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Review article

Intrauterine infection as a possible trigger for labor: the role of toll-like receptors and proinflammatory cytokines

Aishah Alamrani[a], Saeed Mahmoud[b], Mohammed Alotaibi[c]
[a]*College of Applied Medical Sciences, Tabuk University, Tabuk, Saudi Arabia*
[b]*Department of Obstetrics and Gynaecology, College of Medicine, King Saud University and King Khalid University Hospital, Riyadh 11461, Saudi Arabia*
[c]*Department of Physiology, College of Medicine, King Saud University and King Khalid University Hospital, Riyadh 11461, Saudi Arabia*

Background: The mechanisms underlying the initiation of premature uterine contractions during pregnancy are not fully understood. It is now widely accepted that proinflammatory cytokines are key mediators of the inflammatory signaling pathways in term or preterm labor. However, the exact triggers for inflammation-induced labor remain to be identified.
Method: We review the published literature and summarize the possible pathophysiological mechanisms underlying the initiation of uterine contractions with a particular emphasis on intrauterine infection.
Result: Term and preterm labor are associated with inflammation-induced infiltration of leukocytes into the myometrium, cervix, decidua, and fetal membranes. During labor, peripheral leukocytes invade uterine tissues and secrete bactericidal mediators such as proinflammatory cytokines, resulting in initiation of uterine activity and labor. When these pathophysiological mechanisms occur too early in pregnancy, they may lead to preterm labor. The initiation of inflammatory cascades within the myometrium or intrauterine compartments must be tightly regulated to prevent premature activation of the inflammatory signals and to prevent premature uterine activation.
Conclusion: Labor in humans and rodents is associated with inflammation and the increased uterine contractions during labor are regulated by a complex of signaling pathways between pro- and antiinflammatory cytokines and between mother and fetus. Labor can be triggered from different sources including maternal, fetal and general infection. Therefore it is vital for pregnant women to avoid infection-related pathology and seek medical advice immediately to avoid premature uterine contractions or perhaps abortion.

Keywords: Cytokines, infection, intrauterine, labor, myometrium, TLRs, uterus

Labor is a complex process characterized by coordinated strong and progressive uterine activity until the neonate or baby is delivered. The mechanisms underlying the transition from uterine quiescence during pregnancy into a fully active contracting uterus are not fully understood. Normal human pregnancy lasts for 40 weeks and when a neonate is delivered before 37 weeks of gestation, it is considered as a preterm birth. According to the World Health Organization (WHO), about 15 million babies are born preterm (before completing 37 weeks in utero) every year in the world and this number is rising progressively. Preterm birth is subcategorized based on gestational age as: extremely preterm (<28 weeks of gestation), very preterm (28 to <32 weeks), and moderate to late preterm (32 to <37 weeks).

Preterm birth accounts for more than 50% of perinatal mortality and long-term childhood morbidity [1]. The causes of preterm birth are multifactorial. Most preterm births occur spontaneously, but some occur because of medically indicated interventions such as the induction of labor or birth of the neonate by emergency cesarean section to circumvent maternal or fetal risks. Spontaneous labor (with intact fetal membranes or preterm premature rupture of

Correspondence to: Mohammed Alotaibi, Department of Physiology, College of Medicine, King Saud University and King Khalid University Hospital, Riyadh 11461, Saudi Arabia. E-mail: mfalotaibi@ksu.edu.sa

membranes can by caused by infection (intrauterine or extra uterine), inflammation, multiple pregnancies, disruption of maternal hormones, placental abruption, and other factors [2, 3]. Common predisposing factors of preterm birth are chronic conditions such as diabetes mellitus [4] and hypertension [5]. Although many of the causes underlying preterm birth remain unknown, it has been predicted that 40% of spontaneous preterm labor is caused by intrauterine infections [6].

Labor and infections

The main cause of uterine infections is the presence of bacteria that can invade the uterus from different sources. Bacteria may migrate from the abdominal cavity through the fallopian tubes, from the placenta, or ascend from vagina, which may enter eventually the uterine cavity and cause acute or chronic infection [7]. In addition, bacteria can easily traverse the maternal–fetal membrane to cause uterine infection [8]. Bacterial infection can occur at any site in the uterine tissue. It can occur between the maternal tissue and the fetal membrane (choriodecidual infection), within the fetal membrane (chorioamnionitis), within the amniotic fluid (amnionitis), or it can occur within the fetal umbilical cord [7]. Infection or inflammation in amniotic fluid is recognized as a major factor that leads to preterm birth [9]. Usually, the amniotic fluid is sterile, but >1% of pregnant women not in labor at term are likely to have bacterial infection in their amniotic fluid [10]. However, evidence has shown that maternal–fetal membranes [11, 12] and amniotic fluid [13, 14] are not always sterile in pregnant women. Occurrence of infection at any site in female reproductive tract during pregnancy is critical as it may trigger premature strong uterine activity leading to preterm birth.

Term and preterm labor

The exact triggers that induce the onset of labor are unknown. Parturition includes cervical ripening (dilation and effacement), myometrial activation, and fetal membrane rupture/decidual activation. This process is believed to involve influx of immune cells into the myometrium and the decidua to produce an inflammatory response, which promotes the contraction of the myometrium and initiation of labor [15].

The myometrium undergoes different stages of differentiation from early pregnancy to labor and postpartum period. First, the proliferation phase of myocytes during the first trimester, second, the growth phase involving hypertrophy of the myocytes and elaboration of interstitial matrix during the second and the third trimesters, and finally the contractile phase when the growth stops and there is an increase in the expression of various cell adhesion molecules and contraction associated proteins (CAPs) including (gap junctions protein such as connexin 43 or Cx43, receptors for oxytocin and stimulatory prostaglandins, Na^+ and Ca^{2+} ion channels). As term approaches the myometrium becomes more sensitive to uterotonins that increase uterine contractions, such as oxytocin, and prostaglandin E_2 (PGE_2) and F2α (PGF2α) [15, 16].

The key molecules that control the formation of the contractile phenotype of myometrium are extracellular matrix (ECM) proteins, cell–matrix adhesion complexes, contractile proteins, and inflammatory cytokines [15]. At term, the myometrium is more sensitive to contraction triggers because of adequate expression of these contractile proteins. When CAPs are fully expressed, the myometrium becomes well prepared for labor. In addition, accumulating data suggest that labor whether at term or preterm is considered to be inflammatory process [17-20]. During labor there are coordinated strong uterine contractions, progressive dilation of the cervix, and rupture of amniotic membrane, all of which are associated with infiltration of leukocytes, local release of proinflammatory cytokines, and inflammation of decidua and myometrium, which further increase the uterine activity [21]. However, in the case of pathogenic infection, the uterus is infiltrated by proinflammatory cytokines that activate the uterus too early, resulting in preterm labor [7]. Bacteria can breach the amniotic membrane, and trigger a sequential series of immune responses including the induction of proinflammatory cytokines, release of stimulatory prostaglandins, and eventually resulting in initiation of early uterine contractions. Furthermore, the placenta can produce tumor necrosis factor-a (TNF-α), interleukin (IL)-1α, IL-6, IL-8, and IL-10 in response to lipopolysaccharide (LPS) [22, 23]. However, what triggers the release of proinflammatory cytokines during labor is not fully understood. The first line of defence during bacterial or other pathogenic infections is the activation of the innate immune system. Toll-like receptors (TLRs) are part of this system, which recognizes pathogens through various ligands, and initiates a cascade of immune response including

inflammation and infiltration of immune cells into the inflamed tissues. This inflammatory and immune response is believed to induce labor through multiple cellular mechanisms.

Toll-like receptors

TLRs are essential transmembrane receptors of the innate immune system. They recognize ligands from bacterial, fungal, or viral infections collectively known as pathogen associated molecular patterns (PAMPs) in nonspecific way. The TLRs are present in the cells of innate immunity, such as macrophages, dendritic cells, neutrophils, natural killer cells (NK), and epithelial cells [24, 25]. Furthermore, the endothelial cells in the endometrium also express TLRs [26], which support the female reproductive tract to fight infections. TLRs are further classified into two types, TLRs such as TLR1, TLR2, TLR4, TLR5, and TLR6 that recognize extracellular molecules such as lipids and proteins expressed on the cell membrane of the pathogen , or those such as TLR3, TLR7, TLR8, and TLR9 that can recognize nucleic acids from pathogens [27].

Activation of TLRs results in the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), c-Jun N-terminal kinase, and p38 mitogen-activated protein kinase (MAPK), which induce the expression of proinflammatory cytokines such as TNF-α, IL-1, IL-6 [28], IL-10, IL12 [29], and type I interferon [30].

Furthermore, activation of NF-kB has been reported to directly increase the expression of CAPs such as cyclooxygenase-2 (COX-2), PGE_2, gap junction protein connexin 43, and oxytocin receptor, which can all promote labor [31].

The TLRs also recognize and respond to internal ligands called damage-associated molecular patterns (DAMPs) such as reactive oxygen species, proteins released from dead or dying cells, such as high-mobility group box protein 1 (HMGB1), surfactant protein A, fibrinogen, breakdown products of extracellular matrix, such as fragments of fibronectin, hyaluronic acid oligosaccharides, and eosinophil-derived neurotoxin (EDN) [32]. Romero et al. have reported that HMGB1 is highly expressed in preterm labor associated with early rupture of membrane compared with preterm labor with intact membranes, suggesting that rupture of membranes is linked to infection [33]. Nevertheless, the magnitude of the relationship between the activation of different TLRs during labor to DAMPs requires further research and analysis.

The TLRs 1 to 6 are expressed in endometria of nonpregnant women. However, the expression of TLRs 7 to 10 varies among different studies [21, 26, 34-37]. Although it is presumed that the expression of TLRs may be regulated by female sex hormones, the expression level of TLRs 2, 3, 4, 5, 6, 9, and 10 in human endometrium changes in a menstrual cycle-dependent manner. The expression of TLRs 2, 3, 4, and 9 are higher during the premenstrual period and lower in the preovulatory period [36, 37].

The expression of TLRs in the myometrium and decidua during pregnancy is not fully elucidated, although all 10 TLRs are present in the human placenta [38, 39], and decidua [40]. Moreover, TLR2 and TLR4 mRNA are highly expressed in fetal membrane during term or preterm delivery [41]. In addition, there is a difference in the expression of TLRs on immune cells within the uterine compartments compared with immune cells in the peripheral circulation, reflecting the distinctive local features of immune reaction in the uterine compartments during labor [42, 43]. The activated TLRs in the uterus from external or internal ligands will shift the macrophages within the uterus from an immunosuppressant [44] to an immunostimulant phenotype [45].

However, during pregnancy the macrophages in the decidua and the placenta act as a suppressor or modulator of the immune response, which help prevent premature inflammation and the onset of labor. These macrophages are believed to function as immune stimulants under the influence of inflammatory cytokines at the onset of labor.

Studies have found an increase in the expression of TLR2 and TLR4 in human decidua, amnion, and myometrium during preterm labor [46, 47]. Moreover, TLR4 has been implicated in the pathophysiology of the preterm labor in mice and human [48, 49] and its expression is increased incrementally during gestation and peaks at labor [50]. In addition, TLR2 and TLR3 are able to induce preterm labor in pregnant mice [51]. Thus, these studies suggest that TLRs are activated during labor with strong link to infection-derived preterm labor. A summary of the proposed mechanism on how TLRs mediate infection and facilitate the onset of labor is illustrated in **Figure 1**.

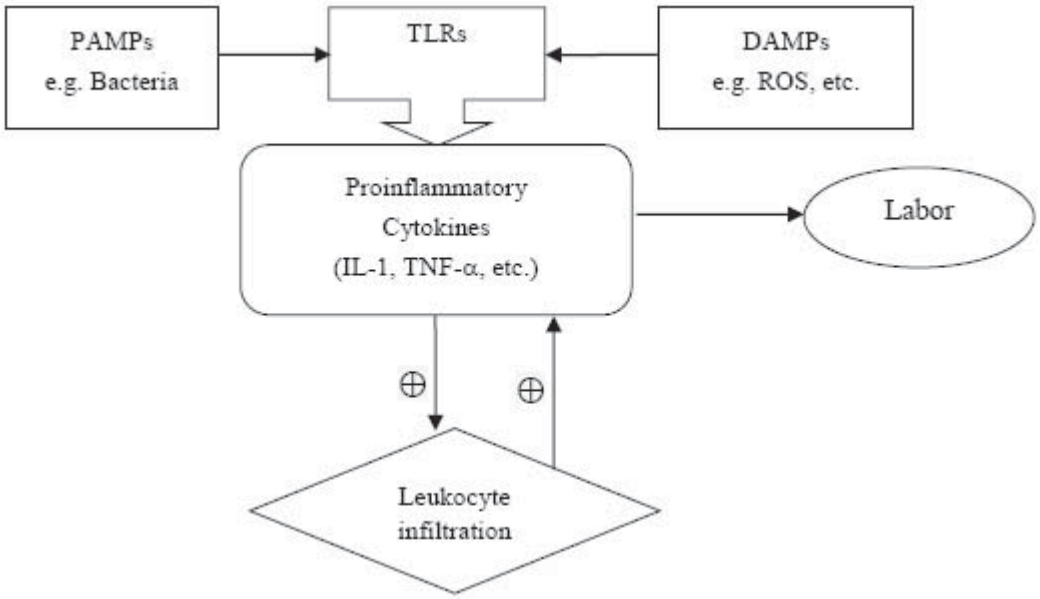

Figure 1. Schematic illustrating the role of toll-like receptors (TLRs) and proinflammatory cytokines in the onset of labor. Both pathogen associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) produced in the uterus from different sources can activate various TLRs leading to the production of proinflammatory cytokines. The proinflammatory cytokines induce leukocyte infiltration and further increase the inflammatory cytokines directly or indirectly within the myometrium. This would create a positive-feedback loop by activating myometrial inflammation resulting in initiation of labor. ROS, reactive oxygen species; IL-1, interleukin-1; TNF-α, tissue necrosis factor α.

Inflammation-induced labor

It is believed that the myometrium itself may act to regulate the immune response, which contributes to the development of an autoinflammatory reaction promoting term or preterm labor [52, 53]. The myometrial smooth muscles express proinflammatory cytokines and chemokines, which could activate and induce migration of peripheral leukocytes (particularly the neutrophils and macrophages) into the inflamed myometrium. Studies have reported that most preterm or term labor is associated with intrauterine inflammation resulting in migration of inflammatory cells into the myometrium [54, 55]. In addition, it has been reported that inflammation of the uterus could upregulate the proinflammatory cytokines/chemokines in the cervix, myometrium, and fetal membranes [19]. However, increased influx of inflammatory cells into the myometrium is associated with the activation of CAPs, which eventually promote the onset labor [56-58].

Role of progesterone

Progesterone is the primary hormone secreted by ovary and placenta and it is essential to maintain uterine quiescence throughout pregnancy. It is also known that progesterone is an important regulator of immune system during gestation.

Progesterone can maintain uterine quiescence during pregnancy and can prevent uterine contractility by various molecular mechanisms. It helps reduce the expression of genes that enhance uterine contractility such as oxytocin receptor [58] and the gap junction protein connexin 43 [59]. There is a 9-fold reduction in the expression of progesterone receptors in the decidua during labor compared to decidua before labor [60] suggesting a role for progesterone in maintaining the uterine quiescence and preventing early uterine activity.

Interestingly, progesterone was found to possess immunomodulatory actions. It has been shown that progesterone decreases leukocyte migration into the uterus [61]. Flores-Espinosa et al. reported that progesterone could significantly reduce the stimulation of TLR4 by the bacterial toxins and block the production of proinflammatory cytokines such as TNF-α, IL-6, IL-8, and IL-10 in prelabor human amniotic epithelium [62], suggesting that progesterone is an inhibitory hormone preventing leukocyte infiltration and aiding uterine quiescence [63, 64]. Moreover, progesterone has a modulatory effect on the TLR-

mediated immune response, which could decrease the production of IL-6, IL12, and nitric oxide [63, 64]. In addition, progesterone inhibits the TLR-mediated activation of NF-κB via its glucocorticoid receptor [27], which helps maintain uterine quiescence during pregnancy.

Cytokines and chemokines

Cytokines are a diverse group of small proteins, peptides, or glycoproteins that act as signaling molecules, which are secreted by various cells in the body, primarily the leukocytes. In peripheral blood, cytokines usually circulate in very low concentrations, and their concentrations can increase by a thousand fold during inflammation or infection [65]. Each cytokine binds to its specific receptor present on its target cell membrane to facilitate intercellular communication. The migration of peripheral leukocytes into the inflamed tissues is mediated primarily by chemotactic cytokines (chemokines).

About 40 chemokine proteins and approximately 20 chemokine receptors have been described [66]. In addition to their ability to attract various leukocytes into the site of inflammation, chemokines can also regulate the homing of leukocytes within the inflamed tissues, promote angiogenesis and angiostasis, and stimulate neutrophil granulation [67, 68]. Hamilton et al. identified 6 chemokines in the inflamed uterine decidua during term or preterm labor, which include chemokine (C-C motif) ligand (CCL)2, CCL4, CCL5, chemokine (C-X-C motif) ligand (CXCL)8, and CXCL10 [69]. Furthermore, CCL8 is upregulated in preterm labor, suggesting a strong correlation between infection and premature activation of the uterus [69].

It has been suggested that within uterine/ intrauterine tissues, the induction of local inflammatory mediators is facilitated by immune regulators that contribute to molecular processes leading to labor such as cervical ripening, rupture of fetal membranes, and activation of uterine activity [70]. Leukocytes (macrophages, neutrophils, and T-lymphocytes) infiltrate the myometrium during labor, which further augment uterine activity [55, 71]. In addition, leukocyte infiltration into the amniotic fluid, placenta, fetal membranes, and decidua [72, 73] occurs during the cervical effacement and parturition [74].

Furthermore, the number of these leukocytes was found to be higher in term and noninflamed preterm labor human decidual samples than term nonlabor samples [75].The decidua (endometrium of pregnant women) and the myometrium can produce chemokines, and the association between the recruitment of leukocytes and the production of a specific chemokine is not fully described [76, 77]. The major source of cytokines found in the myometrium, cervix, placenta, and fetal membranes during labor is the infiltrated leukocytes [19]. In addition, CCL2 was found highly expressed in the amniotic fluid and within the cervical secretions during both term and preterm labor [78-80], suggesting the involvement of local cytokines during labor. NF-κB is a transcription factor associated with cellular inflammation and can be activated by proinflammatory cytokines. During the onset of labor, NF-κB can be activated by IL-1β, TNF-α, and LPS resulting in NF-κB-induced COX-2 [31, 81]. Other studies have shown that NF-κB is associated with the human labor, and functions to increase the expression of COX-2 and prostaglandin needed for uterine contractions during labor [82]. Moreover, inhibition of NF-κB can delay the process of preterm labor in pregnant mice [83]. Thus, activation of NF-κB could be involved in the pathology of preterm labor. Further studies are needed to determine its implication in human parturition.

Matrix Metalloproteinases

Matrix metalloproteinases (MMPs) are enzymes capable of degrading extracellular matrix (ECM) macromolecules and collagens. A few weeks before the onset of labor there is a gradual and progressive degradation and remodeling of the ECM in the placenta, fetal membrane, and cervix. MMPs are the major factors that facilitate this degradation and are released through degranulation of neutrophil granulocytes by IL-8 [84]. The increased expression of MMPs as term approaches contributes to the degradation of the ECM, which results in fetal membrane rupture, placental separation, and cervical ripening [85]. At term, MMP-9 is the major matrix metalloproteinase involved in labor (as reviewed in [86]). In addition, proinflammatory cytokines are important regulators of trophoblastic MMP secretion from the placenta [87]. Moreover, IL-8 and IL-6 increase significantly in the human cervix during the ripening process [88]. These data suggest that activation of leukocytes, the release of proinflammatory cytokines within the inflamed uterine compartments, and the released MMPs could all initiate the onset of labor.

Molecular mechanisms of leukocyte infiltration into the uterine tissues

Infiltration of leukocytes into the myometrium occurs during both preterm and term labor [71]. However, the early onset of labor is characterized by cervical ripening with the accumulation of leukocytes (mainly macrophages and neutrophils) in the cervical stroma [89]. The reasons for leukocyte infiltration into the uterine tissues are not fully understood. Nevertheless, these cells seem to be attracted to the site of inflammation by chemokines (e.g., CCL2, CXCL1) and secrete proinflammatory cytokines (e.g., IL1β, IL6, and TNF-α), prostaglandins, and MMPs [90, 91] that further enhance the inflammatory process in the uterus. The highest level of leukocyte infiltration and cytokine secretion during labor occurs in the uterine decidua [92]. Macrophages are predominant among the infiltrated leukocytes while massive infiltration of neutrophils has been reported in infections [93]. The ability of the infiltrated leukocytes to induce contraction in smooth muscles was observed and studied in the pathogenesis of asthma, a chronic inflammatory disorder of the airway characterized by smooth muscle spasm (bronchospasm). However, bronchospasm induced by the infiltrated leukocytes and the inflammatory process, is mediated via prostaglandins and other mediators including histamine and cysteinyl-leukotrienes [94].

The origin of the signals for leukocyte infiltration and subsequent tissue inflammation is not fully understood. However, there appear three possible sources for these signals: the fetus, the mother, or the infection.

The fetal signal for leukocyte infiltration can be attributed to the mechanical distension of the uterus and stretching of the myometrial cells that usually occurs during multiple pregnancies or can be a result of the release and increase in the expression of some molecules into the amniotic fluid at term, such as surfactants. The maternal signals for leukocyte infiltration can be attributed to hormonal regulation such as the level of progesterone, oxytocin, or cortisol. However, many types of local or systemic infections, which could all lead to the stimulation of the innate immune system and promote inflammation and subsequent activation of the uterus can bring about the signals of infection. These mechanisms will be described in the following sections.

Fetal triggers

One of the proposed mechanisms that could trigger labor is the increased distension of the myometrial cells by fetal growth and development. It has been suggested that increased uterine stretch enhances the production of proinflammatory chemokines and cytokines, and this could facilitate leukocyte infiltration and initiation of labor. The expression of CAP genes in the myometrium (CX43 and oxytocin receptor) is increased when the myometrium is stretched [58, 95, 96]. In addition, when the myometrium is stretched there is increased expression of ECM ligand proteins [97], their integrin receptors [98], activation of focal adhesion [99], and increased signaling by MAPKs [100].

Surfactant protein type A (SPA) produced by the mature lung of the fetus can initiate the onset of labor. In pregnant mice lacking SPA, labor becomes delayed, the expression of inflammatory cytokines and CAPs are significantly decreased compared with normal pregnant mice [101]. In addition, the levels of the SPA protein increases after the 32 week of gestation in humans, and this protein plays a role in the innate immunity of the lung and interacts with TLR2 [102] and TLR4 [103]. The TLRs in turn initiate a proinflammatory state and onset of labor. Another fetal trigger for labor is the maturation of fetal hypothalamic–pituitary–adrenal (HPA) axis. This could lead to an increased level of cortisol in the fetal circulation, which then can act on the placenta to increase the production of prostaglandin and recruit leukocytes, and facilitate the release of proinflammatory cytokines leading to the onset of labor [104]. Intraamniotic inflammation is found in preterm birth, even in the absence of intraamniotic infection. The trigger for this inflammation in the absence of infection is unknown. Intraamniotic inflammation is associated with increased high mobility group box 1 protein (HMGB1) concentration in the amniotic fluid, which is associated with the premature rupture of fetal membranes [33].

Maternal triggers

As term approaches, the level of PGE_2 is increased in the cervix to promote cervical ripening before the onset of labor. PGE_2 increases uterine contractility and promotes cervical ripening [105]. PGE_2 is metabolized by 15-hydroxyprostaglandin dehydrogenase (15-PGDH), which converts the active PGE_2 into inactive 15-keto PGE_2. The expression

of 15-PGDH is decreased at term resulting in an accumulation of PGE_2 and induction of cervical ripening and initiation of labor [106]. The 15-PGDH expression in the human chorion and placenta is regulated hormonally by progesterone and cortisol. Progesterone maintains the expression of 15-PGDH, while cortisol inhibits it [107].

Inflammatory mediators and prostaglandin production are linked by different mechanisms. Proinflammatory mediators, such as NF-κB increase myometrial contractility by increasing the production of contractile molecules such as COX-2 [108]. Furthermore, proinflammatory mediators could decrease the expression of progesterone receptors by reducing their transcriptional activity and decreasing the level of 15-PGDH that metabolizes PGE_2 [108].

At term, there is a functional withdrawal of progesterone, while its level in the blood remains the same. This functional withdrawal is believed to result from the increase in the expression of receptors that inhibit the action of progesterone, and a decrease in the expression of progesterone receptors. In addition, the functional withdrawal of progesterone is postulated to increase the sensitivity of myometrial smooth muscle cells to estrogen by removing the inhibitory effect of progesterone on estrogen receptors [109].

Infection triggers

Infection can induce labor through various mechanisms. It can activate the innate immune response, which recruits inflammatory cells into the uterine compartments. Infection can enhance the expression of CAPs and causes uterine contraction directly via the Rho factor/Rho-associated protein kinase (ROCK) pathway [110, 111]. Infection can cause inflammation and preterm delivery by stimulating the innate immune response through the activation of TLRs and Nod-like receptors (NLRs) [112]. Bacterial toxins can induce expression of proinflammatory cytokines IL6 and IL8 in the fetal membrane and myometrium through the activation of NLRs [113] and TLRs [114]; particularly TLR2 [115], TLR3 [116], and TLR4 [117]. However, it has been postulated that both mechanisms (TLRs and NLRs) work through NF-κB activation pathway [113, 118].

In addition, the stimulation of TLRs by bacterial products can induce uterine contraction independent of the NF-κB and PGE_2 pathways. Stimulation of TLRs by infection can directly induce uterine contraction via the Rho/ROCK pathway. The Rho/ROCK pathway induces uterine contraction via an oxytocin-mediated mechanism [119]. Hutchinson et al. have found that the bacterial toxins can induce myometrial contraction via the Rho/ROCK pathway through the activation of TLR4 leading to labor or premature activation of myometrium independently of the NF-κB pathway [111].

Bacterial toxins such as LPS can also induce the expression of CAPs, which promote uterine contraction and initiate labor [118]. Moreover, clinical evidence indicates that the complement system (part of the innate immune system) is activated during infection-induced preterm labor [120]. In addition, bacteria themselves could produce toxins, which could trigger the production of prostaglandins in maternal plasma thus promoting uterine contractions [121]. Bacteria can release phospholipase, which increases PGE_2 production through the metabolism of arachidonic acid (AA) in the amnion cells, and hence initiation of labor [122, 123]. The production of 15-PGDH is reduced during infection because of the loss of trophoblasts from the fetal membrane, thus elevating the level of PGE_2 and enhancing uterine contractions [124]. Infection during preterm labor is associated with increased levels of MMPs in amniotic fluid [125, 126], which in turn increase the degradation of ECM and collagens, and trigger labor. **Figure 2** summaries the events mediated by infection that may lead to the onset of labor.

Conclusions

There have been major advances in understanding the molecular mechanisms and triggers for uterine contractions. However, the exact mechanisms leading to the onset of labor remain to be identified. Infection is strongly linked to the onset of labor and the mechanisms underlying these phenomena have become evident. The recent advancements in therapeutic approaches cannot fully prevent the onset of preterm labor and the new knowledge has raised many questions. Uterine infection increases local infiltration by leukocytes and the release of proinflammatory cytokines and chemokines into the uterus, which contribute to myometrial contractions and the onset of labor. For therapeutic application, disrupting the production of cytokines and chemokines may provide a new target tool to prevent preterm labor. A thorough understanding of the relationship between intrauterine infection and rupture of fetal membranes

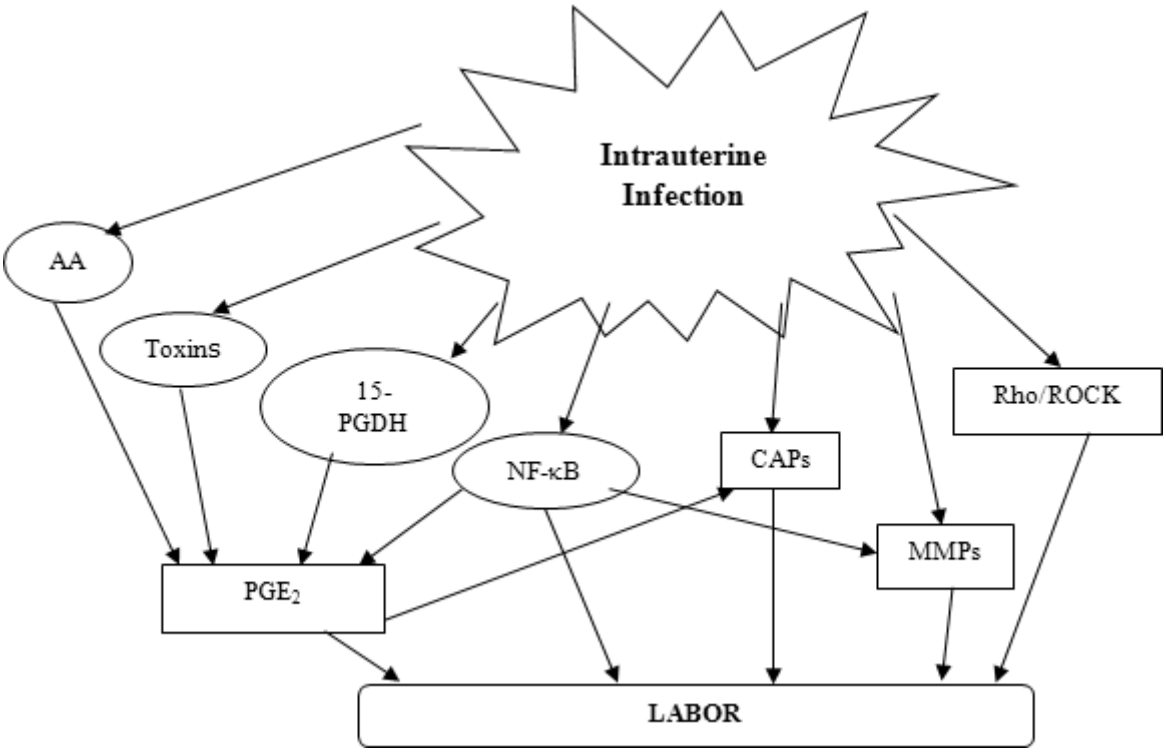

Figure 2. Schematic of proposed mechanisms of infection-induced labor. Infection triggers labor through various cellular mechanisms; the main pathways involved in this process are through contraction associated proteins (CAPs), prostaglandin E_2 (PGE_2), Rho factor/Rho-associated protein kinase (Rho/ROCK), and matrix metalloproteinases (MMPs). Arachidonic acid (AA), toxins, 15-hydroxyprostaglandin dehydrogenase (15-PGDH), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) induced by infections mediate the PGE_2-induced myometrial contractions. The CAPs, PGE_2, Rho/ROCK, NF-κB, and MMPs induced by infection can directly activate the myometrium to initiate the labor.

is vital for clinicians to be able to avoid premature rupture of membranes, reduce fetal morbidity and mortality, and improve outcomes of labor.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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