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Review Article

Genital Tract Infection during Pregnancy and its Association with Preterm Delivery

Yohanes Aditya Adhi Satria[1], Tri Nugraha Susilawati[2]*

[1] Medical Study Program, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia
[2] Department of Microbiology, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia

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ABSTRACT

Genital tract infection (GTI) remains a significant health concern. It is estimated that in 2016, there were 370 million people who suffer from chlamydia, gonorrhea, and trichomoniasis; and 708 million others suffer from genital herpes and condyloma acuminatum. It has been reported that in pregnant women, GTI is associated with preterm delivery. The mechanisms of GTI-associated preterm delivery need to be further understood to prevent neonatal mortality and morbidity that could be the risk factor for neonates' growth and development disorders. This article aims to describe various types of GTI and the associated pathogenesis causing preterm birth. A literature search was conducted to retrieve recent articles published in English from online databases including Pubmed, ScienceDirect, and Google Scholar. This literature study found that GTI evokes inflammatory responses that trigger several mechanisms leading to preterm delivery. The inflammatory responses in GTI include the production of proinflammatory cytokines and robust activation of neutrophils. The key mechanisms that stimulate preterm delivery in GTI include the events of early uterine contraction, preterm premature rupture of membranes, and induction of cervical ripening; which are under normal circumstances in a full-term pregnancy, those mechanisms are regulated by progesterone and prostaglandin levels along with suppression of the inflammatory responses. In conclusion, this paper has described the underlying mechanisms of preterm delivery in pregnant women with ISG. However, such mechanisms remain unclear in candida and gonococcal infection; thus, prompting the need for further studies.

Keywords: *Genital tract infection; sexually transmitted infection; preterm delivery; preterm birth; pregnancy*

ABSTRAK

Infeksi saluran genital (ISG) masih menjadi masalah kesehatan yang penting. Pada tahun 2016, diperkirakan terdapat 370 juta orang yang menderita klamidia, gonore, dan trikomoniasis; dan 708 juta orang lainnya menderita herpes genital dan kondiloma akuminata. Telah dilaporkan bahwa ISG pada wanita hamil berhubungan dengan kasus persalinan preterm. Mekanisme terjadinya persalinan preterm yang berhubungan dengan ISG perlu dipahami secara lebih mendalam untuk mencegah mortalitas dan morbiditas neonatus yang merupakan faktor risiko terjadinya gangguan tumbuh kembang. Artikel ini bertujuan untuk mendeskripsikan berbagai jenis ISG dan patogenesis yang berkaitan dengan terjadinya kelahiran preterm. Data didapatkan melalui penelusuran literatur terkini yang diterbitkan dalam bahasa Inggris pada database online Pubmed, ScienceDirect, dan Google Scholar. Hasil penelusuran literatur menunjukkan bahwa ISG akan menimbulkan respon inflamasi yang memicu terjadinya beberapa mekanisme yang menyebabkan persalinan preterm. Respon inflamasi tersebut meliputi produksi sitokin-sitokin proinflamasi dan aktivasi neutrofil yang masif. Mekanisme utama yang menstimulasi terjadinya persalinan preterm pada ISG meliputi kontraksi dini uterus, ketuban pecah dini sebelum kehamilan genap bulan, dan pematangan serviks; yang normalnya pada kehamilan yang genap bulan, hal-hal tersebut diatur oleh kadar progesteron dan prostaglandin serta penekanan respon inflamasi. Sebagai kesimpulan, makalah ini menjelaskan mekanisme yang mendasari terjadinya persalinan prematur pada kasus kehamilan dengan ISG. Namun, mekanisme tersebut belum

* Corresponding Author:
tri.susilawati@staff.uns.ac.id

sepenuhnya jelas pada infeksi kandida dan gonokokus, sehingga dibutuhkan penelitian lebih lanjut.

Kata kunci: *infeksi saluran genital; infeksi menular seksual; persalinan preterm; kelahiran preterm; kehamilan*

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INTRODUCTION

Preterm delivery is an important health problem as this condition can increase neonatal mortality and morbidity. Preterm delivery defines as parturition that happens between 20 weeks and 37 weeks of gestation.[1] The rates of preterm birth ranges from 5% to 18% globally and are estimated to be 15 million cases every year.[2] Neonates who are born preterm are at a higher risk for developing respiratory distress, hypothermia, hypoglycemia, and sepsis compared to full-term babies. Those who are born preterm may also develop cognitive and behavioral impairment later in life.[3,4] A previous report highlighted the significant contribution of preterm delivery in neonatal mortality, causing 1 million neonatal deaths in 2015.[5]

Untreated genital tract infection (GTI) plays an important role in causing preterm delivery. The exact number of pregnant women who suffer GTI is unclear as the condition is often underdiagnosed, especially in resource-limited settings. Nonetheless, there is a growing concern with regards to GTI in pregnancy because the condition poses a risk for preterm premature rupture of membranes (PPROM), preterm contraction, and cervical ripening that could lead to preterm delivery.[6]

Various agents can cause GTI. For example, GTI could be caused by viruses (condyloma acuminatum, genital herpes), bacteria (chlamydia, gonorrhea, and bacterial vaginosis), fungi (vulvovaginal candidiasis), and protozoa (trichomoniasis).[7,8] In 2016, 370 million people had sexually transmitted infections caused by *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Trichomonas vaginalis* whereas 708 million cases were caused by viruses with condyloma acuminatum accounted for 291 million cases and genital herpes was observed in 417 million cases.[9,10] In addition, 4.5% to 50% of women worldwide had bacterial vaginosis and 134 millions women suffer from vulvovaginal candidiasis annually.[11,12]

Due to the high burden of GTI in the population and the significant complications of prematurity, GTI-associated preterm delivery is regarded as an important subject of consideration. This paper presents the results of literature search in Pubmed, ScienceDirect, and Google Scholar to deepen our knowledge about the underlying mechanisms of GTI causing preterm delivery. The literature search was limited to recent articles published in English.

PATHOGENESIS OF GTI-ASSOCIATED PRETERM DELIVERY

Condyloma acuminatum

Human papillomavirus (HPV) is the causative agent for condyloma acuminatum. This virus can infect cells of genital mucosa and induce epithelial proliferation by the action of viral proteins. Viral protein E5, E6, and E7 enhance epithelial growth via stabilization of epidermal growth factor, binding and degrading cellular p53 protein, and inactivation of cellular retinoblastoma protein, respectively.[13-15] HPV infection manifests as epidermal growth that commonly appears on vulva, vagina, and cervix. The shape of the lesions can be papular, flat or pedunculated.[16]

The E5 and E7 viral proteins generate local immunosuppression through the reduction in toll-like receptors (TLRs) expression, reduction in surface expression of major histocompatibili-

ty complex class I (MHC I), induction of T-regulatory cells attraction, and upregulation of immunosuppressive genes.[17,18] The decrease of the local immunity may facilitate the normal flora of the lower genital tract to gain ascending access and generate bacterial infection to the upper genital tract.[19]

The subsequent bacterial infection generates inflammatory responses via the nuclear factor-kappa B (NF-κB) pathway and increases the risk of preterm delivery through two mechanisms. First, inflammation causes an upregulation of prostaglandin E2 synthesis that plays a vital role in inducing uterine contraction.[20,21] Second, inflammation increases the production of matrix-degrading enzymes that responsible for PPROM and cervical ripening.[22] These events will lead to preterm delivery.

Genital herpes

Genital herpes is caused by the herpes simplex virus (HSV) that could be either HSV-1 or HSV-2 with classically HSV-2 being the more common etiologic agent.[23] Typical manifestations of genital herpes are painful papules that develop into vesicles, ulcerates, or form a crust within the course of the disease.[24] common etiologic agent.[23] Typical manifestations of genital herpes are painful papules that develop into vesicles, ulcerates, or form a crust within the course of the disease.[24]

Untreated HSV infection is a risk factor for preterm delivery. Similar to HPV, HSV infection could lead to a decrease in TLRs expression.[17]

TLRs, especially TLR-4 and TLR-5, are essential in initiating an innate immune response against bacterial antigens. It has been reported that a decrease of TLRs expression in genital herpes is associated with an increased risk of *Escherichia coli* ascending infection.[25] - β (IL-β), IL-6, IL-12, chemokine (C-X-C motif) ligand 1 (CXCL1), monocyte chemoattractant protein-1/ chemokine (C-C motif) ligand 2 (MCP-1/CCL2), macrophage inflammatory proteins-1α/β (MIP-1α/β), and chemokine regulated upon activation, normal T cell expressed and presumably secreted that are released during bacterial infection are considered as the prime movers for remodeling and rupture of the fetal membrane as well as cervical ripening.[17,26]

The cytotoxicity of Zinc(II)-2,4,5-triphenyl-1*H*-imidazole complex compound was determined by CellTiter96® AQ_{uoeus} assay and the recorded CC_{50} value is <100 μg/ml to Vero cells. When compared with a previous study, Copper(II) was HSV infection can change the structural collagen fibers of cervical tissue by increasing the synthesis of hyaluronic acid and facilitating the proliferation of epithelial cells. The increasing amount of hyaluronic acid weakens the cervical collagen network and the proliferation of cervical epithelial cells increases the tissue sensitivity to 17β-estradiol (E2); both events are associated with cervical ripening that intitiate a key process in delivery.[27,28]

Chlamydia infection

(2,4-dihydroxyphenyl)-3,5,7-trihydroxycromen-4-one complex compound defined cytotoxicity with CC_{50} at 3.59 μg/ml.[21] But, the metal-free imidazole more toxic for Vero cells (CC_{50} = 5.03 μg/ml).[22] Activity against HIV-1 strain IIIB and Chlamydia infection is a sexually transmitted disease caused by *C. trachomatis*. This bacteria is an intracellular obligate pathogen with two different forms during its life cycle; i.e., the elementary body as the infectious phase and the reticulate body as the replicative phase.[29] The clinical manifestations of chlamydia infection in women include cervicitis, vaginitis, or urethritis. Chlamydia infection is sometimes accompanied by increased cervical secretion, lower abdominal pain, post-coital bleeding, and dysuria.[30]

A previous prospective cohort study showed that chlamydia infection during pregnancy is associated with preterm delivery before 32 weeks and 35 weeks of gestation.[31] The infection of the upper genital tract could trigger inflammatory responses affecting the placenta along with both maternal and fetal membranes. The involvement of transplacental and

transmembrane leads to chorioamnionitis, an inflammatory condition involving chorion, amnion, and placenta that could trigger preterm delivery.[32] Chorioamnionitis causes upregulation of inflammatory cytokines such as IL-6, IL-8, and tumour necrosis factor-α (TNF-α) in the membranes that facilitates the production of prostaglandin and metalloprotease, resulting in membrane rupture and uterine contraction.[33,34]

The inflammatory responses are the results of the host's direct response to bacterial infection or as the results of the host's response to the heat shock protein produced by the bacteria.[35] Chlamydial heat shock protein (hsp60) is produced by the chlamydial reticulate body and released into extracellular milieu. The protein has an antigenic epitope that could trigger the host's immune responses. It could also induce the production of IL-6 as well as adhesion molecules such as E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1).[29,36] In pregnant women with *C. trachomatis* infection, hsp60 can be isolated from the epithelial cells of the genital tract and placental tissue, suggesting its association with placental inflammation. The sign of placental inflammation is more commonly observed in women with confirmed chlamydia infection compared to those uninfected.[32] Furthermore, IgG antibody associated with placental hsp60 is only detected in women with preterm delivery.[37]

Gonorrhea

Gonorrhea is a disease caused by the diplococci gram-negative *N. gonorrhoeae*.[38] Women infected with this bacteria will develop cervicitis with purulent cervical discharge, dysuria, and lower abdominal pain.[39] Pelvic inflammatory disease (PID) could arise as a complication of gonorrhea infection which causes fallopian tube damage, resulting in women's infertility.[40] The bacteria are resistant against most antimicrobial agents.[41] The currently recommended treatment regimen for gonorrhea is dual therapy with either or cefixime plus azithromycin.[42] However, it has been reported that the bacteria are resistant to third-generation cephalosporins.[43,44]

N. gonorrhoeae infection has been known to be involved in the occurrence of preterm delivery although the underlying mechanisms have not been demonstrated clearly and the association between the entities has not been found as commonly as other types of GTI.[26] A previous retrospective cohort study reported that gonorrhea is associated with an increased risk of spontaneous preterm birth.[45] Another study supports this finding by reporting the involvement of gonorrhea in preterm labor and PPROM but not preterm delivery.[46] Another retrospective cohort study also failed to demonstrate a relationship between preterm delivery and gonorrhea despite finding a trend toward chorioamnionitis during the third trimester of pregnancy with gonorrhea.[47] These findings suggest that gonorrhea's role in inducing chorioamnionitis is time-specific.

A strong neutrophilic inflammatory response may explain the link between *N. gonorrhoeae* infection and preterm delivery as the bacteria is known to cause a robust response of neutrophils. The bacteria possess opacity (Opa) proteins that act as adhesins and bind to the human's surface protein of the family carcinoembryonic antigen-related cell adhesion molecules (CEACAMs).[48] Opa proteins could also evoke inflammatory responses by promoting chemokines production such as MIP-1α, MIP-2, CXCL-1, and TNF-α on CEACAMs-expressing neutrophils.[49] In addition, the bacterial lipo-oligosaccharide (LOS) and the released peptidoglycan fragments would activate TLRs, thereby drive the production of inflammatory cytokines such as IL-1, IL-6, IL-8, and IL-17.[48] These inflammatory responses are believed to cause subsequent events that lead to myometrial contraction, membranes rupture, and cervical ripening that induce preterm delivery.[26]

Trichomoniasis

Trichomoniasis is caused by the protozoan parasite *T. vaginalis*. The infection causes local inflammation as a result of the host's immune

response to the attachment of the parasite to mucosal tissue.[50] The clinical manifestations of trichomoniasis include dysuria, pruritus, and frothy yellowish or greenish vaginal discharge.[51] The disease is associated with preterm birth and other perinatal morbidities such as PPROM and small for gestational age infants.[52]

Lipophosphoglycan (LPG) is the major adhesion molecule of *T. vaginalis* and it is recognized by TLR-4. The antigenic molecules stimulate an abundant production of IL-8 by activating the pathways of NF-κB, extracellular signal-regulated kinases 1 and 2 (ERK1/2), and mitogen-activated protein kinase 1 and 2 (MEK1/2).[53] LPG induces the production of inflammatory cytokines in TLR-4 independent manner by binding to galectin-3 on vaginal epithelial cells. The activation of galectin-3 has been shown to trigger IL-8 expression.[54,55] IL-8 promotes neutrophil migration and activation that leads to collagenase and elastase secretion within the cervix, a key role in cervical ripening that induces the delivery process.[26]

The protozoa could also be parasitized by *Mycoplasma hominis* and transmit the bacterial infection to the human host following treatment with metronidazole.[56,57] Mycoplasma can migrate into the upper genital tract and cause chorioamnionitis. The presence of mycoplasma in amniotic fluid is a predictive factor for preterm delivery.[58,59] Mycoplasma infection causes an increase of inflammatory markers in amniotic fluid, including TNF-α, IL-6, IL-8, and matrix metalloproteinase-8 (MMP-8). [60]

Bacterial vaginosis

Bacterial vaginosis (BV) is a condition when there is a shift in the vaginal microbiome in which the population of lactobacillus is significantly depleted and the vaginal microbiome is dominated by anaerobic polymicrobial organisms such as *Gardnerella vaginalis, Atopobium vaginae, Peptostreptococcus spp., Prevotella spp.*, and other BV-associated bacteria.[61,62] It has been reported that there is a decrease in the growth of hydrogen peroxide-producing lactobacillus during HSV-2 infection. [63] The exact mechanism of lactobacillus depletion in HSV-2 infection remains unknown but the infection causes dysbiosis in vaginal flora, resulting in BV. BV typically presents with minimal signs and symptoms so that the diagnosis is frequently missed. The diagnosis of BV can be made by using Amsel criteria as follows: (1) increased homogenous and thin vaginal discharge; (2) vaginal pH of >4.5; (3) positive whiff test or amine aroma generated after KOH treatment; and (4) clue cells in microscopy examination. The distinctive amine smell or fishy odor is an important clinical indicator for BV. The diagnosis of BV is confirmed when there are minimally 3 criteria present.[64]

The bacteria causing BV could ascend to the upper genital tract and cause inflammatory responses. The local inflammatory responses induce the secretion of prostaglandin that promotes early uterine contraction as well as metalloproteinase enzymes that cause PPROM.[20,65]

Vulvovaginal candidiasis

Vulvovaginal candidiasis is an inflammatory condition of the vulva and vagina caused by fungi from the Candida genus with *Candida albicans* being the most common etiologic agent.[66] The condition is characterized by white curdy vaginal discharge, erythema of the vulva and vagina, dysuria, and dyspareunia.[67] The diagnosis of vulvovaginal candidiasis could be made by either stained or unstained wet mount microscopy can be used as a confirmatory diagnostic test. The diagnosis is confirm when blastospores and pseudohyphae are present. If neither is present, the sample must undergo culture to ascertain diagnosis.[68]

It has been demonstrated that women with vulvovaginal candidiasis have a higher risk of chorioamnionitis and preterm delivery compared to those without the infection.[69,70] A previous meta-analysis showed that antifungal treatment of asymptomatic candidiasis in pregnant women is associated with a lower incidence of preterm birth compared to untreated cases.[71] It is uncertain how vulvovaginal candidiasis could lead to preterm birth but it has been suggested that vulvovaginal candidiasis increases the susceptibility of the host to ascending bacterial infection.[72]

It has been reported that the pathogenic *C. albicans* is a potent inducer of IL-10.[73] Thus, in vulvovaginal candidiasis, the host's immune response is being suppressed and an alteration of the vaginal normal flora develops, favoring bacteria to generate infection in the upper genital tract.[72,73] This subsequent bacterial infection drives the production of pro-inflammatory cytokines, thereby leads to the elevation of prostaglandin and the increased production of matrix-degrading enzymes, similar to the events following HPV and HSV infection that lead to preterm delivery.

Figure 1 summarizes the mechanisms involved in GTI-associated preterm delivery. The common pathway that results in early uterine contraction, PPROM, and cervical ripening is the production of proinflammatory cytokines. In particular, the immune response to chlamydia infection is triggered either by direct stimulation or as the subsequent response against heat shock protein produced by the reticulate body of chlamydia.[29,32,35,36] induced via robust neutrophils activation whereas in bacterial vaginosis, the production of proinflammatory cytokines occurs without a robust neutrophilic response.[26,48,49,53,65]

HPV, HSV, and *C. albicans* stimulate cytokines production by interfering cervical immune responses that facilitate bacterial infection.[17,19,27,72,73] The cytokines production is followed by an elevation in the levels of prostaglandin and matrix-degrading enzymes such as MMP-2, MMP-9, MMP-8, MMP-3, and MMP-10 that leads to PPROM, early uterine contraction, and cervical ripening.74 Similarly, robust activation of neutrophils can induce PPROM and cervical ripening. Altogether, early uterine contraction, PPROM, and cervical ripening are the key mechanisms leading to preterm delivery.[20,21,22,26,75-78] It is important to note, however, that the pathogenesis of preterm birth associated with candida and gonococcal infection is not clearly understood.

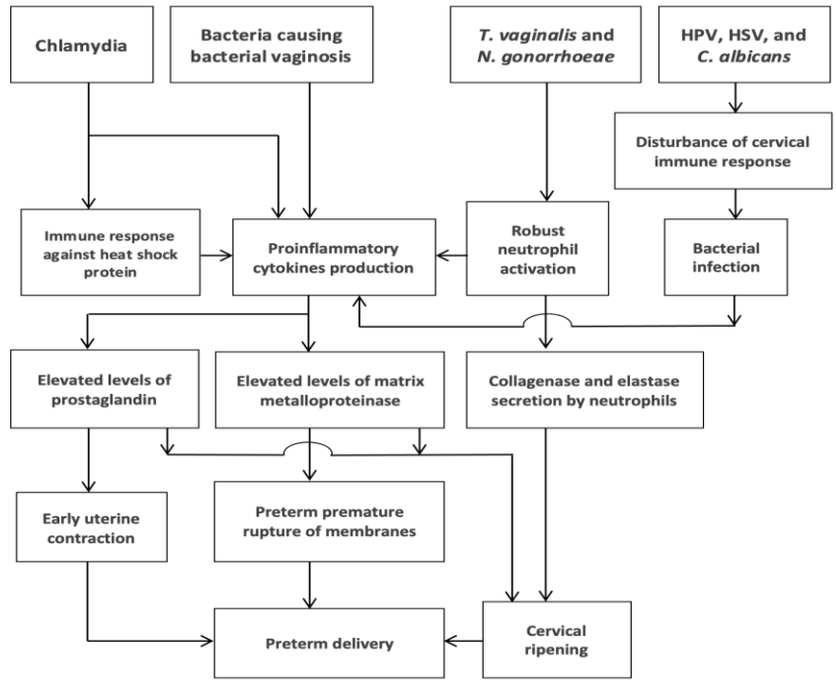

Figure 1. Summary of the mechanisms involved in GTI-associated preterm delivery

Immune Activation and Inflammatory Responses in Preterm Delivery

The production of proinflammatory cytokines in *T. vaginalis* and *N. gonorrhoeae* infection is

Early uterine contraction

Uterine contractility is maintained through progesterone withdrawal and an increase in

prostaglandin E2 level.[20] Progesterone increases cyclic adenosine or guanosine monophosphate (cAMP or cGMP) which in turn inhibit the release of intracellular calcium. Thus, progresterone withdrawal will initiate uterine contraction.[21]

Prostaglandin E2 causes myometrial contractions via prostaglandin prostanoid receptors (EP). There are four different subtypes of EP; i.e, EP1, EP2, EP3, and EP4 (Figure 2). When prostaglandin E2 is secreted, all the EP receptors are expressed continuously on different anatomical sites, producing different effects on the uterus during the delivery process. EP1 and EP3 are classified as contractility enhancers and they are expressed highest in fundal tissue. EP1 facilitates Ca^{2+} influx into myometrium whereas EP3 inhibits adenylate cyclase activity and cAMP production. EP2 and EP4 are located in the lower uterine segment and classified as muscle relaxants that increase cAMP molecules.[79,80] The difference in anatomical sites of EP expression and their effects on the uterus is important to allow passage of the fetus during the delivery process.

GTI stimulates the NF-κB pathway of inflammation, which in turn promotes prostaglandin synthesis by the upregulation of prostaglandin E synthetase and downregulation of 15-hydroxyprostaglandindehydrogenase.[20,21] Prostaglandin E synthetase is the enzyme required in the terminal step of the production of prostaglandin E2 while 15-hydroxyprostaglandin dehydrogenase is required in the prostaglandin inactivation pathway.[76,81] It has been reported that inflammatory signals may stimulate the expression of 20α-hydroxysteroid dehydrogenase (20α-HSD), an enzyme that promotes the inactivation of progesterone.[22] Thus, GTI-induced inflammation could lead to an increase in uterine contractility by altering progesterone-prostaglandin level, one of the factors that determine uterine contractility leading to parturition.

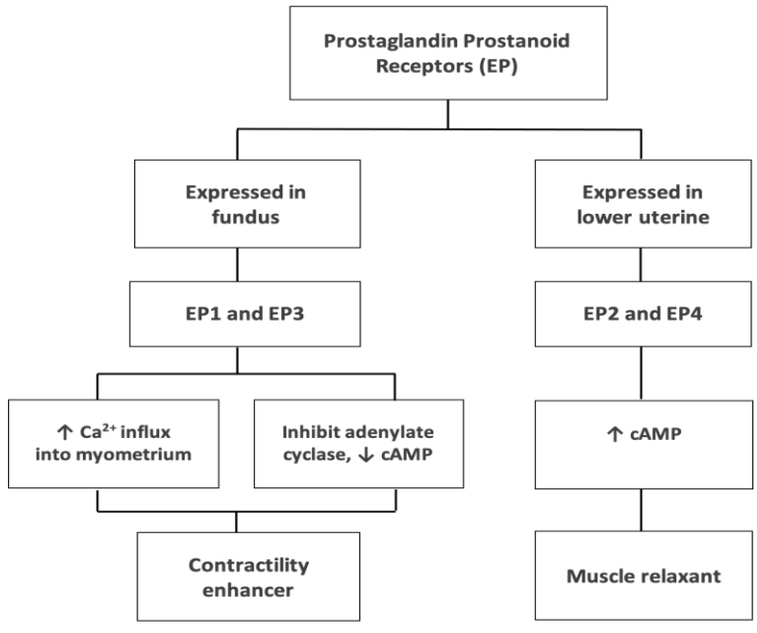

Figure 2. EP receptors and their effects on uterus

Preterm premature rupture of the membranes (PPROM)

Uterine contraction and the rupture of membranes are crucial steps to initiate the delivery process, which are controlled

In at least 35% of women with preterm delivery, contraction happened after the membranes rupture.[75,82] PPROM is a pre-labor rupture of the membranes occurring before 37 weeks of gestation.[77]

Infection is responsible for about 55% of PPROM by promoting the release of proinflammatory cytokines.[75] The major proinflammatory cytokines that contribute to PPROM is TNF-α. Proinflammatory cytokines induce amnion epithelial apoptosis and increase the synthesis of matrix-degrading enzymes such as matrix-metalloproteinase and caspase that stimulate the degradation of the membranes' extracellular matrix. The degradation of the membranes' extracellular matrix weakens the fetal membranes and eventually leads to membranes rupture.[78]

Cervical ripening

Cervical ripening is is an important phase to initiate vaginal delivery of the fetus. The condition is characterized by a gradual decrease in collagen concentration of the matrix and an increase in cervix extractability to dilate.[83] Cervical ripening is regulated by several factors, including progesterone level and inflammatory reaction.[84]

It has been reported that the administration of vaginal progesterone could reduce the risk of preterm birth.[85] Progesterone suppresses inflammatory responses by reducing macrophages activity, decreasing migration of neutrophils, and augmenting $CD4^+$ T regulatory activity. In addition, progesterone action through progesterone receptors (PRs) has been shown to repress Cx43 gene transcription. Cx43 gene plays a vital role in the initiation of full-term or preterm birth through cell communication to generate myometrial contraction. Progesterone withdrawal thereby promotes the activation of this gene and leads to the generation of myometrial contraction.[22,86]

Inflammatory responses generated from GTI could induce cervical ripening through the following mechanisms. First, GTI-induced inflammation promotes the migration of neutrophils and monocytes into the extracellular matrix of the cervix. These activated cells secrete matrix-degrading enzymes such as matrix metalloproteinase and collagenase into the extracellular milieu of the cervix. As the consequence, cervix remodeling occurs and results in the decrease of matrix collagen and an increase in cervix extractability to dilate.[6,84]

The predominating cytokines that are associated with cervical ripening in GTI-induced inflammation include IL-1, IL-6, and TNF-α. A significant elevation of chemoattractant molecules such as CXCL-2, IL-8, and MCP-1 is also observed as well as an increase in prostaglandin levels.[87,88] Subsequently, inflammatory responses withdraw progesterone action by decreasing progesterone level. In addition, IL-1β promotes the expression of 20α-HSD enzyme in cervical fibroblasts. This enzyme catalyzes the metabolism of progesterone into its inactive form, thereby reducing progesterone level.[89] The decrease of progesterone level is a key mechanism that promotes cervical ripening and uterine contractility, thus initiating delivery.

CONCLUSION

Understanding factors that contribute to preterm delivery is important in order to deliver appropriate management. Our review shows that GTI-induced inflammatory responses are involved in the initiation of preterm delivery; i.e., early uterine contraction, PPROM, and cervical ripening. The underlying mechanisms of preterm delivery in candida and gonococcal infection, however, are not fully understood. Therefore, further studies in this area are needed.

CONFLICT OF INTEREST

There is no conflict of interest of this study.

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