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Review

Vaginal microbiota in pregnancy: Role in induction of labor and seeding the neonate's microbiota?

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Compared to other human microbiota, vaginal microbiota is fairly simple with low bacterial diversity and high relative abundance of *Lactobacillus* species. *Lactobacillus* dominance is even more pronounced during pregnancy. Genetic factors, such as ethnicity, along with environmental, individual and lifestyle factors all have an impact on vaginal microbiota composition. The composition of the vaginal microbiota appears to play an important role in pregnancy as recent studies have linked it to adverse obstetric outcomes such as preterm birth, a leading cause of neonatal morbidity and mortality worldwide. However, the same vaginal microbiota does not seem to cause the same response in all women, calling for future research to fully understand the complex host–microbiota interplay in normal and complicated pregnancies.

Keywords. *Lactobacillus*; parturition; pregnancy; vaginal microbiota

Abbreviations: BV, bacterial vaginosis; CST, community state type; pPROM, preterm premature rupture of membranes; PTB, preterm birth; SES, socioeconomic status; VMB, vaginal microbiota

1. Introduction

Human vaginal microbiota (VMB) is unique in its composition compared to the other human microbiotas or other species' VMB with its *Lactobacillus* dominance and low bacterial diversity (Belizário and Napolitano 2015; Human Microbiome Project Consortium 2012). The vaginal mucosa differs from other mucosae also with respect to epithelial structure, mucus composition and innate and adaptive immune mechanisms (Kumamoto and Iwasaki 2012). IgG rather than IgA takes a dominant role in maintaining hemostasis in the vagina during health and infection (Bard *et al.* 2002) as well as in parturition by neutralizing pathogens and activating the innate immune system via complement activation (van de Bovenkamp *et al.* 2016).

VMB varies among healthy women. Based on the dominant bacterium VMB can be clustered into at least five distinct community state types (CSTs) (Ravel *et al.* 2011): those dominated by *Lactobacillus crispatus*, *L. gasseri*, *L.iners* or *L. jensenii* (CST I–III and CST V, respectively). CST IV lacks lactobacilli and consists of anaerobic bacteria, such as *Gardnerella, Atopobium, Sneathia and Prevotella* that are typical in women with, e.g., bacterial vaginosis (BV). Age, ethnicity, lifestyle habits, use of contraceptives, anti- and probiotics and the prevailing hormonal milieu, all impact the composition of VMB (Brooks *et al.* 2017; Macklaim *et al.* 2015; Ravel *et al.* 2011) (figure 1). Other environmental factors, including dietary habits, are known to influence the human gut microbiome potentially more than the host genetics (Rothschild *et al.* 2018), but the impact of diet on VMB is yet unknown and thus calls for future studies. The socioeconomic status (SES), e.g., education, is associated to VMB composition, but currently which particular SES factors are involved and to what extent they affect the VMB remains elusive (Ding and Schloss 2014).

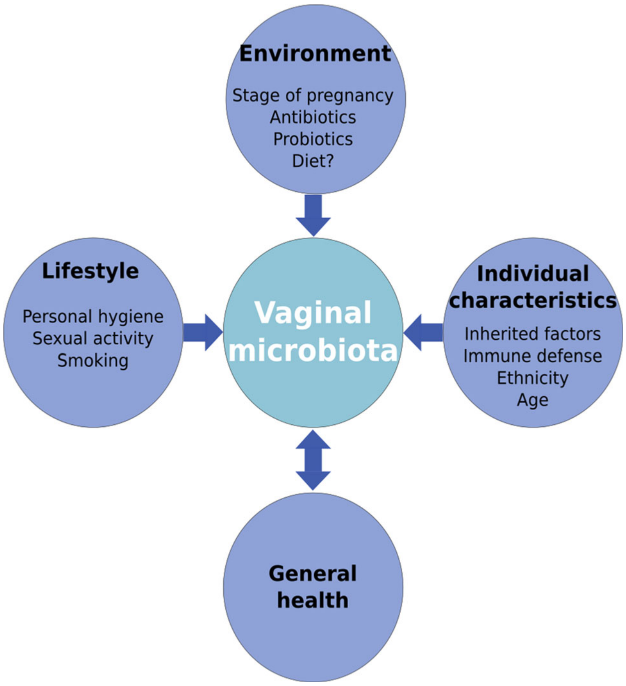

Figure 1. Factors known to affect vaginal microbiota (VMB) composition during pregnancy. VMB composition during pregnancy is more stable compared to the non-pregnant state. Environmental, lifestyle and individual factors do, however, have an impact on VMB composition also during pregnancy. VMB's and host's crosstalk have an influence on the woman's and neonate's health.

Pregnancy is characterized by high circulating estrogen levels produced by the placenta (Siiteri and MacDonald 1966). Estrogen increases glycogen deposition on the vaginal epithelium, favoring proliferation and dominance of lactobacilli that metabolize the breakdown products of glycogen to lactic acid, leading to low pH (<4,5) prevailing in the healthy vagina (MacIntyre *et al.* 2015; O'Hanlon *et al.* 2013). The VMB composition undergoes some changes as the pregnancy progresses, but overall it is less variable and diverse, and even more *Lactobacillus* dominant than in the non-pregnant state (Aagaard *et al.* 2012; Goltsman *et al.* 2018; Romero *et al.* 2014a; Walther-António *et al.* 2014). The stability is hypothesized to be due to more stable hormonal levels and potential changes in sexual habits during pregnancy (Walther-António *et al.* 2014). Also, the lack of menstrual bleeding, shown to have a significant effect on the VMB stability (Gajer *et al.* 2012), might enhance VMB stability in pregnancy. The diversity of VMB is highest during the first trimester of pregnancy and diminishes during the second and third trimester (Kroon *et al.* 2018; Walther-António *et al.* 2014), possibly due to yet rising estrogen levels with progressing gestational age. During pregnancy VMB may typically change from one *Lactobacillus* spp. dominant CST to another but rarely to mixed community, i.e. CST IV (Romero *et al.* 2014b). As in non-pregnant women (Gajer *et al.* 2012; Petrova *et al.* 2017), *L. crispatus* appears as the most distinctive to a healthy state that also promotes the stability of normal VMB, whereas *L. iners* is more prone to convert to abnormal VMB (Verstraelen *et al.* 2009) (figure 2). *L. iners* has been shown to be more prevalent in older pregnant women (Walther-António *et al.* 2014) as well as among pregnant African-American women compared to other ethnic backgrounds, similar to CST IV (Hyman *et al.* 2014; Tabatabaei *et al.* 2018).

Interestingly, as the pregnancy progresses towards term, VMB might become more similar to the non-pregnant state (Aagaard *et al.* 2012). Especially in *L. iners*-dominated communities a clear increase in taxonomic richness can be seen towards the end of pregnancy (Goltsman *et al.* 2018). The potential significance of such VMB changes, for example, to the duration of pregnancy remains unclear.

2. Microbiota and preterm birth

Most studies on VMB during pregnancy have focused on its role in preterm birth (PTB) (Aagaard *et al.* 2012; Brown *et al.* 2018; Callahan *et al.* 2017; Digiulio *et al.* 2015; Freitas *et al.* 2018; Goldenberg *et al.* 2008; Goltsman *et al.* 2018; Hyman *et al.* 2014; Kindinger *et al.* 2016; Kroon *et al.* 2018; Liu *et al.* 2016; Walther-António *et al.* 2014). PTB is the leading cause of neonatal mortality and morbidity worldwide, causing around million deaths each year (Liu *et al.* 2016). Despite intensive research, the ultimate trigger behind spontaneous PTB remains unclear. Overall, infections are thought to cause up to half of spontaneous PTB cases (Goldenberg *et al.* 2008), classically as ascending infections, drawing more attention to VMB during the recent years.

The role of VMB in PTB is controversial and seems to vary depending on the ethnicity of the cohort studied (Callahan *et al.* 2017). Most probably genetic factors affect and alter host–microbiome interactions so that the same microbial community structure causes divergent responses in women with different ethnic backgrounds. High VMB diversity and low lactobacilli count as signs of vaginal dysbiosis are linked to PTB in Caucasian (Brown *et al.* 2018; Digiulio *et al.* 2015; Freitas *et al.* 2018; Kindinger *et al.* 2016; Tabatabaei *et al.* 2018), but not in African-American women (Callahan *et al.* 2017; Romero *et al.* 2014a). African-American and black women are at increased risk of PTB compared to white women (Goldenberg *et al.* 2008) and their VMB diversity during pregnancy appears as most diverse (Hyman *et al.* 2014; Tabatabaei *et al.* 2018). Somewhat surprisingly, in a recent study on mainly African-American women the diversity and richness of VMB decreased significantly over pregnancy in women with preterm birth, especially between the first and second trimesters (Stout *et al.* 2017). Increased community instability was also associated with PTB (Stout *et al.* 2017), which has been shown also in Caucasian women (Callahan *et al.* 2017).

L. crispatus is seen as a protective factor against PTB in all ethnicities (Callahan *et al.* 2017; Kindinger *et al.* 2017; Tabatabaei *et al.* 2018), whereas *L. iners* dominance in the second trimester might increase the risk of PTB at least in Caucasian women (Kindinger *et al.* 2017; Petricevic *et al.*

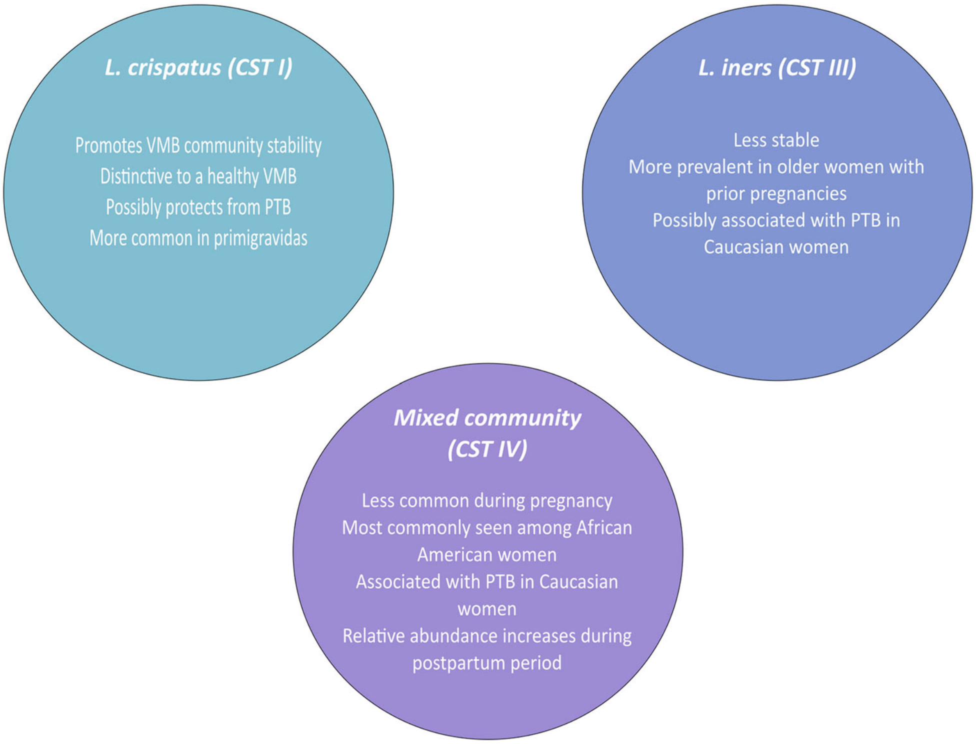

Figure 2. Community state type (CST) I, III and IV. CST I and III are the most common community state types during pregnancy. CST IV, a mixed community where lactobacilli are replaced with anaerobic bacteria, has been linked to adverse pregnancy outcomes such as preterm birth (PTB) in Caucasian women.

2014). Vaginal dysbiosis might be associated with premature cervical remodeling and PTB, most likely through activation of a local tissue inflammation process (Kindinger *et al.* 2016).

PTB has multiple clinical presentations and heterogenous underlying etiologies. Inflammatory neutrophils and macrophages in the uterus, decidua, fetal membranes and cervix are activated during labor (Girardi 2018; Gomez-Lopez *et al.* 2013; Thomson *et al.* 1999; Young *et al.* 2002). Complement activation leads to the chemotactic recruitment of immune cells, microbial phagocytosis, antigen uptake by dendritic cells and their delivery to local lymph node for the generation of a sterile pro-inflammatory state leading to labor (Nadeau-Vallée *et al.* 2016; Romero *et al.* 2018). Furthermore, spontaneous PTB can present as preterm premature rupture of membranes (pPROM) or cervical dilatation. PTB has also iatrogenic causes (e.g. due to maternal or fetal complications). Many VMB studies have included all PTB cases, even iatrogenic, causing probable misinterpretation of the results. Considering pPROM's strong connection to intra-amniotic infection (Goldenberg *et al.* 2008) it conceivably has a stronger link to VMB than other clinical presentations. Thus, further studies are needed before definitive connections of VMB and PTB can be indicated.

3. Prolonged and post-term pregnancy

Prolonged (>41 weeks' gestation) and post-term pregnancies (>42 weeks' gestation) are associated with several adverse neonatal and maternal outcomes compared to term pregnancies (Olesen *et al.* 2003). Primiparity, previous post-term pregnancy, male fetus, genetic predisposition, obesity, maternal age and ethnicity have all been linked to susceptibility for post-term pregnancy (Caughey *et al.* 2009). Genetic factors, both fetal and maternal, attribute up to 30–50% of prolonged pregnancies (Laursen *et al.* 2004; Oberg *et al.* 2013). Despite intensive research the exact mechanisms leading to prolonged or post-term pregnancy are yet unknown. VMB has been linked to PTB which calls attention to VMB's potential significance behind prolonged pregnancy as well. Until today this connection has not yet been studied and thus opens a very interesting field of research in determining the interplay between VMB and host immune system during induction of labor.

4. Microbiota and parturition

To date, only few studies exist on VMB during labor. This is surprising given the anticipated role of VMB in the induction of labor as well as in neonatal colonization. A study comparing the VMB composition at 36 gestational weeks and at the onset of labor found increased VMB diversity at the time of labor onset (Avershina *et al.* 2017). Bacteria related to CST IV were significantly overrepresented at labor compared to samples at 36 weeks. Although there was less intra- than interindividual variation, a shift in CST was seen in 18% of the study cohort, most often to CST IV.

It is tempting to speculate that the increase in VMB diversity prior to labor onset could associate with or even cause a local immune and inflammatory response that starts or enhances the cervical remodulation process. An increased ratio of L- to D-lactic acid, seen in *L. iners* dominant VMB compared to *L. crispatus* dominant, has been associated with increased expression of vaginal extracellular matrix metalloproteinase inducer (EMMPRIN) and activation of matrix metalloproteinase-8, the latter being an enzyme involved in remodeling the cervix prior to onset of labor (Witkin *et al.* 2013). Vaginal communities dominated by *L. crispatus* are also associated with lower levels of pro-inflammatory cytokines than those colonized by *L. iners* or bacterial vaginosis associated bacteria that also induced secretion of pro-inflammatory cytokines (e.g. IL-1α, IL-1β, and IL-8) from human vaginal cells *in vitro* (Anahtar *et al.* 2015). The potential role of VMB in activating the onset of parturition remains yet to be elucidated.

Recent high-resolution analyses of mother-infant microbiomes indicate that vaginal bacteria are detected in the neonate only transiently and play minor or no role in stable intestinal colonization (Ferretti *et al.* 2018; Sakwinska *et al.* 2017). However, the maternal VMB may still have a major impact on the neonate's early immunity as the exposure to high quantities of vaginal bacteria (up to 10^9 bacteria per gram vaginal secretions; re-calculated from Virtanen *et al.* 2017 data (Virtanen *et al.* 2017)) conceivably activate and stimulate toll-like and other bacterial sensing innate immune receptors, e.g., in the airways. However, currently there is no data to support the transfer of maternal vaginal content to a neonate born via elective C-section nor can it be recommended due to the risk of transferring pathogenic bacteria or viruses to the neonate (Haahr *et al.* 2018).

5. Microbiota after pregnancy

After parturition the estrogen levels decline fast (Nott *et al.* 1976) causing a dramatical change in VMB composition, characterized by a reduction in *Lactobacillus* spp. and an increase in alpha-diversity irrespective of ethnicity, mode of delivery, or community structure during pregnancy (Digiulio *et al.* 2015; Huang *et al.* 2015; MacIntyre *et al.* 2015). This is accompanied with a decrease in community stability. These changes can be seen to prevail up to a year after giving birth (Digiulio *et al.* 2015). Accordingly, the VMB composition during the first trimester of pregnancy was shown to associate with pregnancy history, *L. crispatus* being more abundant in women with their first pregnancy and *L. iners* in women with prior childbirth or spontaneous or induced abortion (Nasioudis *et al.* 2017). Since BV related bacteria and a diverse VMB have been linked to adverse pregnancy outcomes, such as PTB and spontaneous abortion (Kroon *et al.* 2018), these findings could favor a longer interval between pregnancies. However, the length of this diverse community prevalence remains to be elucidated before any recommendations concerning the time before subsequent conception can be given.

6. Summary

Understanding of VMB's composition and its interactions with the host during pregnancy has vastly expanded during the recent years. VMB is known to associate at least indirectly with preterm birth, while its role on labor onset or in prolonged pregnancies has received much less attention and should hence be addressed in the future studies. Similarly, the effect of diet and other lifestyle factors that vary greatly between different populations should be investigated for their potential contribution to VMB variation and intentional microbiota modulation to support women's health.

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