturition in rodents is initiated by decreases in circulating P_4 levels resulting from ovarian luteolysis, the demise of the ovarian corpus luteum which synthesizes P_4 .

Given that levels of P_4 do not decline before parturition in humans, human parturition is speculated to involve a ‘functional P_4 withdrawal’: compromised signaling downstream of P_4 . P_4 acts via the progesterone receptor (PR), and the PR antagonist mifepristone (RU-486) induces cervical ripening and uterine contractions, leading to labor in humans⁷. This labor induction by mifepristone constitutes the functional withdrawal of P_4 -PR signaling in human parturition, but the exact mechanism is not yet clearly understood.

PR has two major isoforms, PR-A and PR-B, which exhibit differential transcriptional regulation to execute P_4 ’s diverse physiological roles. Genetic studies in mice show that whereas PR-A is essential for normal uterine function and P_4 responsiveness, PR-B is less important⁸. On the other hand, an increase in the PR-A/PR-B ratio in the myometrium has been claimed to induce functional P_4 withdrawal and myometrial activation in humans⁹, but how the two isoforms contribute to this functional withdrawal is still obscure.

In addition, PR activity in mice is subject to various steroid receptor co-regulators that may have roles in human parturition. These co-regulators—including steroid receptor coactivator (SRC)-2, SRC-3 and cAMP-response element-binding protein (CBP)—are down-regulated in the human myometrium during labor, suggesting that their aberrant functions confer functional P_4 withdrawal in humans¹⁰. PTB-associated RNA splicing factor (PSF) and p54nrb, recently identified PR co-repressors¹¹, are also prospective candidates for regulating PR activity. PR function is also modulated by a steroid receptor chaperone complex: FKBP52, an immunophilin co-chaperone and a part of the steroid receptor complex, is required for optimal PR activity. FKBP52-null mice with normal PR expression and circulating P_4 levels show diminished uterine P_4 responsiveness with exacerbated estrogenic influence, leading to implantation failure¹². However, implantation and full-term pregnancy may be rescued with excess P_4 supplementation depending on the genetic background of the mouse¹². Whether FKBP52 deficiency confers uterine P_4 resistance in human pregnancy awaits further investigation.

One major role of P₄ is to antagonize the effects of estrogen. Circulating levels of estrogens in humans rise from mid-gestation until birth. There is evidence that estrogen is an inducer of human uterine contractions that are attenuated by P₄ (ref. 13). Because estrogen receptor α (ER- α) expression in the human myometrium is upregulated during labor⁹, 'functional estrogen activation' in parallel with functional P₄ withdrawal may be involved in human parturition. Moreover, estradiol levels are prematurely elevated in the amniotic fluid and plasma in women with preterm delivery compared to those with term delivery¹⁴, suggesting untimely functional estrogen activation in preterm birth.

Given such promising yet incomplete clues, further *in vivo* assessment using animal models should provide mechanistic information that would help in defining how P₄-PR signaling operates in human preterm labor. Although rodent models of preterm birth induced by inflammatory agents such as lipopolysaccharides (LPS) are widely used, adverse systemic effects on both the fetus and mother confound the results and their interpretation. Furthermore, parturition in rodents is induced primarily by a drop in P₄, which does not occur in human parturition. In these contexts, rodent models of spontaneous preterm labor without luteolysis are more desirable in studying the underlying mechanisms of human parturition. Such models scarcely exist, and efforts need to be directed toward creating such mouse models by inducible conditional gene expression or deletion at specific pregnancy stages of interest. In this respect, mice with conditional loss or gain of function of uterine PR-A, FKBP52 or ER- α may prove useful.

Other factors are also important in parturition. For instance, disruption in prostaglandin signaling, which is involved in uterine muscular contractions, may alter the timing of labor. In addition, defective implantation or decidualization propagates adverse ripple effects throughout the course of fetal development, compromising pregnancy outcome¹⁵. Indeed, mice with conditional deletion of uterine *Tip53* (encoding transformation-related protein 53) show premature decidual senescence with increased amounts of cyclooxygenase-2 (COX2)-derived prostaglandin F_{2 α} (PGF_{2 α}), and show preterm birth and neonatal death without early luteolysis, mimicking an aspect of human preterm delivery¹⁶. Transgenic mice carrying hypomorphic alleles of *Hpgd* (encoding hydroxyprostaglandin dehydrogenase 15) also show spontaneous preterm labor with increased PGF_{2 α} in the absence of P₄ withdrawal¹⁷. These mouse models may be used to study P₄ resistance and other signaling pathways involved in preterm labor.

Guinea pigs¹⁸ and higher mammals, notably great apes¹⁹, that do not show a drop in P₄ levels before parturition could be explored as possible models of preterm birth in humans. However, developing such models in these animals using genetic and molecular approaches would be difficult. Thus, for now efforts should be directed toward creating animal models of spontaneous preterm labor in which trans-genic approaches are available to identify key targets of P₄-PR signaling, with the hope of developing potential therapies to combat preterm birth in humans.

By elucidating the molecular mechanisms behind parturition, we can prevent or substantially reduce the rate of preterm birth. If we are successful in identifying key molecules that regulate labor, which will require intense research, we could potentially develop more effective and efficient preventive strategies by manipulating key regulators in the labor 'pathway.' For example, the onset of preterm labor in humans is often associated with increased inflammatory and immune responses along with altered prostaglandin synthesis driven by COX2. Will it then be plausible to treat patients with rational combinations of P₄ (among its various roles, a potent immunosuppressant) and a COX2 inhibitor (anti-inflammatory) to improve efficacy and reduce toxicity in preventing preterm labor in high-risk populations?

Because P₄ alone is thought to be insufficient to substantially reduce preterm births in twin pregnancies, as opposed to singleton pregnancies, dissecting differences in labor induction pathways between singleton pregnancies and those involving twins and multiples will be crucial to developing specific therapies. Such preclinical approaches could be tested using appropriate mouse and other animal models, including primates, and could potentially be used in the clinic. In addition, polymorphism and mutation of genes associated with P₄ resistance can be identified to screen for populations predisposed to preterm delivery.

These efforts at the bench by basic and clinical scientists with a mutual appreciation for the complexities of preterm birth will provide new insights into reducing the incidence of prematurity in humans.

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Figure 1.

Molecular signaling in parturition. Coordinated signaling through progesterone and estrogen regulates the normal timing of parturition by engaging local mediators in programming uterine muscular contractions and cervical ripening. Pathological conditions—such as progesterone resistance, inflammation or cervical aberration, or some combination of these factors—disrupt normal programming and prematurely induce preterm labor. PR, progesterone receptor; PPROM, preterm premature rupture of membranes; PGs, prostaglandins; OXT, oxytocin; CX43, connexin-43.