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Changes in the microbiome as a factor in the development of isthmic cervical insufficiency

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ABSTRACT

The status of a woman's cervicovaginal microbiome may correlate with the risk of obstetric complications such as isthmic cervical insufficiency (ICI) and preterm delivery (PD). This review examined the relationship between the microbiome and ICI. The dominance of *Lactobacillus crispatus* and, possibly, *L. gasseri* in the microbiome was associated with full-term pregnancy, whereas the predominance of other *Lactobacillus* species and anaerobic bacteria led to the preterm rupture of membranes and PD. Notably, high levels of the antimicrobial peptide β-defensin 2, even without *L. crispatus* dominance, are also associated with full-term pregnancy. The analysis of the cervicovaginal and amniotic fluids of women who subsequently gave birth prematurely revealed an increase in the levels of proinflammatory cytokines, such as interleukin (IL)-2, IL-8, and IL-10. Changes in the microbiome composition and an increase in the maternal immune response lead to premature remodeling and softening of the cervix, i.e. ICI. Thus, early detection of changes in the cervicovaginal microbiome and cervicovaginal and amniotic fluids may be a prognostic marker for ICI and PD.

Keywords: pregnancy; preterm delivery; cervical insufficiency; cervicovaginal microbiome; lactobacilli; amniotic fluid microbiome; short cervix; bacterial vaginosis.

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Изменения микробиома как один из факторов развития истмико-цервикальной недостаточности

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АННОТАЦИЯ

Существует гипотеза, что состояние цервиковагинального микробиома женщины может коррелировать с вероятностью таких акушерских осложнений, как истмико-цервикальная недостаточность (ИЦН) и преждевременные роды (ПР). В этом обзоре мы рассмотрели взаимосвязь микробиома и ИЦН. Оказалось, что доминирование в микробиоме *Lactobacillus crispatus* и, возможно, *L. gasseri* ассоциировано с доношенной беременностью, тогда как преобладание других видов *Lactobacillus* и анаэробных бактерий приводит к преждевременному разрыву плодных оболочек и ПР. Стоит обратить внимание на то, что высокое содержание антимикробного пептида β-дефензина 2 даже при отсутствии доминирования *L. crispatus* также ассоциировано с доношенной беременностью. При изучении цервиковагинальной и амниотической жидкостей женщин, впоследствии родивших преждевременно, выявляется повышение содержания провоспалительных цитокинов, таких как IL-2, IL-8, IL-10 и др. Изменение состава микробиома и повышение иммунного ответа матери приводят к преждевременному ремоделированию и размягчению шейки матки — то есть к истмико-цервикальной недостаточности. Таким образом, раннее выявление изменений в цервиковагинальном микробиоме, цервиковагинальной и амниотической жидкостях может быть прогностическим маркером ИЦН и ПР.

Ключевые слова: беременность; преждевременные роды; недостаточность шейки матки; цервиковагинальный микробиом; лактобациллы; микробиом околоплодных вод; короткая шейка матки; бактериальный вагиноз.

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Preterm birth (PTB) is commonly defined as a birth before 37 weeks of gestation. PTB is a major obstetric healthcare concern worldwide. In the United States, one in ten babies are born preterm. The incidence of PTB continues to rise annually, with an unexpectedly elevated rate in African-American females, which is approximately 50% higher than that in White or Hispanic females [1]. PTB has been associated with a wide range of maternal or fetal characteristics, such as extragenital diseases, reproductive disorders, stress factors, race, age, etc. Fuchs et al. demonstrated that a maternal age of 30–34 years was associated with the lowest risk of PTB, whereas an advanced age of 40 years and over was a strong risk factor for prematurity [2]. Moreover, vaginal microbial dysbiosis, which may result in an ascending bacterial infection from the vagina through the cervix into the uterine cavity, and cervical insufficiency (CI) may also be considered potential causes of PTB [3]. The objective of this review is to investigate the relationship between these two causes of PTB.

CI is defined by cervical shortening (<25 mm) and/or dilation (>10 mm). It is characterized by rapid, painless cervical shortening in the second or early third trimester of pregnancy, which is followed by late miscarriage or PTB. The amniotic sac may prolapse through the cervical canal, causing premature rupture of membranes (PROM). Transvaginal ultrasound (ultrasound vaginal cervicometry) is considered the most effective approach for detecting cervical insufficiency in pregnant women [4]. A lower gestational age (16–22 weeks) and a shorter cervix are associated with an increased risk (50%) of early PTB (at <32 weeks). However, this risk decreases to 15% at a later gestational age [5].

Microbiota is the set of microorganisms that colonize specific anatomical body sites. The term "microbiome" refers to both the microbiota (a set of microorganisms) and the collection of microbial genetic material in their living environment [6]. The microbiota composition may be investigated using next-generation DNA sequencing, with targeting 16S rRNA gene hypervariable regions (V1–V3 and V3–V5) as specific markers for a bacterial cell. This method offers a comprehensive qualitative and quantitative analysis of the microbiome composition [7-8]. The vaginal microbiome may be dominated by various *Lactobacillus* species, and several community state types (CSTs) of vaginal bacterial communities can be distinguished: *L. crispatus* (CST I), *L. gasseri* (CST II), *L. iners* (CST III), and *L. jensenii* (CST V). Another alternative is the dominance of anaerobic bacteria (*Gardnerella, Atopobium, Mobiluncus, Prevotella, Streptococcus, Ureaplasma, Megasphaera, Escherichia, Shigella*, etc.) and a reduction in *Lactobacillus* species, which contributes to bacterial vaginosis (CST IV) [9].

Menarche is associated with higher circulating estrogen levels, which leads to the proliferation of epithelial cells in the vagina and the deposition of glycogen, which is then metabolized by lactobacilli alpha-amylase to lactic acid. *Lactobacillus* species protect the vaginal epithelium against invasion and colonization by pathogenic and opportunistic microorganisms. The antimicrobial activity is ensured by the production of hydrogen peroxide, bacteriocins that increase the permeability of target cells, biosurfactants, and lactic acid, which reduces the pH of the medium to create unfavorable conditions for the growth and reproduction of pathogenic microorganisms. Lactic acid also facilitates the dissolution of damaged epithelial cells of the vaginal mucosa through a lysis mechanism, accompanied by glycogen production. This ultimately results in the termination of the metabolic cycle. Mucins, β-defensins, antibodies, etc. [10–11] also serve as protective agents. Lower vaginal pH (<4) is associated with higher *Lactobacillus* dominance, while higher pH contributes to lower *Lactobacillus* dominance and higher levels of anaerobic bacteria [9, 12]. Consistently high levels of estrogen, amenorrhea, and thickened endometrium during pregnancy create a favorable environment for the growth and reproduction of lactobacilli [7, 13]. PTB is associated with a highly diverse microbiome characterized by a lower dominance of *Lactobacillus* species (especially *L. crispatus*), while the vaginal microbiome of women who deliver at term is a low-diversity environment predominated by *L. crispatus.* Consequently, the dominance of *L. crispatus* is considered to be a contributing factor to full-term pregnancy [14–18]. Nevertheless, the presence of the *L. crispatus*-based vaginal community is not a prerequisite for full-term pregnancy and delivery at term, which are also possible with the dominance of another bacterial community [19].

In their Maternity and Microbiome (M&M) study, Elovitz et al. demonstrated that Mobiluncus curtisii/mulieris (CST IV) were most strongly associated with PTB, particularly at <34 weeks of gestation. With the low dominance of Lactobacillus spp., Mobiluncus curtisii/mulieris increase the risk of PTB, while the high dominance of Lactobacillus spp. eliminates this risk. This finding confirms a beneficial role of Lactobacillus spp. in eliminating the risk of PTB even in the presence of pathological flora [20]. A significant proportion of African-American females exhibit the low dominance of L. crispatus in their cervicovaginal microbiome, which is associated with unfavorable pregnancy outcomes. In contrast, White females demonstrate a prevalence of this Lactobacillus species. The risk of PTB in African-American females is thereby twice as high, with a higher risk of bacterial vaginosis [21–22]. However, the dominance of L. crispatus does not protect against PTB in both African-American and White females. A study of the effect of the local immune response on pregnancy outcomes, namely the role of β-defensin 2, an antimicrobial peptide that is used by immune cells to destroy phagocytized antigen, found that high levels of β-defensin 2 eliminate the risk of PTB associated with a low dominance of Lactobacillus spp. However, low levels of this antimicrobial peptide may be associated with PTB even if Lactobacillus spp. predominates [20]. During pregnancy, lower levels of β-defensin 2 may be attributed to psycho-emotional stress, and the combination of these two factors dramatically increases the risk of PTB [23].

Gerson et al. conducted a secondary analysis of the M&M study and found that the detection rate of CST IV in cervical swab specimens from women with spontaneous PTB was nearly 45%. Women with a short cervix were more susceptible to CST IV compared to other types of vaginal bacterial communities. In addition, the incidence of PTB-associated PROM was slightly higher among patients with CST IV. A short cervix and cervical CST IV have been reported to increase the risk of PTB. Furthermore, this combination was most common in African-American females [24].

Interestingly, the microbiome dominance of *L. iners* at 16 weeks of gestation results in preterm cervical shortening and PTB before 34 weeks of gestation, whereas the dominance of *L. crispatus* is associated with normal term delivery at the same gestational age. *L. crispatus* has been shown to dominate in White females, while African-American females exhibited the dominance of *L. iners* and CST IV [3]. This may be due to the fact that *L. crispatus* is a major source of D- and L-lactic acid, and *L. iners* produces only L-isomer, which has lower protective properties against pathogenic bacteria compared to D-isomer [10, 25]. Di Paola et al. showed that *L. iners*-dominated microbiota (among all *Lactobacillus*-dominated microbiotas) is most often associated with an extremely short cervix (<10 mm) and considered a risk factor for cervical remodeling and CI, as is the microbiota dominated by anaerobic bacteria (CST IV) [26]. Moreover, *L. jensenii* dominance could increase the risk of PTB, while *L. gasseri* may have a protective effect similar to that of *L. crispatus* and is associated with full-term pregnancy [27]. *L. iners* and *G. vaginalis* significantly increased cervical epithelial cell permeability, allowing for the water influx to the cervical stroma resulting in cervical softening, cervical remodeling, and PTB. In contrast, *L. crispatus* protects the cervical epithelial barrier against invading pathogens [28].

Vaginal dysbiosis induces an increased production of pro-inflammatory cytokines [29]. Sierra et al. demonstrated that cervicovaginal colonization by *G. vaginalis* results in increased mucin secretion and initiation of interleukin-6 (IL-6) synthesis in both cervicovaginal and amniotic fluids, despite the absence of ascending infection to the fetal membranes, placenta, and uterus. This suggests that pathogens have the ability to activate a local inflammatory response in the cervicovaginal space, which may result in reduced cervical elasticity, cervical remodeling, and PTB [30–31]. Women with an extremely short cervix (<15 mm) have a higher amniotic fluid concentrations of IL-6 and other pro-inflammatory mediators than those with a short cervix (15–25 mm). The amniotic fluid concentrations of IL-2 were increased in women with an extremely short cervix who ultimately delivered preterm compared to those who delivered at term [32]. Tarca et al. found that patients with a short cervix had increased concentrations of pro-inflammatory proteins in the amniotic fluid samples obtained by amniocentesis, particularly IL-8, MIP-1β, IL-6, and IL-10 at 16–22 weeks; IL-8, MIP-1β, and IL-6 at 22–26 weeks; and only IL-8 at 26–31 weeks. Consequently, a shorter cervix and a lower gestational age were associated with higher levels of pro-inflammatory proteins and the increased risk of early PTB (at less than 32 weeks). These proteins, also known as cytokines, are produced by macrophages and lymphocytes. They are chemotactic factors that attract neutrophils and other granulocytes to the site of inflammation [5]. The amniotic fluid from full-term pregnancies was found to be sterile [33].

The levels of D-lactic acid were highest in CST I (*L. crispatus*) communities, followed by CST V (*L. jenseni*) communities. Meanwhile, these communities had the lowest TIMP-1 (endogenous tissue inhibitor of matrix metalloproteinases) levels, which was associated with normal cervical length. The highest levels of L-lactic acid were associated with CST III (*L. iners*). The highest TIMP-1 levels were observed in CST IV (*G. vaginalis*) and CST III communities, which was associated with a short cervix and adverse pregnancy outcomes, such as PTB [34]. Yoo et al. showed that cervical insufficiency (>10 mm) and short cervix (<25 mm) correlated with cervicovaginal TIMP-1 and high levels of vitamin D binding protein (VDBP) and Dickkopf-related protein 3 (DDK-3). A combination of these markers appears to be a more useful predictor of PTB than each marker alone [35]. Concentrations of matrix metalloproteinase-8 (MMP-8) were higher in patients delivering preterm [36]. Thus, these concentrations may be useful as predictors of PTB.

Lower levels of *L. crispatus* and anaerobic dominance (*Bacteroides, Fusobacteriales* and *Clostridiales*) may be associated with PROM and PTB in the future [35]. Women delivered within 9 days at 24–28 weeks and within 5 days of PROM [36]. The recommended treatment for early PROM is currently aimed at accelerating fetal lung maturation (pulmonary surfactant production) by using glucocorticosteroids. Oral erythromycin 250 mg for 10 days is also required to prevent ascending infection [37]. However, Brown et al. found that erythromycin therapy induced vaginal dysbiosis and *Lactobacillus* depletion, particularly in women initially colonized by *Lactobacillus* (dominant). This was associated with a high risk of chorioamnionitis. However, erythromycin therapy in women colonized by pathogenic bacteria decreased the diversity in pathogenic communities and improved *Lactobacillus* dominance. Thus, there are two groups of women: those for whom erythromycin therapy is detrimental and those for whom it is potentially beneficial [16].

The above data support the hypothesis that woman's vaginal microbiome may correlate with the risk of obstetric complications such as CI or preterm birth. *L. crispatus* protects the cervical and vaginal epithelial barrier, which is associated with delivery at term, while the other vaginal communities are associated with the risk of CI and PTB. Activation of the maternal immune response to pathogens with increased levels of pro-inflammatory cytokines in the cervicovaginal and amniotic fluids is another risk factor for CI and PTB. However, the prevention and treatment strategies for CI and PTB should be further investigated.

ADDITIONAL INFO

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