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Review

The gut microbiome in pregnancy and pregnancy complications

Sondra Turjeman[1], Maria Carmen Collado[2] and Omry Koren[1]

Abstract

During gestation, the female body undergoes a number of changes; accordingly, her microbiota also undergoes marked changes throughout the duration of her pregnancy. Some shifts in the microbial community are imprinted even before pregnancy and may affect a woman's ability to conceive. Prepregnancy obesity and inflammatory bowel disease are associated with gestational dysbiosis, as are several conditions occurring during pregnancy, including gestational diabetes mellitus and preeclampsia. Here, we review pregnancy and associated complications in the context of the gut microbiota, but dysbiosis in other microbial communities, including those of the vagina, oral cavity, and cervix, is also associated with pregnancy-related conditions. We not only highlight the numerous studies conducted thus far but also discuss some of the shortcomings in the field and provide important directions for future research.

Addresses

[1] Azrieli Faculty of Medicine, Bar Ilan University, Safed, Israel
[2] Institute of Agrochemistry and Food Technology (IATA-CSIC), National Research Council, Valencia, Spain

Corresponding author: Koren, Omry (omry.koren@biu.ac.il)

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Healthy pregnancy

The unique changes that occur during gestation and influence every organ in the female body have been reported to influence the gut microbiome as well [1–5]. These drastic changes, which include altered hormonal levels, modulation of the immune system, and metabolic changes, impact the microbiome directly and indirectly. One such example that we reported recently is the influence of progesterone on the microbiome composition in general and on the levels of *Bifidobacterium* specifically. We demonstrated increased levels of Bifidobacteria in women and in mice, and *in vivo* and *in vitro* experiments showed the direct effect of progesterone [3]. Bifidobacteria are of extreme importance in the neonatal period as they are known to degrade human milk oligosaccharides; hence, we proposed that the elevated levels of progesterone toward the end of pregnancy cause an increase in Bifidobacteria so that they can be transferred to the offspring. Other changes that occur toward the end of pregnancy, compared with women before and early in pregnancy, include an increase in beta diversity, a decrease in alpha diversity, and increased relative abundance of opportunistic pathogens [4], which may be involved in educating the infant immune system. In an experiment wherein the gut microbiota of women in their first and third trimester was transplanted into germ-free mice, the 3rd-trimester microbiome led to greater weight gain and increased low-grade inflammation and insulin resistance in these mice than in mice that received the 1st-trimester microbiota [4]. More studies are needed to fully characterize the changes that occur in the gut microbiome during healthy pregnancy as some studies reported other changes or no significant changes [6,7]. The reasons for these discrepancies could be several. Changes in diet [8], differences in body mass index (BMI) [9], nulliparous versus multiparous pregnancies [2], antibiotic use [10], and more could all influence the microbiome and need to be controlled for.

The maternal pregnancy microbiome is important for fetal development and the mother's health. For example, Li et al. [11] hypothesized that maternally derived bacterial metabolites are transmitted to the fetus to educate its immune system and prepare the fetal gut for bacterial colonization after birth. Priming of the fetal immune system by the maternal microbiome was also shown in mice by Gomez de Aguero et al. [12], who transiently colonized pregnant germ-free mice and showed an effect on the offspring immune system. Recently, it was also demonstrated in mice that the maternal microbiome modulates fetal neurodevelopment [13], and it has been suggested that bacterial peptidoglycans play a role [14]. Some studies have even been able to directly associate the presence or absence of certain bacteria in pregnancy with the health of the offspring. For example, the presence of *Prevotella* in the maternal microbiome is associated with protection against food allergies in offspring [15].

Interestingly, we recently demonstrated that children with food allergies have lower levels of *Prevotella* than nonallergic controls [16]. In summary, during pregnancy, the microbiome has several roles: (1) maintenance of a healthy pregnancy, (2) contribution to fetal development, and (3) acquisition of necessary bacteria by the neonate for the first days outside the womb. Any changes in this delicate interplay may lead to pregnancy complications or have lasting effects on the offspring.

Infertility

Even before pregnancy, microbiota can affect fertility. There is evidence of gut dysbiosis in infertile women characterized by increased levels of Verrucomicrobia and decreased levels of *Stenotrophomonas*, *Streptococcus*, and *Roseburia*, as compared with control subjects [17]. Furthermore, it has been reported that gut microbiota may drive development of polycystic ovary syndrome and insulin resistance, thus affecting metabolic homeostasis and reproductive health [18,19].

Prepregnancy conditions and the gestational microbiome

As discussed, the gut microbiota plays a role in fertility, and the microbial community changes throughout pregnancy. There are also some prepregnancy conditions that have been described to uniquely influence the microbiota in women beyond typical pregnancy-related changes, including obesity [9] and inflammatory bowel disease (IBD) [2]. These microbial changes have an impact on neonatal microbiota development [20,21] and increase the risk of disease in the infant.

Obesity

High BMI before pregnancy is associated with maternal obesity and excessive weight gain during pregnancy, which, in turn, shape the gut microbiota [21,22]. A lower population of *Bifidobacterium* spp. has been identified in pregnant women with obesity, as well as in mothers who gained excessive weight during pregnancy, than in lean women and women with normal weight gain [23]. Lower levels of *Bacteroides* spp., along with higher abundances of *Staphylococcus* and proinflammatory bacteria such as *Escherichia coli* spp., have been also identified in overweight pregnant women than in lean ones [22]. Furthermore, maternal obesity was associated with lower microbial diversity [24]. Higher specific inflammatory markers, including haptoglobin, higher Firmicutes levels, and a higher Firmicutes:Bacteroidetes ratio were also observed in overweight pregnant women and pregnant women with obesity than in lean mothers [9].

Inflammatory bowel disease

Owing to the modulation of the immune system during pregnancy, the status of several immune-related diseases changes in patients. Some experience remission during pregnancy, whereas others experience relapse in their disease condition [25]. One such example that has been recently studied in the context of pregnancy and the microbiome is IBD [2]. Patients with IBD, who suffer from microbial dysbiosis, had lower alpha diversity than healthy pregnant controls during the first trimester, but during the second and third trimesters, there were no significant differences in the diversity. The study also describes that pregnant women with IBD had more similar microbiomes to one another (lower beta diversity) than healthy pregnant women. Unfortunately, in the described study, it was only possible to compare the diversity indices but impossible to report specific differences in bacterial species as the methods of DNA extraction differed between healthy women and women with IBD [2]. However, Torres et al. [20] reported that besides changes in diversity, pregnant women with IBD also had a different bacterial composition compared with the controls, with increased relative abundance of Gammaproteobacteria and decreased levels of Bacteroidetes. The authors also suggest decreased diversity and different bacterial compositions in newborns of mothers with IBD [20].

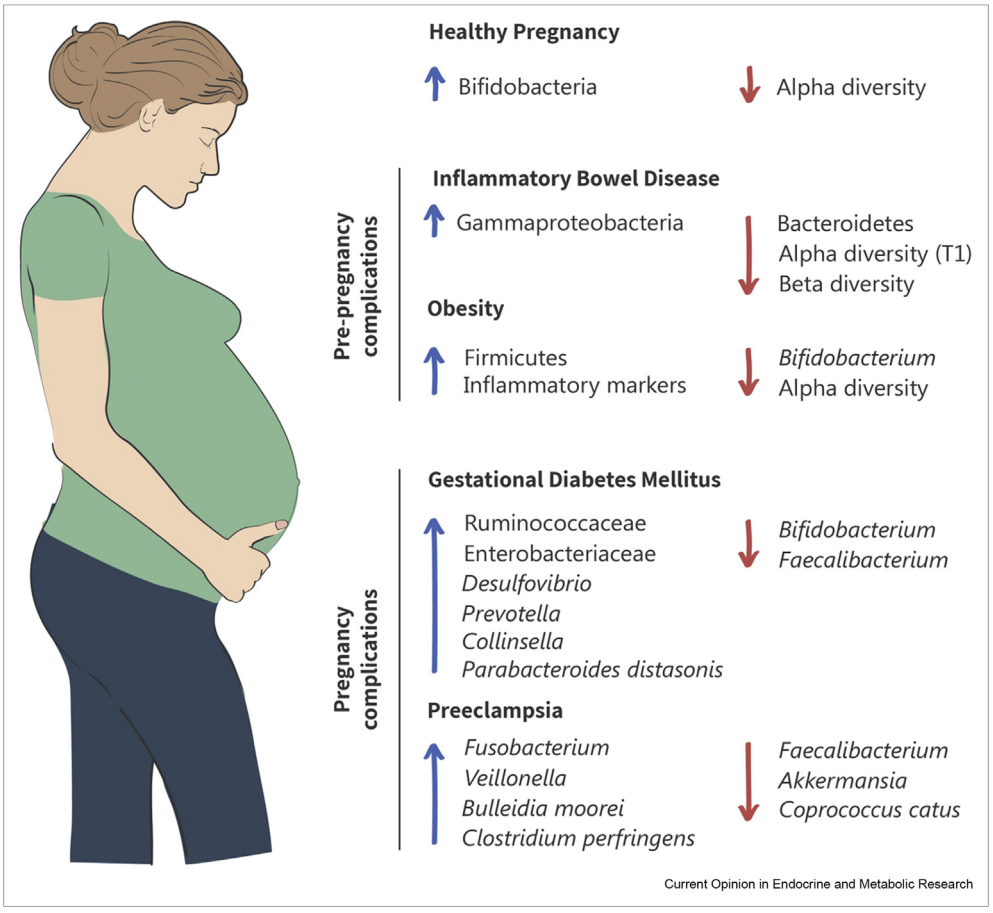
Microbial dysbiosis during pregnancy: pregnancy complications

The aforementioned factors, which can lead to microbial dysbiosis before pregnancy, can also cause pregnancy complications. Similarly stress and other psychosocial and physical factors may influence microbiota composition and diversity with consequences on pregnancy and maternal–fetal outcomes through, for example, gestational diabetes, infections, and risk of preeclampsia (PE) and preterm birth. We review these complications in the following sections.

Gestational diabetes

Gut microbiota dysbiosis has been extensively studied in those suffering from type 2 diabetes mellitus [25–28], and similar dysbiosis is starting to emerge in women diagnosed with gestational diabetes mellitus (GDM; reviewed in the study by Hasain et al. [29]). To date, most studies on the interplay between gut microbiota and GDM focused on later-pregnancy microbiota composition. One study, however, examined the microbiota of women in the first trimester and found significant dysbiosis in GDM-positive versus GDM-negative women (increased Ruminococcaceae family [30]). Patterns of GDM-associated dysbiosis continued throughout pregnancy [31–33], even when taking into account normal background changes [4]. Taxa associated with GDM were varied and differed across studies but generally included Ruminococcaceae, Enterobacteriaceae, *Desulfovibrio*, *Parabacteroides distasonis*, *Prevotella*, and *Collinsella*; on the other hand, *Faecalibacterium* and *Bifidobacterium* were typically less abundant [29]. Accordingly, there is some evidence of correlation between these taxa and inflammation, adiposity, and

Figure 1



General microbiota dynamics in healthy pregnancies and those with complications. The presented patterns of change are for the gut microbiota. T1 refers to the first trimester.

glucose intolerance. Dysbiosis among GDM positive women was also reported shortly after pregnancy [33,34], but the exact patterns varied between studies. Furthermore, in a study looking at long-term microbiota changes, there was no effect of GDM five years after pregnancy [35]. Meconial microbiota were also significantly different among neonates born to GDM-positive versus GDM-negative mothers [36].

Risk of Preeclampsia

Little is known about the impact of gut microbiota on the risk of PE, but one small study found that the gut microbiota of Chinese women with PE had a different microbial profile than those with healthy pregnancies [37] and were characterized by higher abundance of *Bulleidia moorei* and *Clostridium perfringens* and decreased abundance of the propionate producer *Coprococcus catus*. Furthermore, a second study on women with PE found higher abundance of *Fusobacterium* and *Veillonella* as well as opportunistic pathogens and a reduction in the beneficial bacteria *Faecalibacterium* and *Akkermansia* [38]. These changes were correlated with increased blood pressure, both in the study of PE and in other studies of microbial dysbiosis.

Prospectus

Studies of gut microbiota composition and dysbiosis are most common in the literature, but many conditions, including pregnancy-related ones, have been studied as they relate to other microbial communities such that an integrative study across body sites is of paramount importance. Before conception, the presence of vaginal microbiota dysbiosis has been associated with infertility [39] and reduced in vitro fertilization success [40–42]. In addition, a large study of the vaginal microbiota in pregnant women with Group B *Streptococcus* (GBS) revealed that specific microbial taxa were associated with GBS colonization, highlighting a potential role of the microbiota in promotion or inhibition of GBS [43]. Similarly, a depletion of *Lactobacillus* spp. and altered vaginal and cervical microbiota have been linked to a higher risk of preterm premature rupture of membranes

[44–46], which can increase the risk of neonatal sepsis [47]. Furthermore, microbial dysbiosis in the oral cavity has been implicated in PE [48]. Accumulating data also show that vaginal microbiota dysbiosis during pregnancy is linked to an increased risk of preterm birth and that there are marked community differences between full-term and preterm deliveries [49–51]. An integrated study examining community dynamics throughout the body as they relate to one or more pregnancy-related conditions can help illuminate microbial cross talk and provide a better understanding of the complexities underlying the condition's etiology.

Also of interest are metabolomics studies that compare metabolic profiles among various study groups and also relate them to microbiota diversity. Metabolic disruption has been observed both when comparing pregnant and nonpregnant women [52] and when examining pregnancy progression [53]. There is also evidence, for example, of specific metabolic profiles in women with GDM [54]. Although further study is needed, correlations were found between mother and newborn urine metabolite profiles [55], suggesting metabolic disruption could also be passed to neonates.

Although tens of studies have been conducted, understanding true, consistent associations between pregnancy complications and gut microbiota is still challenging. Consistent and corroborated patterns of gut microbiota dynamics as they relate to pregnancy and associated complications are presented in Figure 1, but much is still unknown. Sequencing methods and 16S rRNA gene variable regions vary, making it difficult to compare operational taxonomic units or amplicon sequence variants across studies. Furthermore, study participants span a wide geographical range and recruitment criteria vary, resulting in a wide range of ages, sampling time(s), and individual parameters (e.g. BMI). There are also known short- and long-term effects of antibiotic use (and that of other drugs) on the microbiome, both in pregnant women and their newborns [52]. Large longitudinal (first, second, and third trimesters and after pregnancy), paired (case–control) studies with standardized protocols across a diverse geographical range are important, especially because incidence of some complications can be ethnically based. With these types of data sets, we anticipate preventative probiotic (reviewed in the studies by Taylor et al [56] and Pan et al [57]) and postbiotic measures as well as the possibility of early prediction of complications toward reducing severity or preventing the onset.

Conflict of interest statement

Nothing declared.

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