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REVIEW ARTICLE

Developmental Biology: Model Systems - A Series of Reviews

This is the third of five articles in a series of reviews covering topics in developmental biology. In this review Drs. Ratajczak and Muglia focus on the genetically-modified, murine model as a tool to uncover the mechanisms of parturition.

Sherin U. Devaskar, M.D.
Editor-in-Chief

Insights Into Parturition Biology From Genetically Altered Mice

CHRISTINE K. RATAJCZAK AND LOUIS J. MUGLIA

Departments of Pediatrics, Developmental Biology, and Obstetrics and Gynecology, Washington University School of Medicine, St. Louis, Missouri 63110

ABSTRACT: With the growing frequency of preterm birth, increased effort has been made to elucidate the physiology of normal and aberrant parturition. As with many developmental processes, the study of genetically altered mice has led to an increased understanding of mechanisms controlling the maintenance and resolution of pregnancy. Studies in genetically altered mice have implicated critical roles for both prostaglandin synthesis and degradation in luteolysis and the progression of labor. The importance of local modulation of progesterone activity to cervical ripening has also been demonstrated. Although a decline in levels of serum progesterone is a part of normal labor initiation in mice but not humans, murine labor without progesterone withdrawal has been reported in some cases. These findings emphasize the importance of other components of the parturition cascade that are shared in mice and humans and highlights the importance of an increased understanding of the physiology of mouse parturition. **(*Pediatr Res* 64: 581–589, 2008)**

Parturition is the culmination of mammalian reproduction, a task essential for survival of the species. After a period of uterine quiescence to allow fetal growth and development, changes occur in myometrial contractility that result in efficient expulsion of the fetus. These events have likely evolved to enhance survival of both the fetus and the mother. The nature of these pathways, however, is at best incompletely defined.

Increased knowledge of the cascade of events that occur at parturition may lead to advances in combating preterm labor (PTL) or optimization of protocols for medically induced labor. As preterm birth is associated with both increased risk of neonatal mortality and chronic sequelae such as respiratory illness, cerebral palsy, and vision and hearing impairment, it is a major public health concern (1). In the United States, 12.7% of births are preterm (2). Although approximately 50% of preterm births are idiopathic (3), genetic factors seem to be important. Women whose mothers or sisters delivered preterm are at increased risk for premature labor (4,5), indicating a genetic component in the timing of labor. In addition, a study of a Utah population indicates greater genetic relatedness between families with preterm deliveries than control families (6). Because the population studied was descended from the people who established Mormonism in Utah and Mormons have low rates of substance abuse and sexually transmitted diseases, the population used in this study may represent individuals with few environmental risk factors for PTL (6). These studies highlight a role for genetic, and not just environmental factors in predisposition to PTL and serves as a call to researchers to identify and study genes important for parturition.

The mouse is a useful research tool for dissecting genetic factors involved in developmental processes. Mice are tractable to genetic manipulation, resulting in an array of available and potential knockout and transgenic mice suitable for studying the roles of specific genes in complex processes. Important

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Correspondence: Louis J. Muglia, M.D., Ph.D., Departments of Pediatrics, Developmental Biology, and Obstetrics and Gynecology, Washington Universitiy School of Medicine, 660 So. Euclid Ave. Campus Box 8208, St. Louis, MO 63110; e-mail: Muglia_L@kids.wustl.edu

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Abbreviations: 5α-R1, 5α-reductase type 1; **15-HPGD,** 15-hydroxyprostaglandin dehydrogenase; **20α-HSD,** 20α-hydroxysteroid dehydrogenase; **COX,** cyclooxygenase; **cPLA$_2$,** cytoplasmic phospholipase A$_2$; **Cx43,** connexin43; **FP,** prostaglandin F$_{2\alpha}$ receptor; **HA,** hyaluronan; **HAS2,** hyaluronan synthase 2; **HKE,** heat-killed *Escherichia coli*; **LPS,** lipopolysaccharide; **OT,** oxytocin; **OTR,** oxytocin receptor; **OVX,** ovariectomy; **PGE$_2$,** prostaglandin E$_2$; **PGF$_{2\alpha}$,** prostaglandin F$_{2\alpha}$; **PR,** progesterone receptor; **PTL,** preterm labor; **RLX,** relaxin; **SK3,** small-conductance, calcium-activated K$^+$ isoform 3; **SP-A,** surfactant protein-A

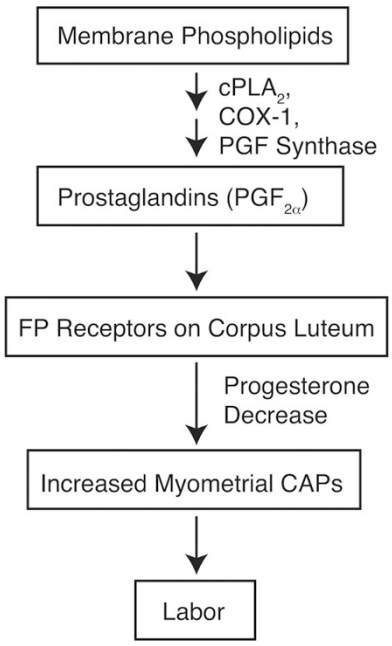

Figure 1. Schematic for the cascade of events culminating in murine labor. Increased synthesis of $PGF_{2\alpha}$ in the uterine epithelium by the sequential actions of $cPLA_2$, COX-1, and PGF synthase results in luteolytic action through FP receptors in the ovary. A drop in circulating progesterone with luteolysis induces expression of myometrial CAPs and labor. CAP, contractile-associated protein; $cPLA_2$, cytoplasmic phospholipase A_2; COX-1, cyclooxygenase-1; FP, $PGF_{2\alpha}$ receptor; $PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$.

to the study of parturition, mice have a conveniently short duration of gestation. Although the mouse has many advantages as a research tool, its relevance for increasing the understanding of human parturition has been questioned because of some dissimilarity in the parturition cascades of mice and humans. At the onset of normal murine parturition, prostaglandins trigger luteolysis, the structural and functional degradation of the steroidogenic corpora lutea, and a withdrawal of progesterone (Fig. 1) (7). Humans exhibit no such decline of serum progesterone at term (8). However, a functional progesterone withdrawal, mediated by a decrease in the progesterone receptor's (PR's) transcriptional activity, may be a part of normal human parturition (9). Furthermore, genetically altered mice in which parturition occurs without a dependence on declining serum progesterone levels have been described (10,11). This emphasizes the importance of other mechanisms of the parturition cascade known to be present in both mice and humans. In each species, there is an up-regulation of contractile-associated proteins (CAPs), such as oxytocin receptor (OTR), prostaglandin $F_{2\alpha}$ receptor (FP), and connexin43 (Cx43), in the uterus at term (12–15). Parturition studies using genetically altered mice are reviewed here (Table 1).

PROGESTERONE WITHDRAWAL

Throughout gestation, progesterone maintains uterine quiescence. A fall in circulating progesterone occurs with the onset of murine (7), but not human (8) labor. In mice, ovariectomy (OVX) induces PTL, whereas administration of progesterone delays parturition (16). Genetically altered mice have been used to study mechanisms for declining serum progesterone levels in mice and possible alternative mechanisms of progesterone withdrawal in humans.

20α-Hydroxysteroid Dehydrogenase Impacts Serum Progesterone Levels

20α-HSD has an important role in coordinating progesterone withdrawal at term in mice (17). 20α-hydroxysteroid dehydrogenase (20α-HSD) converts progesterone to an inactive metabolite and is expressed in the ovary (18). Although expression of 20α-HSD is barely detectable during mid to late gestation, it is up-regulated considerably at term (17). 20α-$HSD^{-/-}$ mice fail to initiate labor at term (17). Instead, labor is delayed 2–3 d compared with 20α-$HSD^{+/+}$ controls, and the pups die in utero (17). In term 20α-$HSD^{-/-}$ females, progesterone fails to fall to the same level that it does in term wild-type mice (17). Administration of the progesterone antagonist RU486 to 20α-$HSD^{-/-}$ females 1 d before term results in productive parturition the next day without a decrease in circulating progesterone levels (17). This result indicates that the singular role for 20α-HSD in gestation and parturition is to regulate the levels of serum progesterone (17).

Prostaglandins Mediate Luteolysis and Progesterone Withdrawal

Progesterone withdrawal in mice is concurrent with luteolysis, the structural and functional degradation of the corpora lutea. A role for prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) in luteolysis and progesterone withdrawal in mice has been demonstrated by the study of FP knockout mice (7). FP is normally expressed in the corpus luteum (19). $FP^{-/-}$ females establish and maintain pregnancies normally, but they fail to initiate labor (7). Serum progesterone levels do not decline in these animals at term, indicating that their corpora lutea retain their steroidogenic function (7). OVX in these dams leads to progesterone withdrawal and successful parturition (7). Mice deficient for prostaglandin receptors other than FP have no parturition defects, indicating that $PGF_{2\alpha}$ is the critical prostaglandin isoform for inducing luteolysis (20).

The importance of prostaglandins in precipitating luteolysis and progesterone withdrawal is further supported by similar phenotypes in cytoplasmic phoshospholipase A_2 $(cPLA_2)^{-/-}$ and cyclooxygenase-1 $(COX\text{-}1)^{-/-}$ mice (21–24). $cPLA_2$ and COX-1 are enzymes responsible for the synthesis of prostaglandins. $cPLA_2$ converts membrane phospholipids to arachidonic acid. Arachidonic acid is then converted to prostaglandin H_2 (PGH_2), the intermediate required by PGF synthase, by different isoforms of COX (Fig. 2). $cPLA_2{}^{-/-}$ females have a delay in labor (21,24). Administration of PR antagonist to gravid $cPLA_2$-deficient females precipitates labor, indicating that persistent progesterone levels are responsible for delayed labor in these mice (24). $COX\text{-}1^{-/-}$ females also exhibit delayed parturition (22,23) and persistent progesterone levels (22). Labor can be induced at term by administration of $PGF_{2\alpha}$ (22). No parturition phenotype has been reported for $COX\text{-}2^{-/-}$ mice because defects in ovulation and implantation prevent progression of gestation to this stage (25).

Table 1. *Parturition phenotype of genetically altered mice*

Genetically altered mouse	Phenotype	References
Progesterone withdrawal		
20α-Hydroxyprostaglandin dehydrogenase (20α-HSD)$^{-/-}$	Delay in labor; fetal demise; no P4 withdrawal	17
$PGF_{2\alpha}$ receptor (FP)$^{-/-}$	Fail to initiate labor; fetal demise; no P4 withdrawal	7
Cytoplasmic phospholipase A_2 ($cPLA_2$)$^{-/-}$	Delay in labor; fetal demise; no P4 withdrawal	21, 24
Cyclooxygenase-1 (COX-1)$^{-/-}$	Delay in labor; fetal demise no P4 withdrawal	22, 23
Krüppel-like factor 9 (Klf9)$^{-/-}$	Delay in labor; aberrant PR expression	29
Myometrial contraction		
Oxytocin (OT)$^{-/-}$	No parturition phenotype	35, 37
Oxytocin receptor (OTR)$^{-/-}$	No parturition phenotype	36
Cyclooxygenase-1 (COX-1)$^{-/-}$/oxytocin (OT)$^{-/-}$	Prolonged labor initiated at normal time	32
Myometrial connexin43 (Cx43)$^{-/-}$	Delayed labor; fetal demise	39
15-Hydroxyprostaglandin dehydrogenase (15-HPGD)$^{-/-}$	Early labor; early PGF2α increase; no progesterone withdrawal	11
SK3 channel overexpressor	Prolonged labor; weaker uterine contractions at term	50, 51
Cervical ripening		
Relaxin (RLX)$^{-/-}$	Low penetrance nonproductive labor; impaired cervical ripening	57
LGR7$^{-/-}$ (relaxin receptor)	Low penetrance nonproductive labor	58
Steroid 5α-reductase type 1 (5α−R1)$^{-/-}$	Delayed labor; prolonged labor; impaired cervical ripening	60, 61
Circadian influence on labor		
Clock mutant	Increased incidence of extended but nonproductive labor	74
Oxytocin (OT)$^{-/-}$	Phase advance or delay alters birth timing	75
Bacterially induced PTL		
IL-1 receptor (IL-1RI)$^{-/-}$	Susceptible to bacterially induced PTL	87
IL-1β (IL-1β)$^{-/-}$	Susceptible to bacterially induced PTL	88
IL-6 (IL-6)$^{-/-}$	Susceptible to bacterially induced PTL	89
IL-1 receptor (IL-1R1)$^{-/-}$/TNF receptor (Tnfsrsfa)$^{-/-}$	Decreased susceptibility to bacterially induced PTL	91
Toll-like receptor 4 (TLR4) mutant	Resistant to bacterially induced PTL	46

However, COX-2 is up-regulated in the myometrium during parturition suggesting a role for this COX isoform in labor progression rather than initiation (26).

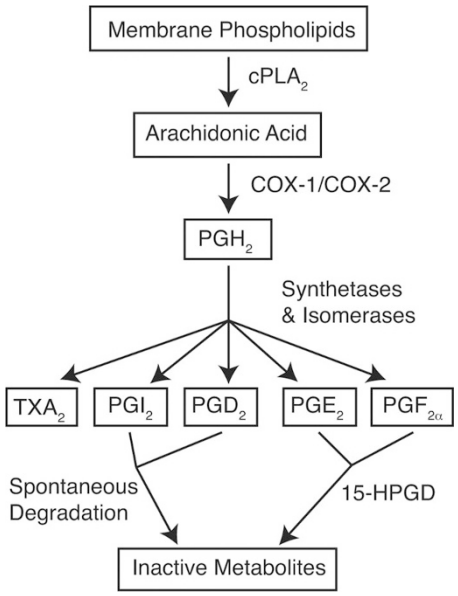

Figure 2. Biochemical pathway of prostaglandin synthesis and degradation. Arachidonic acid conversion to the metastable intermediate PGH_2 occurs through the action of the COX enzymes. PGH_2 is converted to the specific prostanoid isoforms for receptor action by their respective synthases/isomerases. PGE_2 and $PGF_{2\alpha}$, the main prostaglandins involved in parturition, are degraded by 15-HPGD. 15-HPGD, 15-hydroxyprostaglandin dehydrogenase; $cPLA_2$, cytoplasmic phospholipase A_2; COX, cyclooxygenase; PG, prostaglandin; TXA_2, thromboxane A_2.

Models for Functional Progesterone Withdrawal in Humans

Although serum progesterone does not fall at term in humans (8), questions remain as to whether or not a functional progesterone withdrawal is part of human parturition. In some cases, administration of the PR antagonist mifepristone augments cervical ripening and precipitates labor in term women (27), indicating that functional progesterone withdrawal may have a role in human labor. Because it has been observed that each of the PR isoforms has distinct properties as a transcription factor (28), differential expression of PR isoforms at term seems a likely mechanism for functional progesterone withdrawal in humans. A recent mouse study indicates a potential importance of PR regulation at term. Mice deficient for Krüppel-like factor, Klf9, an Sp6 family transcription factor, have a delay in parturition with corresponding aberrant PR isoform A expression in the myometrium and insensitivity to progesterone antagonist at late gestation (29). Studies have been conducted on the ratio of expression of the different PR isoforms in the laboring human myometrium (30,31), but it is difficult to draw a compelling argument for PR regulation as a means of functional withdrawal from the data. However, evidence supporting functional progesterone withdrawal in humans comes in the form of an observed decrease in coactivators with histone acetylase activity in both humans and mice at term (9). Both expression of coactivators with histone acetylase activity and acetylated histone H3 are decreased at term in humans and mice (9). When trichostatin A (TSA), a histone deacetylase inhibitor, was administered to pregnant mice daily during the late gestation, parturition was delayed

24–48 h (9). TSA administration in this fashion leads to 200 times the histone acetylation of an untreated mouse at term (9). It is proposed that a decrease in coactivators and acetylation at term interrupts the transcriptional activity of the progesterone-PR complex leading to a functional progesterone withdrawal (9).

MYOMETRIAL CONTRACTION

Preparation for the myometrium to contract as one powerful unit is an important step in the start of the parturition cascade. As term approaches, expression of the CAPs, including Cx43, OTR, and FP, increases in the myometrium of humans and mice (12–15). The myometrium is thus activated and therefore able to respond to stimulants such as prostaglandins, which induce myometrial contractions and sensitize the myometrium to other uterotonic agents. Uterine $PGF_{2\alpha}$ also increases to its highest levels just before labor begins (12). Prostaglandins and CAPs are important players for transforming the uterus, quiescent for most of gestation, to the powerful contractile organ necessary for expelling the fetus.

The Uterotonic Agent Oxytocin is Not Necessary for Parturition

Oxytocin (OT) is a strong uterotonic agent and is frequently used to induce labor (32,33). Although OTR expression increases in the myometrium approximately 10-fold at term (34), $OTR^{-/-}$ and $OT^{-/-}$ females have a normal timing and duration of labor (35–37). Surprisingly, COX-$1^{-/-}$/$OT^{-/-}$ mice have a prolonged labor that initiates at normal term (22). This is also in contrast to the COX-$1^{-/-}$ mouse, which has impaired luteolysis and delayed labor (22,23). COX-$1^{-/-}$/$OT^{-/-}$ mice undergo luteolysis normally (22). Therefore, it seems that in addition to having a role as a contractile agonist at the level of the uterus, OT has a role at the level of the ovary for maintaining the corpus luteum (22). Further examination of the role of OT in gestation and parturition has shown that infusion of OT leads to a delay in labor at low doses, highlighting its role in maintaining the corpus luteum, and precipitation of labor at high doses indicating its role as a uterine contractile agonist (38).

Expression of the Gap Junction Protein Cx43 in the Myometrium is Necessary for Parturition

The necessity of the CAP Cx43, which synchronizes myometrial cells, for successful parturition has been demonstrated by study of a novel genetically altered mouse (39). Because conventional $Cx43^{-/-}$ mice die shortly after birth (40), Cre-LoxP technology (41) was used to generate mice deficient for Cx43 specifically in smooth muscle tissues including the myometrium (39). Whereas the vast majority (89%) of gravid control mice deliver their litters between 4 and 8 am on d 19.5 of gestation, few (18%) of the myometrial $Cx43^{-/-}$ females deliver during this time period (39). The majority of myometrial $Cx43^{-/-}$ mice instead deliver after 8 am on d 19.5, with approximately half of that group delivering dead pups on d 20–22 of gestation (39). Uterine OTR and FP are up-regulated and serum progesterone declines normally in the myometrial $Cx43^{-/-}$ mice at term (39). This study highlights the importance of Cx43 and the coupling of myometrial cells for productive uterine contractility as well as the utility of the conditional knockout system for studying parturition.

15-Hydroxyprostaglandin Dehydrogenase Decreases at Term to Allow Prostaglandin Up-regulation

Mutant mice have shown a role for the synthesis and action of prostaglandins in the initiation of parturition (7,21–24). However, less is known about how the degradation of prostaglandins may be regulated to achieve increased prostaglandin levels and parturition at term. 15-Hydroxyprostaglandin dehydrogenase (15-HPGD) is the principal enzyme responsible for the breakdown of $PGF_{2\alpha}$ as well as the less robustly expressed prostaglandin E_2 (PGE_2) (42,43). In humans, 15-HPGD mRNA decreases in chorion trophoblast cells in both term and preterm laboring women *versus* nonlaboring women (44,45). A similar decrease is noted in laboring mice (46). To examine the role of regulation of expression of this gene in the parturition cascade, mice hypomorphic for 15-HPGD were generated (11). These animals have a significant decrease in 15-HPGD activity in placenta, uterus, and fetal membranes compared with control animals (11). When mated to hypomorphic males, hypomorphic females labor approximately 1 d early (11). In the case of these pregnancies, $PGF_{2\alpha}$ and PGE_2 levels rise early (11). Interestingly, their labor proceeds without progesterone withdrawal, perhaps due to an ability of PGE_2 to maintain the corpus luteum in the face of increasing $PGF_{2\alpha}$ levels (11). These data indicate a role for decreased catabolism of prostaglandins, in addition to increased synthesis, in initiation of the parturition cascade (11). It also suggests that prostaglandins can mediate the induction of labor by mechanisms besides luteolysis and resulting progesterone withdrawal.

Small-Conductance, Calcium-Activated K^+ Isoform 3 Channel Expression Decreases in Term Myometrium to Promote Contractility

The activity of several types of K^+ channels in the myometrium is regulated throughout pregnancy to maintain uterine quiescence during gestation and generate forceful contractions at term (47–49). The role of small-conductance, calcium-activated K^+ isoform 3 (SK3) channels in parturition has been examined using genetically altered mice. SK3-overexpressing females exhibit defective parturition, manifested by prolonged delivery and mortality of pups and dams (50). Weaker contractions are observed in uterus from term SK3-overexpressing *versus* wild-type females (51). Moreover, when administered stimuli precipitate PTL in wild-type mice, SK3-overexpressing mice do not complete labor even if serum progesterone levels decline (51). SK3 expression is decreased in both mice and humans at term (49,51), indicating an importance of regulation of this channel for parturition in both species.

CERVICAL RIPENING

Along with conversion of the quiescent uterus to a powerfully contracting unit, remodeling of the formerly rigid cervix is an important process for enabling successful parturition. During pregnancy, the cervix must be firm so that the fetus is not prematurely expelled. However, as term draws near, cervical softening and remodeling occurs, making the cervix more compliant and amenable to the birthing process. This process involves tissue growth, increase in cervical secretions, infiltration by inflammatory cells, and alterations in the extracellular matrix (52).

Relaxin Mediates Normal Cervical Ripening

Relaxin (RLX) is a hormone known to be important for connective tissue remodeling in sites including the cervix and pelvic ligaments (53,54). The primary source of rodent RLX is the corpus luteum (55). In rodents, levels of RLX increase during the second half of pregnancy (56). Studies in rats have indicated that in the absence of circulating RLX, labor is prolonged or prevented (53). The RLX knockout mouse is fertile, but has a low penetrance nonproductive labor phenotype (57). Duration of labor, measured as the time elapsed from delivery of the first pup until delivery of the last, was reported to be approximately 2 h in seven of seven $RLX^{+/+}$ and six of eight $RLX^{-/-}$ mice (57). The remaining two $RLX^{-/-}$ females had abnormal labor. One of these females had a prolonged labor lasting approximately 15 h (57). The other birthed two dead pups and was killed 12 h later because of distress (57). Postmortem analysis revealed the presence of 10 additional dead pups *in utero* (57). Accordingly, a low penetrance phenotype of nonproductive parturition was also observed in dams deficient for LGR7, the highest affinity RLX receptor (58). The protracted labor phenotype associated with these two knockout models can perhaps by explained by a lack of normal pregnancy-related changes in the cervix, pubic symphysis, and vagina of $RLX^{-/-}$ females (57,59). Weight of pubic symphysis, vagina, and cervix in $RLX^{-/-}$ females does not increase by 1 d before term at the magnitude it does in $RLX^{+/+}$ females (59). In addition, pregnant $RLX^{-/-}$ females have denser collagen staining in vagina, pubic symphysis, and cervix than do $RLX^{+/+}$ females 1 d before term (59). Also, the pubic bones of $RLX^{-/-}$ females fail to widen to the extent that they do during the second half of pregnancy in wild-type gravid females (57). These data support a role for RLX in preparation of the birth canal for labor.

Progesterone Metabolism by Steroid 5α-Reductase Type 1 at the Cervix Allows Ripening

5α-Reductase type 1 $(5\alpha\text{-R1})^{-/-}$ mice also have a parturition defect attributable to poor cervical ripening (60,61). 5α-R1 metabolizes progesterone, and its expression has been noted in many tissues of the female reproductive tract (60). The majority of $5\alpha\text{-R1}^{-/-}$ dams have prolonged labor at 2–3 d postterm (60). A quarter of these females die during labor (60). If the pups are delivered via caesarean section at term, they are normal and can be nursed by foster mothers (60). $5\alpha\text{-R1}^{-/-}$ females delivering on time were noted to have decreased litter size (60). During the second half of gestation, circulating steroid hormone levels are comparable between $5\alpha\text{-R1}^{+/+}$ and $5\alpha\text{-R1}^{-/-}$ dams (60). Additionally, gravid $5\alpha\text{-R1}^{-/-}$ females exhibit contractions that are sufficient for labor (61). However, at term, $5\alpha\text{-R1}^{-/-}$ females have a matrix of collagen fibers that is denser and more compact than that observed in $5\alpha\text{-R1}^{+/+}$ females at term (61). Further analysis revealed that progesterone is elevated in the cervix and uterus of $5\alpha\text{-R1}^{-/-}$ females at term, despite the fact that a serum progesterone decline is observed (61). The prolonged labor phenotype observed can be reversed by administration of PR antagonists or OVX, as well as by administration of some 5α-reduced steroids, RLX, or OT (60,61). This novel report suggests the importance of local progesterone metabolism to the process of cervical ripening. Local progesterone concentrations also seem to be regulated for cervical ripening in humans, although by a different enzyme. 17β-Hydroxysteroid dehydrogenase, which converts 20α-hydroxyprogesterone to progesterone, is down-regulated in the endocervical cells in term women, leading to decreased local progesterone levels and favorable conditions for cervical ripening (62).

Additional studies using $5\alpha\text{-R1}^{-/-}$ female mice have indicated some potentially important participants in the process of cervical ripening. Hyaluronan (HA) increases during late pregnancy in a variety of mammals studied including the mouse and human and is the primary glucosaminoglycan present in the cervix at labor (63–66). HA is speculated to be important in cervical ripening because it has a high water affinity and increased tissue hydration may prevent the aggregation of collagen fibrils and reduce the tensile strength of this tissue (65,67). In $5\alpha\text{-R1}^{+/+}$ females, hyaluronan synthase 2 (HAS2) mRNA is the HAS isoform found in greatest abundance in cervix 1 d before parturition, when cervical HA content is also increased (68). In the $5\alpha\text{-R1}^{-/-}$ female, HAS2 expression is reduced by 70% compared with $5\alpha\text{-R1}^{+/+}$ females 1 d before term, correlating with a 68% reduction in HA compared with $5\alpha\text{-R1}^{+/+}$ females (68). HAS2 up-regulation is also observed in women in labor (68). These data indicate a potential importance for the regulation of this enzyme in remodeling of the cervical extracellular matrix near term (68). In addition, $5\alpha\text{-R1}^{-/-}$ females do not display the late pregnancy-associated changes in expression of aquaporins and tight junction proteins seen in $5\alpha\text{-R1}^{+/+}$ females, indicating a role for these types of proteins in mediating changes in cervical water content associated with cervical ripening (69,70).

CIRCADIAN INFLUENCE ON LABOR

A newly emerging area of interest is the relationship between circadian rhythmicity and parturition. Circadian rhythmicity is manifested by daily oscillations in locomotor activity, hormone levels, metabolism, and other parameters (71). A molecular clock comprised of several genes, among them the heterodimer partners Clock and Bmal1, underlies this phenomenon (71). The onset of parturition seems to be under circadian influences. Epidemiologic data from two separate studies indicate that humans tend to labor in the early morning

hours (72,73). Time of day seems to factor into murine labor as well, as mice tend to labor during the dark phase of their daily cycle. This raises the question of how the molecular clock interacts with molecular events of the parturition cascade. The Clock mutant mouse, which has a deletion in Clock's transcriptional activation domain, has been noted to have a high incidence of extended but nonproductive labor indicating a role for genes of the molecular clock in the parturition process (74). In addition, we recently reported a possible role for OT in maintaining the normal circadian gating of labor in mice (75). A 6-h phase advance or delay in wild-type dams starting on d 4.5 of gestation precipitated no overall change in birth timing, whereas the same 6-h phase advance or delay in $OT^{-/-}$ dams leads to a random scattering of the time of birth throughout the day (75). OT is released in a circadian fashion. This rhythmicity of secretion is not altered in wild-type gravid females upon change in light:dark cycle although both wild-type and $OT^{-/-}$ dams shift their locomotor activity patterns in response to the disturbance (75). Therefore, it seems OT secretion may maintain the onset of labor with original circadian entrainment of pregnancy (75).

BACTERIALLY INDUCED PTL

Infection seems to contribute to or precipitate PTL in many instances, with 30% of PTL cases exhibiting intrauterine microbial colonization or histologic features of chorioamnionitis (76). Bacterially induced PTL is associated with an activation of the inflammatory response, including up-regulation of cytokines, chemokines, and prostaglandins (Fig. 3) (77). Even normal spontaneous labor has elements of an inflammatory response (78–80). Much study has been conducted in mice to better define the pathogenesis of bacterially induced PTL. Most mouse studies relevant to this phenomenon use injections of heat-killed *Escherichia coli* bacteria (HKE) (77) or lipopolysaccharide (LPS) (81), a component of the outer membrane of Gram-negative bacteria, to induce PTL.

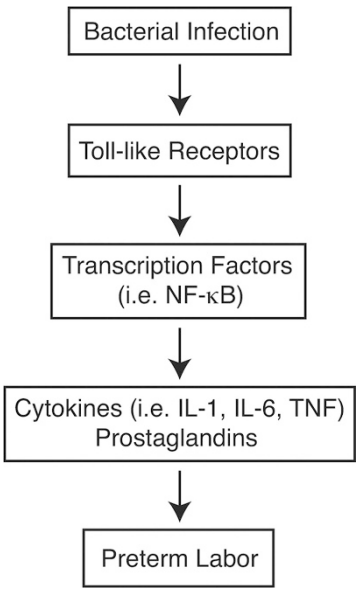

Figure 3. Bacterial infection-associated preterm birth pathway. Bacterial products, for example, endotoxin (LPS), activate toll-like receptors to produce proinflammatory products such as cytokines and prostaglandins that accelerate the time for parturition. NF-κB, nuclear factor-κB.

No Progesterone Withdrawal in Bacterially Induced Labor?

Reports on whether or not bacterially induced labor is accompanied by progesterone withdrawal in mice are conflicting. Fidel et al. (81) observed a significant decrease in serum progesterone in mice injected peritoneally with LPS to precipitate PTL. However, Hirsch and Muhle (10) found that intrauterine injection of a high dose (10^9) of HKE did not result in a decrease of circulating progesterone of the magnitude observed resulting from OVX. However, the high dose of HKE precipitated labor more quickly than OVX (10). Whereas administration of progesterone at pharmacological levels lengthened the time to delivery in both the high-dose HKE and OVX groups, administration of progesterone at physiologic levels lengthens time to delivery in the OVX group only (10). The results of this study indicate that progesterone withdrawal is not the chief mechanism for bacterially induced PTL (10). The conflicting nature of these two reports may be because of the different routes of infection, with the peritoneal LPS injections in the first study leading to a systemic infection and the intrauterine HKE injection of the latter study leading to a more localized infection (10).

Cytokine Roles in Bacterially Induced PTL

A host of cytokines, such as IL-1, IL-6, and TNF, are found to be up-regulated in cases of infection-associated PTL in humans and mice (77). In animal models, IL-1 and TNF can induce increased prostaglandin levels, CAP up-regulation, uterine contractility, and PTL (82–86). Genetically altered mice have been helpful in determining the importance of specific cytokines in bacterially induced PTL. No individual cytokine has been found necessary for the pathogenesis of bacterially induced PTL. Mice deficient for IL-1 receptor (IL-1RI), which are completely devoid of IL-1 signaling, are not protected from PTL precipitated by HKE injections at multiple sites (87). Accordingly, IL-1$\beta^{-/-}$ females inoculated with HKE or LPS were as likely to undergo PTL as wild-type females undergoing the same treatment (88). Similarly, IL-6 seems to be dispensable for the pathogenesis of bacterially induced PTL as IL-$6^{+/+}$ and IL-$6^{-/-}$ females are equally susceptible to PTL triggered by uterine HKE inoculation (89). To test the hypothesis that cytokines have redundant roles in the pathogenesis of bacterially induced PTL, mice lacking signaling from multiple cytokine receptors were examined. Mice treated with the anticytokines IL-1 receptor antagonist (IL-1ra) and soluble TNF receptor Fc fusion protein in combination with LPS undergo PTL at similar frequency as wild-type females treated with LPS alone (90). However, another report using IL-1 receptor (IL-1R1)$^{-/-}$/TNF receptor (Tnfsrsf1a)$^{-/-}$ mice shows a decreased susceptibility to PTL induced by inoculation with HKE in the double knockouts (91). Perhaps, the discrepancy is due to complete eradication of receptor signaling in the knockout paradigm in contrast to

residual receptor signaling in the case of anticytokine treatment. If this is the case, higher doses of these anticytokines may be more effective in inhibiting the observed PTL. The IL-1R1$^{-/-}$/Tnfsrsf1a$^{-/-}$ study seems to indicate that having either IL-1 or TNF is necessary for the pathogenesis of bacterially induced PTL. However, there has been no report on the phenotype of Tnfsrsf1a single knockout mice. Such a study is warranted to establish whether the necessity for TNF signaling is responsible for the double knockout phenotype (91).

The role of cytokines in the pathogenesis of bacterially induced PTL was further explored in the IL-1R1$^{-/-}$/Tnfsrsf1a$^{-/-}$ system (91). The double knockout mice showed significantly lower myometrial expression of COX-2 upon HKE inoculation compared with wild-type females indicating the importance of COX-2 in the pathogenesis of bacterially induced PTL (91). They did not show differential regulation of genes associated with cervical ripening compared with treated wild-types, indicating that the process of cervical ripening in bacterially induced PTL differs from that in term laboring females (91).

Toll-like Receptor Dependence of Bacterially Induced PTL

Bacteria are thought to initiate the inflammatory process and thereby precipitate PTL by interacting with toll-like receptors (TLRs), which orchestrate an immediate immune response. TLR stimulation leads to the activation of nuclear factor-κB (NF-κB), which induces cytokine and chemokine transcription (77). To examine whether TLRs are necessary for bacterially induced PTL, mice with normal TLR4 and mice with mutant TLR4, leading to LPS hyporesponsiveness, were used (46). Intrauterine injection of HKE resulted in PTL in the normal TLR4 but not mutant TLR4 strain at most doses (46). At the highest HKE dose (10^{10}), 28% of mutant TLR4 females and 100% of normal TLR4 females underwent PTL (46). At 5×10^9 HKE, a dose sufficient to cause PTL in 100% of normal mice but none of the TLR4 mutant mice, cytokine and COX-2 up-regulation was observed in both strains (46). However, HPGD expression decreased in normal but not mutant females in response to HKE (46). This indicates that TLR4 may facilitate PTL by lowering prostaglandin catabolism (46).

Nonsteroidal Anti-inflammatory Drugs as Therapeutics

Because bacterially induced PTL is associated with an increase in prostaglandin production (77), inhibiting the synthesis of prostaglandins is a logical therapy in cases of potential infection-related PTL. Administration of nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit prostaglandin synthesis, have been shown to curtail the progression of both term labor and PTL (16,92–94). Currently used NSAIDs, such as indomethacin, block COX-1 and COX-2. Treatment with these drugs is associated with fetal and maternal side effects that have precluded their use (92,95). The efficacy of NSAIDs that inhibit a single COX isoform and their associated side effects were studied in mice as a potential remedy to these problems (96). Inoculation with LPS resulted in PTL within 24 h in all gravid females, whereas administration of LPS and indomethacin led to PTL in only 20% of dams (96). Most of the nonlaboring females demonstrated *in utero* fetal death (96). Coadministration of LPS and the COX-1 inhibitor SC-560 resulted in PTL in 58% of females, with 40% of nonlaboring females exhibiting *in utero* fetal demise (96). More successful was the coadministration of LPS and the COX-2 inhibitor SC-236 (96). This treatment resulted in PTL in only 8% of treated females, with 73% of the remaining females delivering viable fetuses (96). These data, in concert with the observation that 88% of gravid COX1$^{-/-}$ females treated with LPS deliver within 24 h, indicate that COX-2 derived prostaglandins are important for bacterially induced PTL and that COX-2 is a potentially important target for stopping PTL (96).

SURFACTANT PROTEIN-A AS PARTURITION SIGNAL

Pulmonary surfactant may have a role in regulating the inflammatory response associated with even normal term labor (97). Surfactant production begins in the fetal lung during the final third of gestation in humans and mice (97,98). Inadequate surfactant production results in respiratory distress in infants (98). A recent study suggests that in addition to its role in pulmonary function, secretion of surfactant, particularly surfactant protein-A (SP-A), from fetal lung has a role in signaling for parturition to begin in mice (97). It is proposed to play this role by activating amniotic fluid macrophages which travel to the maternal uterus and incite the inflammatory response (97). SP-A is found to up-regulate IL-1β and NF-κB in cultured amniotic fluid macrophages (97). Experiments using wild-type dams carrying fetuses heterozygous for β-galactosidase revealed that macrophages of fetal origin increase in the maternal uterus during the timeframe at which SP-A is secreted from fetal lung (97). Intraamniotic injection of SP-A caused PTL in gravid female mice within 6–24 h (97). Conversely, the injection of an SP-A antibody or NF-κB inhibitor led to a delay of labor more than 1 d postterm (97). In laboring humans, macrophages of fetal origin are not present in the myometrium (99,100). Although SP-A appears not to promote migration of fetal macrophages to the myometrium in women, it may have a different role in precipitating human labor (100).

CONCLUSION

The mouse has proved to be an important resource for increasing our knowledge of the processes related to parturition. Although the importance of CAPs and prostaglandins is evident in both humans and mice, the differences in progesterone regulation between the two species is more perplexing. Research into potential functional progesterone withdrawal in the human may lead us to an increased appreciation of similarity between human and murine labor. Additionally, the established murine models recapitulating infection-associated PTL are promising for increasing the understanding of inflammatory processes related to labor. Further knowledge on cervical ripening gained from the RLX and 5α-R1 knockout mice may lead us to new therapeutic targets for stimulating or

delaying labor. The expanding circadian field provides us with a new group of genes whose roles in parturition merit further exploration. The ability of 15-HPGD hypomorphic mice, and potentially mice experiencing bacterial infection, to labor without a dependence on progesterone withdrawal indicates the importance of other mechanisms that are a part of labor initiation. Because these other mechanisms crucial for labor initiation are likely shared between mice and humans, continuing analysis of rodent models should yield further understanding of the physiology of pregnancy across species.

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REFERENCES

1. Wickelgren I 2004 Premature labor. Resetting pregnancy's clock. Science 304:666–668
2. Hamilton BE, Miniño AM, Martin JA, Kochanek KD, Strobino DM, Guyer B 2007 Annual summary of vital statistics: 2005. Pediatrics 119:345–360
3. Slattery MM, Morrison JJ 2002 Preterm delivery. Lancet 360:1489–1497
4. Winkvist A, Mogren I, Hogberg U 1998 Familial patterns in birth characteristics: impact on individual and population risks. Int J Epidemiol 27:248–254
5. Porter TF, Fraser AM, Hunter CY, Ward RH, Varner MW 1997 The risk of preterm birth across generations. Obstet Gynecol 90:63–67
6. Ward K, Argyle V, Meade M, Nelson L 2005 The heritability of preterm delivery. Obstet Gynecol 106:1235–1239
7. Sugimoto Y, Yamasaki A, Segi E, Tsuboi K, Aze Y, Nishimura T, Oida H, Yoshida N, Tanaka T, Katsuyama M, Hasumoto K, Murata T, Hirata M, Ushikubi F, Negishi M, Ichikawa A, Narumiya S 1997 Failure of parturition in mice lacking the prostaglandin F receptor. Science 277:681–683
8. Challis JRG, Matthews SG, Gibb W, Lye SJ 2000 Endocrine and paracrine regulation of birth at term and preterm. Endocr Rev 21:514–550
9. Condon JC, Jeyasuria P, Faust JM, Wilson JW, Mendelson CR 2003 A decline in the levels of progesterone receptor coactivators in the pregnant uterus at term may antagonize progesterone receptor function and contribute to the initiation of parturition. Proc Natl Acad Sci USA 100:9518–9523
10. Hirsch E, Muhle R 2002 Intrauterine bacterial inoculation induces labor in the mouse by mechanisms other than progesterone withdrawal. Biol Reprod 67:1337–1341
11. Roizen JD, Asada M, Tong M, Tai HH, Muglia LJ 2008 Preterm birth without progesterone withdrawal in 15-hydroxyprostaglandin dehydrogenase hypomorphic mice. Mol Endocrinol 22:105–112
12. Cook JL, Zaragoza DB, Sung DH, Olson DM 2000 Expression of myometrial activation and stimulation genes in a mouse model of preterm labor: myometrial activation, stimulation, and preterm labor. Endocrinology 141:1718–1728
13. Brodt-Eppley J, Myatt L 1999 Prostaglandin receptors in lower segment myometrium during gestation and labor. Obstet Gynecol 93:89–93
14. Fuchs AR, Fuchs F, Husslein P, Soloff MS, Fernstrom MJ 1982 Oxytocin receptors and human parturition: a dual role for oxytocin in the initiation of labor. Science 215:1396–1398
15. Garfield RE, Sims S, Daniel EE 1977 Gap junctions: their presence and necessity in myometrium during parturition. Science 198:958–960
16. Skarnes RC, Harper MJ 1972 Relationship between endotoxin-induced abortion and the synthesis of prostaglandin F. Prostaglandins 1:191–203
17. Piekorz RP, Gingras S, Hoffmeyer A, Ihle JN, Weinstein Y 2005 Regulation of progesterone levels during pregnancy and parturition by signal transducer and activator of transcription 5 and 20alpha-hydroxysteroid dehydrogenase. Mol Endocrinol 19:431–440
18. Wiest WG 1968 On the funciton of 20 alpha-hydroxypren-4-en-3-one during parturition in the rat. Endocrinology 83:1181–1184
19. Sugimoto Y, Hasumoto K, Namba T, Irie A, Katsuyama M, Negishi M, Kakizuka A, Narumiya S, Ichikawa A 1994 Cloning and expression of a cDNA for mouse prostaglandin F receptor. J Biol Chem 269:1356–1360
20. Gross G, Imamura T, Muglia L 2000 Gene knockout mice in the study of parturition. J Soc Gynecol Investig 7:88–95
21. Bonventre JV, Huang Z, Taheri MR, O'Leary E, Li E, Moskowitz MA, Sapirstein A 1997 Reduced fertility and postischaemic brain injury in mice deficient in cytosolic phospholipase A2. Nature 390:622–625
22. Gross GA, Imamura T, Luedke C, Vogt SK, Olson LM, Nelson DM, Sadovsky Y, Muglia LJ 1998 Opposing actions of prostaglandins and oxytocin determine the onset of murine labor. Proc Natl Acad Sci USA 95:11875–11879
23. Langenbach R, Morham SG, Tiano HF, Loftin CD, Ghanayem BI, Chulada PC, Mahler JF, Lee CA, Goulding EH, Kluckman KD, Kim HS, Smithies O 1995 Prostaglandin synthase 1 gene disruption in mice reduces arachidonic acid-induced inflammation and indomethacin-induced gastric ulceration. Cell 83:483–492
24. Uozumi N, Kume K, Nagase T, Nakatani N, Ishii S, Tashiro F, Komagata Y, Maki K, Ikuta K, Ouchi Y, Miyazaki J, Shimizu T 1997 Role of cytosolic phospholipase A2 in allergic response and parturition. Nature 390:618–621
25. Lim H, Paria B, Das S, Dinchuk J, Langenbach R, Trzaskos J, Dey S 1997 Multiple female reproductive failures in cyclooxygenase 2-deficient mice. Cell 91:197–208
26. Tsuboi K, Sugimoto Y, Iwane A, Yamamoto K, Yamamoto S, Ichikawa A 2000 Uterine expression of prostaglandin H2 synthase in late pregnancy and during parturition in prostaglandin F receptor-deficient mice. Endocrinology 141:315–324
27. Herrmann W, Wyss R, Riondel A, Philibert D, Teutsch G, Sakiz E, Baulieu E 1982 The effects of an antiprogesterone steroid in women: interruption of the menstrual cycle and of early pregnancy. C R Seances Acad Sci III 294:933–938
28. Vegeto E, Shahbaz M, Wen D, Goldman M, O'Malley B, McDonnell D 1993 Human progesterone receptor A form is a cell- and promoter-specific repressor of human progesterone receptor B function. Mol Endocrinol 7:1244–1255
29. Zeng Z, Velarde MC, Simmen FA, Simmen RC 2008 Delayed parturition and altered myometrial progesterone receptor isoform a expression in mice null for Kruppel-like factor 9. Biol Reprod 78:1029–1037
30. Condon JC, Hardy DB, Kovaric K, Mendelson CR 2006 Up-regulation of the progesterone receptor (PR)-C isoform in laboring myometrium by activation of nuclear factor-kappaB may contribute to the onset of labor through inhibition of PR function. Mol Endocrinol 20:764–775
31. Mesiano S, Chan EC, Fitter JT, Kwek K, Yeo G, Smith R 2002 Progesterone withdrawal and estrogen activation in human parturition are coordinated by progesterone receptor A expression in the myometrium. J Clin Endocrinol Metab 87:2924–2930
32. Challis J, Lye S 1994 The Physiology of Reproduction. Raven, New York, pp 1003–1004
33. Gainer H, Wray S 1994 The Physiology of Reproduction. Raven, New York, pp 1099–1129
34. Zingg HH, Rozen F, Chu K, Larcher A, Arslan A, Richard S, Lefebvre D 1995 Oxytocin and oxytocin receptor gene expression in the uterus. Recent Prog Horm Res 50:255–273
35. Nishimori K, Young LJ, Guo Q, Wang Z, Insel TR, Matzuk MM 1996 Oxytocin is required for nursing but is not essential for parturition or reproductive behavior. Proc Natl Acad Sci USA 93:11699–11704
36. Takayanagi Y, Yoshida M, Bielsky IF, Ross HE, Kawamata M, Onaka T, Yanagisawa T, Kimura T, Matzuk MM, Young LJ, Nishimori K 2005 Pervasive social deficits, but normal parturition, in oxytocin receptor-deficient mice. Proc Natl Acad Sci USA 102:16096–16101
37. Young WS 3rd, Shepard E, Amico J, Hennighausen L, Wagner KU, LaMarca ME, McKinney C, Ginns EI 1996 Deficiency in mouse oxytocin prevents milk ejection, but not fertility or parturition. J Neuroendocrinol 8:847–853
38. Imamura T, Luedke CE, Vogt SK, Muglia LJ 2000 Oxytocin modulates the onset of murine parturition by competing ovarian and uterine effects. Am J Physiol Regul Integr Comp Physiol 279:R1061–R1067
39. Doring B, Shynlova O, Tsui P, Eckardt D, Janssen-Bienhold U, Hofmann F, Feil S, Feil R, Lye SJ, Willecke K 2006 Ablation of connexin43 in uterine smooth muscle cells of the mouse causes delayed parturition. J Cell Sci 119:1715–1722
40. Reaume AG, de Sousa PA, Kulkarni S, Langille BL, Zhu D, Davies TC, Juneja SC, Kidder GM, Rossant J 1995 Cardiac malformation in neonatal mice lacking connexin43. Science 267:1831–1834
41. Branda CS, Dymecki SM 2004 Talking about a revolution: the impact of site-specific recombinases on genetic analyses in mice. Dev Cell 6:7–28
42. Okita RT, Okita JR 1996 Prostaglandin-metabolizing enzymes during pregnancy: characterization of NAD(+)-dependent prostaglandin dehydrogenase, carbonyl reductase, and cytochrome P450-dependent prostaglandin omega-hydroxylase. Crit Rev Biochem Mol Biol 31:101–126
43. Tai HH, Ensor CM, Tong M, Zhou H, Yan F 2002 Prostaglandin catabolizing enzymes. Prostaglandins Other Lipid Mediat 68–69:483–493
44. Sangha RK, Walton JC, Ensor CM, Tai HH, Challis JR 1994 Immunohistochemical localization, messenger ribonucleic acid abundance, and activity of 15-hydroxyprostaglandin dehydrogenase in placenta and fetal membranes during term and preterm labor. J Clin Endocrinol Metab 78:982–989
45. Van Meir CA, Ramirez MM, Matthews SG, Calder AA, Keirse MJ, Challis JR 1997 Chorionic prostaglandin catabolism is decreased in the lower uterine segment with term labour. Placenta 18:109–114
46. Wang H, Hirsch E 2003 Bacterially-induced preterm labor and regulation of prostaglandin-metabolizing enzyme expression in mice: the role of toll-like receptor 4. Biol Reprod 69:1957–1963
47. Khan RN, Smith SK, Morrison JJ, Ashford ML 1993 Properties of large-conductance K+ channels in human myometrium during pregnancy and labour. Proc Biol Sci 251:9–15
48. Lundgren DW, Moore JJ, Chang SM, Collins PL, Chang AS 1997 Gestational changes in the uterine expression of an inwardly rectifying K+ channel, ROMK. Proc Soc Exp Biol Med 216:57–64
49. Mazzone JN, Kaiser RA, Buxton IL 2002 Calcium-activated potassium channel expression in human myometrium: effect of pregnancy. Proc West Pharmacol Soc 45:184–186
50. Bond CT, Sprengel R, Bissonnette JM, Kaufmann WA, Pribnow D, Neelands T, Storck T, Baetscher M, Jerecic J, Maylie J, Knaus HG, Seeburg PH, Adelman JP 2000 Respiration and parturition affected by conditional overexpression of the Ca2+-activated K+ channel subunit, SK3. Science 289:1942–1946
51. Pierce SL, Kresowik JD, Lamping KG, England SK 2008 Overexpression of SK3 channels dampens uterine contractility to prevent preterm labor in mice. Biol Reprod 78:1058–1063
52. Leppert PC 1995 Anatomy and physiology of cervical ripening. Clin Obstet Gynecol 38:267–279
53. Downing SJ, Sherwood OD 1985 The physiological role of relaxin in the pregnant rat. I. The influence of relaxin on parturition. Endocrinology 116:1200–1205

54. Kroc RL, Steinetz BG, Beach VL 1959 The effects of estrogens, progestagens, and relaxin in pregnant and nonpregnant laboratory rodents. Ann NY Acad Sci 75:942–980
55. Evans BA, John M, Fowler KJ, Summers RJ, Cronk M, Shine J, Tregear GW 1993 The mouse relaxin gene: nucleotide sequence and expression. J Mol Endocrinol 10:15–23
56. O'Byrne EM, Steinetz BG 1976 Radioimmunoassay (RIA) of relaxin in sera of various species using an antiserum to porcine relaxin. Proc Soc Exp Biol Med 152:272–276
57. Zhao L, Roche PJ, Gunnersen JM, Hammond VE, Tregear GW, Wintour EM, Beck F 1999 Mice without a functional relaxin gene are unable to deliver milk to their pups. Endocrinology 140:445–453
58. Krajnc-Franken MA, van Disseldorp AJ, Koenders JE, Mosselman S, van Duin M, Gossen JA 2004 Impaired nipple development and parturition in LGR7 knockout mice. Mol Cell Biol 24:687–696
59. Zhao L, Samuel CS, Tregear GW, Beck F, Wintour EM 2000 Collagen studies in late pregnant relaxin null mice. Biol Reprod 63:697–703
60. Mahendroo MS, Cala KM, Russell DW 1996 5 alpha-reduced androgens play a key role in murine parturition. Mol Endocrinol 10:380–392
61. Mahendroo MS, Porter A, Russell DW, Word RA 1999 The parturition defect in steroid 5alpha-reductase type 1 knockout mice is due to impaired cervical ripening. Mol Endocrinol 13:981–992
62. Andersson S, Minjarez D, Yost N, Word R 2008 Estrogen and progesterone metabolism in the cervix during pregnancy and parturition. J Clin Endocrinol Metab 93:2366–2374
63. Anderson JC, Raynes JG, Fitzpatrick RJ, Dobson H 1991 Increased hyaluronate synthesis and changes in glycosaminoglycan ratios and molecular weight of proteoglycans synthesised by cultured cervical tissue from ewes at various stages of pregnancy. Biochim Biophys Acta 1075:187–190
64. Downing SJ, Sherwood OD 1986 The physiological role of relaxin in the pregnant rat. IV. The influence of relaxin on cervical collagen and glycosaminoglycans. Endocrinology 118:471–479
65. El Maradny E, Kanayama N, Kobayashi H, Hossain B, Khatun S, Liping S, Kobayashi T, Terao T 1997 The role of hyaluronic acid as a mediator and regulator of cervical ripening. Hum Reprod 12:1080–1088
66. Rajabi MR, Quillen EW Jr, Nuwayhid BS, Brandt R, Poole AR 1992 Circulating hyaluronic acid in nonpregnant, pregnant, and postpartum guinea pigs: elevated levels observed at parturition. Am J Obstet Gynecol 166:242–246
67. Laurent TC, Fraser JR 1992 Hyaluronan. FASEB J 6:2397–2404
68. Straach KJ, Shelton JM, Richardson JA, Hascall VC, Mahendroo MS 2005 Regulation of hyaluronan expression during cervical ripening. Glycobiology 15:55–65
69. Anderson J, Brown N, Mahendroo MS, Reese J 2006 Utilization of different aquaporin water channels in the mouse cervix during pregnancy and parturition and in models of preterm and delayed cervical ripening. Endocrinology 147:130–140
70. Timmons BC, Mitchell SM, Gilpin C, Mahendroo MS 2007 Dynamic changes in the cervical epithelial tight junction complex and differentiation occur during cervical ripening and parturition. Endocrinology 148:1278–1287
71. Reppert SM, Weaver DR 2002 Coordination of circadian timing in mammals. Nature 418:935–941
72. Glattre E, Bjerkedal T 1983 The 24-hour rhythmicity of birth. A populational study. Acta Obstet Gynecol Scand 62:31–36
73. Kaiser IH, Halberg F 1962 Circadian periodic aspects of birth. Ann NY Acad Sci 98:1056–1068
74. Miller BH, Olson SL, Turek FW, Levine JE, Horton TH, Takahashi JS 2004 Circadian clock mutation disrupts estrous cyclicity and maintenance of pregnancy. Curr Biol 14:1367–1373
75. Roizen J, Luedke CE, Herzog ED, Muglia LJ 2007 Oxytocin in the circadian timing of birth. PLoS One 2:e922
76. Gibbs RS, Romero R, Hillier SL, Eschenbach DA, Sweet RL 1992 A review of premature birth and subclinical infection. Am J Obstet Gynecol 166:1515–1528
77. Hirsch E, Wang H 2005 The molecular pathophysiology of bacterially induced preterm labor: insights from the murine model. J Soc Gynecol Investig 12:145–155
78. Liggins G, Fairclough R, Frieves S, Forster C, Knox B 1977 Parturition in the Sheep. Elsevier, Amsterdam, pp 5–30
79. Osman I, Young A, Ledingham MA, Thomson AJ, Jordan F, Greer IA, Norman JE 2003 Leukocyte density and pro-inflammatory cytokine expression in human fetal membranes, decidua, cervix and myometrium before and during labour at term. Mol Hum Reprod 9:41–45
80. Yellon SM, Mackler AM, Kirby MA 2003 The role of leukocyte traffic and activation in parturition. J Soc Gynecol Investig 10:323–338
81. Fidel PI Jr, Romero R, Maymon E, Hertelendy F 1998 Bacteria-induced or bacterial product-induced preterm parturition in mice and rabbits is preceded by a significant fall in serum progesterone concentrations. J Matern Fetal Med 7:222–226
82. Baggia S, Gravett MG, Witkin SS, Haluska GJ, Novy MJ 1996 Interleukin-1 beta intra-amniotic infusion induces tumor necrosis factor-alpha, prostaglandin production, and preterm contractions in pregnant rhesus monkeys. J Soc Gynecol Investig 3:121–126
83. Brown NL, Alvi SA, Elder MG, Bennett PR, Sullivan MH 1998 Interleukin-1beta and bacterial endotoxin change the metabolism of prostaglandins E2 and F2alpha in intact term fetal membranes. Placenta 19:625–630
84. Bry K, Hallman M 1993 Transforming growth factor-beta 2 prevents preterm delivery induced by interleukin-1 alpha and tumor necrosis factor-alpha in the rabbit. Am J Obstet Gynecol 168:1318–1322
85. Romero R, Mazor M, Tartakovsky B 1991 Systemic administration of interleukin-1 induces preterm parturition in mice. Am J Obstet Gynecol 165:969–971
86. Challis JRG 2000 Mechanism of parturition and pretem labor. Obstet Gynecol Surv 55:650–660
87. Hirsch E, Muhle R, Mussalli G, Blanchard R 2002 Bacterially induced preterm labor in the mouse does not require maternal interleukin-1 signaling. Am J Obstet Gynecol 186:523–530
88. Reznikov LL, Fantuzzi G, Selzman CH, Shames BD, Barton HA, Bell H, McGregor JA, Dinarello CA 1999 Utilization of endoscopic inoculation in a mouse model of intrauterine infection-induced preterm birth: role of interleukin 1beta. Biol Reprod 60:1231–1238
89. Yoshimura K, Hirsch E 2003 Interleukin-6 is neither necessary nor sufficient for preterm labor in a murine infection model. J Soc Gynecol Investig 10:423–427
90. Fidel PL Jr, Romero R, Cutright J, Wolf N, Gomez R, Araneda H, Ramirez M, Yoon BH 1997 Treatment with the interleukin-I receptor antagonist and soluble tumor necrosis factor receptor Fc fusion protein does not prevent endotoxin-induced preterm parturition in mice. J Soc Gynecol Investig 4:22–26
91. Hirsch E, Filipovich Y, Mahendroo M 2006 Signaling via the type I IL-1 and TNF receptors is necessary for bacterially induced preterm labor in a murine model. Am J Obstet Gynecol 194:1334–1340
92. Besinger RE, Niebyl JR, Keyes WG, Johnson TR 1991 Randomized comparative trial of indomethacin and ritodrine for the long-term treatment of preterm labor. Am J Obstet Gynecol 164:981–986; discussion 986–988
93. Fidel PL Jr, Romero R, Wolf N, Cutright J, Ramirez M, Araneda H, Cotton DB 1994 Systemic and local cytokine profiles in endotoxin-induced preterm parturition in mice. Am J Obstet Gynecol 170:1467–1475
94. Kurki T, Eronen M, Lumme R, Ylikorkala O 1991 A randomized double-dummy comparison between indomethacin and nylidrin in threatened preterm labor. Obstet Gynecol 78:1093–1097
95. Norton ME, Merrill J, Cooper BA, Kuller JA, Clyman RI 1993 Neonatal complications after the administration of indomethacin for preterm labor. N Engl J Med 329:1602–1607
96. Gross G, Imamura T, Vogt S, Wozniak D, Nelson D, Sadovsky Y, Muglia L 2000 Inhibition of cyclooxygenase-2 prevents inflammation-mediated preterm labor in the mouse. Am J Physiol Regul Integr Comp Physiol 278:R1415–R1423
97. Condon JC, Jeyasuria P, Faust JM, Mendelson CR 2004 Surfactant protein secreted by the maturing mouse fetal lung acts as a hormone that signals the initiation of parturition. Proc Natl Acad Sci USA 101:4978–4983
98. Avery ME, Mead J 1959 Surface properties in relation to atelectasis and hyaline membrane disease. AMA J Dis Child 97:517–523
99. Kim CJ, Kim JS, Kim YM, Cushenberry E, Richani K, Espinoza J, Romero R 2006 Fetal macrophages are not present in the myometrium of women with labor at term. Am J Obstet Gynecol 195:829–833
100. Leong AS, Norman JE, Smith R 2008 Vascular and myometrial changes in the human uterus at term. Reprod Sci 15:59–65