The Pregnancy Microbiome

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Abstract

In recent years, microbiome research has revealed multiple essential roles of the microorganisms residing within the human body in host metabolism, immunity, and overall health. Numerous physiological and pathological states, including obesity and the metabolic syndrome, have been correlated with microbial changes, termed dysbiosis. Our microbiomes change in response to our environment, diet, weight, hormones, and other factors. It is, therefore, not surprising that there are also significant changes in the microbiome during pregnancy when dramatic weight gain and metabolic and immunological changes occur. In this review, we summarize the known changes in microbial composition throughout pregnancy at a variety of body sites, including the gut, vagina, oral cavity, and placenta, and we describe several studies that have linked pregnancy complications with microbial changes. Unlike the case of certain disease states, such as obesity, where dysbiosis is considered to have negative effects, we believe that the microbial alterations observed during pregnancy are vital for a healthy pregnancy. While more research in this field is required to reveal specific mechanisms and pathways regulating these alterations, the microbial changes during pregnancy are likely coordinated with the immune, endocrine, and metabolic states.

Introduction

The human microbiome includes hundreds of different microbial species residing within and on us, playing essential roles in our metabolism and immune and endocrine system. These microbial populations have been shown to change during our lifetime, from infancy to childhood, adulthood, and old age.
The microbial populations are also highly affected by weight gain, diet, and immune and hormonal changes. Therefore, it is not surprising that there are distinct alterations in the microbiota at multiple sites within the body during pregnancy. Pregnancy, a complex physiological process, is associated with simultaneous hormonal changes, weight gain, and immune system modulations, which must all be synchronized to preserve the health of both the mother and the offspring [1]. In this review, we describe the pronounced microbial changes that occur in the pregnant female. We hypothesize that an appropriate microbiota is essential for the healthy early development of the fetus and pregnancy maintenance. Moreover, we suggest that the microbial changes during pregnancy are highly correlated with other physiological changes, including those in hormones, immunity, and metabolism. Understanding the roles of the microbiome throughout pregnancy in health and disease is of great importance for opening new research avenues and suggesting new therapeutic approaches. Yet, there remains much to be discovered regarding the precise microbial alterations during pregnancy, their timing, and, potentially, their further effects.

Studying the microbiota in pregnancy opens another fascinating question of whether the fetus is exposed to microbes, and, if so, at what stage of development. While it has been thought for over a century that we are born germ free [2], numerous pieces of evidence now cast doubt on this hypothesis and suggest that a bacterial presence already exists in the fetoplacental unit [3, 4]. The enigma of whether a placental microbiota exists as well is still not fully resolved.

The Healthy Microbiome

The human microbiome is a collection of bacteria, archaea, fungi, and viruses, all residing within our bodies and including their genetic material. Within each one of us, there are trillions of microbial cells representing hundreds of different species. Together, they play important roles in host metabolism, immunity, endocrinology [5], and overall health. The microbial compositions vary between people and are greatly affected by diet, additional environmental factors, weight gain, and immune state, etc. Different body sites harbor different microbial populations due to varying levels of pH, oxygen, nutrients, humidity, and temperature [5]. Therefore, the gut, oral cavity, and vagina each harbor distinct bacterial communities, potentially playing different beneficial roles. In this review, we mainly discuss alterations during pregnancy in bacterial communities of the microbiome, as these are the best studied to date. It is important to remember that pregnancy is a healthy physiological process in which beneficial microbial alterations are expected. This is in contrast to disease states such as obesity,
inflammatory bowel disease (IBD), diabetes, and the metabolic syndrome, in which an unhealthy shift in microbiota composition, termed dysbiosis, may occur [5].

**Factors Affecting the Microbiota during Pregnancy**

One group of initial changes that occur during pregnancy is hormonal changes. Most importantly, progesterone and estrogen levels rise dramatically, with numerous physiological effects. These hormonal levels are likely to affect the microbiome composition since it has previously been shown that microbial components can respond to and regulate host hormones, and that host hormones influence bacterial growth. On the other hand, the microbiota can also produce and secrete hormones, emphasizing the bidirectional nature of the interplay between microbiota and hormones. Nonetheless, direct effects of progesterone and estrogen on the microbiota, and the effects of the microbiota on these hormones, have not yet been proven [6].

Additionally, significant immune changes occur during pregnancy, and these are likely to affect the microbiota. The immune changes are complex in order to protect the fetus and mother from infection on the one hand, while nevertheless enabling fetal immune development and preventing fetal rejection by the maternal immune system. The microbial components are crucial players in this immune modulation; however, they themselves are also affected by immune changes.

Finally, metabolic changes occur during pregnancy, including changes in energy homeostasis, fat storage, and hormonal regulation. In many ways, the metabolic changes associated with pregnancy are similar to those that occur in the metabolic syndrome, including weight gain, elevated fasting blood glucose levels, insulin resistance, glucose intolerance, low-grade inflammation, and changes in metabolic hormone levels [7]. While the microbiota plays active roles in these metabolic processes, it is also highly affected by host metabolism, as seen by dysbiosis in obesity, the metabolic syndrome, and diabetes. Therefore, the metabolic changes occurring during pregnancy are expected to influence the microbiota composition.

**Pregnancy Leads to Changes in the Gut Microbiota**

Several alterations in the gut microbiota have been associated with pregnancy progression. In general, pregnancy is characterized by an increase in the bacterial load and profound alterations in the composition of the gut microbiota [7]. Most
of the changes relative to nonpregnant women are seen in late pregnancy. These
dramatic changes are characterized by reduced individual richness (α diversity),
increased between-subject diversity (β diversity), and alterations in abundance of
certain species [8]. Increased abundance of members of the Actinobacteria and
Proteobacteria phyla are observed at the expense of reduced abundance of *Faecalibacterium* and other short-chain fatty-acid producers. *Faecalibacterium* is a
butyrate-producing bacterium with anti-inflammatory activities, which is depleted
in metabolic syndrome patients [9]. This is of particular interest, since pregnancy
shares some characteristics with the metabolic syndrome, including weight gain,
inulin sensitivity, and higher levels of low-grade inflammatory markers [8].
However, in contrast to metabolic syndrome patients, in the context of pregnan-
cy, these parameters are normal requirements for healthy fetal development. Fur-
ther comparisons between the microbial signatures of pregnancy and disease
states such as the metabolic syndrome may highlight common as well as unique
pathways and microbial involvement in each condition.

When starting to dissect the roles of the gut microbiota during pregnancy,
the third-trimester microbiota was shown to cause increased weight gain, insu-
lin resistance, and a greater inflammatory response compared to the first-tri-
merstern microbiota when transferred to germ-free mice [8]. These findings dem-
onstrate that the microbial components actively contribute to changes in host
immunology as well as metabolism. Gut microbiota have also been suggested to
play a role in host weight gain during pregnancy via increased absorption of glu-
cose and fatty acids, increased fasting-induced adipocyte factor secretion, induc-
tion of catabolic pathways, and stimulation of the immune system [8, 10].

Since the microbial communities are greatly affected by the host diet and ini-
tial weight, the microbiota of pregnant women differ accordingly [10]. Over-
weight pregnant women exhibit significantly higher levels of gut *Bacteroides* and
*Staphylococcus* than pregnant women of normal weight [10]. While most studies
show significant alterations in gut microbiota during pregnancy, DiGiulio et al.
[11] did not detect any changes in gut or vaginal microbiota composition includ-
ing richness indexes during gestation.

Antibiotics administered during pregnancy were shown to affect the micro-
biome composition and diversity, as well as to promote weight gain in rodents
[12]. It is especially intriguing to understand the consequences of the maternal
microbiome composition during pregnancy on the offspring in terms of weight
gain, immunity, and infant health [13]. Recently, the maternal microbiota was
shown to shape the offspring’s immune system in terms of immune gene expres-
sion and numbers of innate cells [14], and it was also hypothesized that micro-
bial exposure during pregnancy may be of great importance for preventing al-
lergic disease in the offspring [15].
Pregnancy Leads to Changes in the Vaginal Microbiota

The vaginal microbiome undergoes significant changes during pregnancy as well [7], including a significant decrease in overall diversity, increased stability, and increased abundance of *Lactobacillus* species [16]. *Lactobacillus* species are lactic acid-producing bacteria that normally dominate the vaginal microbiota. Their increase during pregnancy correlates with a decrease in the vaginal pH, creating a barrier against pathogenic bacteria and viral infections, and an increase in vaginal secretions [17, 18]. The major changes in the vaginal microbial compositions occur in early pregnancy, while the communities at the later stages of pregnancy resemble those of the nonpregnant state [16]. In pregnancy, there is often a dominant *Lactobacillus* species, although the specific species varies according to the ethnic group [19, 20]. As expected, during the postpartum period, the vaginal microbiome gradually reverts to baseline characteristics, including a decrease in *Lactobacillus* species abundance, an increase in α diversity, and enrichment of bacteria associated with vaginosis, such as Actinobacteria [19].

Pregnancy Leads to Changes in the Oral Microbiota

The main change occurring in the oral microbiota during pregnancy is an increase in the microbial load. A study which compared the abundance of 7 common bacterial species in the oral cavity of nonpregnant women and women at different stages of pregnancy found that the total viable microbial counts were higher during pregnancy, as were levels of the pathogenic bacteria *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*, and *Candida* [21].

It remains to be discovered how pregnancy leads to changes in the oral composition. There have also been several studies that found correlations between oral infections and pregnancy complications, further suggesting mechanisms connecting the oral microbiome with the state of pregnancy. One explanation for the increased oral microbial load may be the overall immune changes (suppression) during pregnancy.

Debate over the Placental Microbiota

Until recently, the fetoplacental unit was considered to be germ free, and the first exposure to microbes was assumed to occur during delivery. Accordingly, any signs of bacteria in the placenta or embryonic fluids were considered to be
a result of contamination originating from the lower genital tract and posing a potential danger to the pregnancy [22]. However, with the recent leap in understanding the complexity of our microbiota and its important roles in healthy states, multiple studies have tried to examine whether a healthy placental microbiota exists. Several findings using both culture and metagenomic techniques suggest the presence of bacteria in the healthy placenta. First, bacteria have been cultured from placentas of healthy women without chorioamnionitis [23]. Furthermore, using whole-genome shotgun sequencing of samples from 320 subjects, Aagaard et al. [4] reported that the placenta contains a unique microbiome, somewhat resembling the oral one. This similarity between the oral and placental microbiota may be less surprising than it initially appears, since periodontal infections have previously been linked to an increased risk of pregnancy complications [7]. One hypothesis is that bacteria may pass from the oral cavity to the placenta through an unknown mechanism. In contrast, other studies highly doubt the presence of a placental microbiome, since even when such colonization is found, it is of extremely low biomass and may therefore represent contamination rather than a real phenomenon. It was in fact shown that low-biomass samples many times resemble contamination controls due to commercial reagents, as opposed to unique placental microbiota [24]. Such technical contaminations are especially prevalent when placental samples are received following natural births, when contaminations from the birth canal are likely.

As for amniotic fluid, a number of studies have shown the presence of microbes in healthy women using cultivation and PCR techniques [13]. Additionally, it was claimed that the bacterial populations detected in meconium might represent prenatal bacterial exposure. This may explain differences in microbial compositions found in meconium between infants of mothers who received probiotics during pregnancy compared to controls [25].

The debate over the placental microbiome remains an intriguing, open question. If indeed future research will verify the existence of these populations, further studies should investigate the potential roles of microbiota in gestation and fetal development.

**Pregnancy Complications Are Correlated with Dysbiosis and Infections**

Pregnancy complications occur commonly (usually with unknown etiology), are observed in approximately 1 in every 6 pregnancies, and pose a serious risk for both maternal and fetal health and survival [26]. The most common pregnancy complications include preeclampsia, eclampsia, intrauterine growth
restriction, and preterm birth. While some bacterial infections have been correlated with pregnancy complications, precise causal mechanisms are, as yet, unknown [27]. Several more recent studies have attempted to test for correlations between the microbial communities present during pregnancy and pregnancy complications [28].

Two studies demonstrated a correlation between high α (within-individual) diversity in gut microbiota and preterm birth [20], while a third study did not [29]. Additionally, certain vaginal communities in early pregnancy stages were significantly associated with an elevated rate of preterm birth [11]. These communities include higher abundances of Gardnerella and Ureaplasma, lower abundances of Lactobacillus sp., and higher α diversity. Additionally, the presence of certain vaginal fungi, even when asymptomatic, such as Candida albicans, is correlated with higher rates of preterm birth [30].

Finally, oral infections have been reported as risk factors for pregnancy complications such as preterm birth [31, 32]. There are several theories regarding potential mechanisms for this effect, including the direct contact with microbiota via the placenta or more systemic inflammation and hormone production leading to preterm birth [4, 33, 34].

Conclusions

In this review, we discuss the dramatic changes observed in the microbiome composition at multiple sites (gut, vagina, oral cavity, and placenta) during healthy pregnancy and in complicated pregnancy. We try to present these changes in the context of the overall unique physiology during pregnancy. Pregnancy is a natural process of growth and development, in which many physiological changes occur, including changes in body composition, weight gain, hormonal levels, inflammation, and metabolic states. These multiple changes have distinct effects on the microbiota, which is altered accordingly. These changes are finely synchronized to ensure the healthy development of the embryo and fetus, and to meet the growing needs of the fetus up to delivery.

The debate over the sterile fetus has not been resolved. While some studies provide evidence for the presence of bacteria in the placenta, others contradict this, claiming that the bacteria observed were introduced by contamination. Additional studies are, therefore, required to resolve this issue. The possibility of early microbial colonization of the fetus suggests that from the very beginning of development, there may be reciprocal interactions between the developing host and microbiota, and that maternal microbial components may be transferred very early in development.
Future research will likely reveal the interactions and pathways linking the various physiological changes to the microbial changes, thereby explaining the significance of each change observed. Such studies may also have clinical relevance in terms of recommendations for antibiotic treatments, probiotics, and potential therapies for pregnancy complications.

**Disclosure Statement**

The authors declare that no financial or other conflict of interest exists in relation to the contents of the chapter.

**References**
