

# PLACENTAL MICROBIOME

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## Abstract

The placenta is one of the most poorly understood human organs, particularly with regard to the presence of microbes within it. Until recently the placenta and developing fetus were considered to be germ free, containing no apparent microbiome.

When studying the role of the microbiota in pregnancy, it is crucial to consider the stage at which the essential interaction between the host and its microbes begins. This strengthens the fact that more studies are needed to understand the effects of pregnancy on the gut microbiota.

Bacterial vaginosis is the most prevalent reproductive disorder and is linked with gynecological complications, like spontaneous preterm labor, abortion, and endometriosis.

Bacterial vaginosis can be cured by restoring the representative vaginal components of the microbiota with probiotic formula, usually species of the genus *Lactobacillus*.

The objective was to assess the available scientific evidence regarding the placental microbial composition of a healthy pregnancy, the quality of this evidence.

## Keywords:

*placenta, microbiome, pregnancy*

The placenta, a transient organ responsible for fetal nutrition, waste disposal, immune tolerance, and maternal-fetal gas exchange, is important for a healthy pregnancy.

The placenta is the principal organ nurturing the fetus during pregnancy and was traditionally considered to be sterile.

Recent work has revealed that the placenta is not sterile.

Recent work has suggested that the placenta harbours microbial communities, however the location and possible function of these microbes remain to be confirmed and elucidated.

Microbiome populations have been well-characterized in many distinct body-sites. Interestingly, there is a lack of knowledge in the microbiome of the placenta, an environment that was long thought to be sterile.

Investigating the placenta is important toward understanding the microbiome in human development, especially in light of previous evidence demonstrating that human microbiota populations fluctuate extensively in the first year(s) of life.

The hypothesis that the human placenta harbors living bacteria is a radical departure from currently accepted dogma and the many years of pathologic examination of human placentas by many clinicians and researchers.

Although the presence of bacterial rDNA (ribosomal DNA) in amniotic fluid has been previously well described.

Aagaard and colleagues hypothesized that bacteria translocate from the mother's oral cavity into the placenta, contributing to in utero colonization of the fetal gut.

The amniotic sac in which a fetus grows is a sterile environment, but the placenta - an organ the fetus shares with the mother - is home to a bacterial community.

The results support the existence of a low biomass placental microbiota in healthy pregnancies. Some of the microbial taxa found in the placenta might have an oral origin.

The existence of a placental microbiota is debated.

The human placenta has historically been considered sterile and microbial colonization was associated with adverse pregnancy outcomes. Yet, recent DNA sequencing investigations reported a microbiota in typical human term placentas.

However, this detected microbiota could represent background DNA or delivery-associated contamination.

Contemporary DNA sequence-based evidence does not support the existence of a placental microbiota, (Fig.1).



tect the fetus from infections. However, several lines of evidence suggest the presence of bacteria in the normal placenta, itself.

This review will focus on the current understanding of the placental microbiota in normal healthy pregnancy. Factors known to alter the composition of the placental microbiota will be discussed in the final part of this review.

Similarities between microbial communities in the placental and oral niches have suggested that the oral mucosa is a possible source of the placental microbiome, (Fig.2).

Both a healthy womb and the placenta that nourishes the growing fetus are sterile. If bacteria do sneak in, they're intruders and bad news for the fetus.

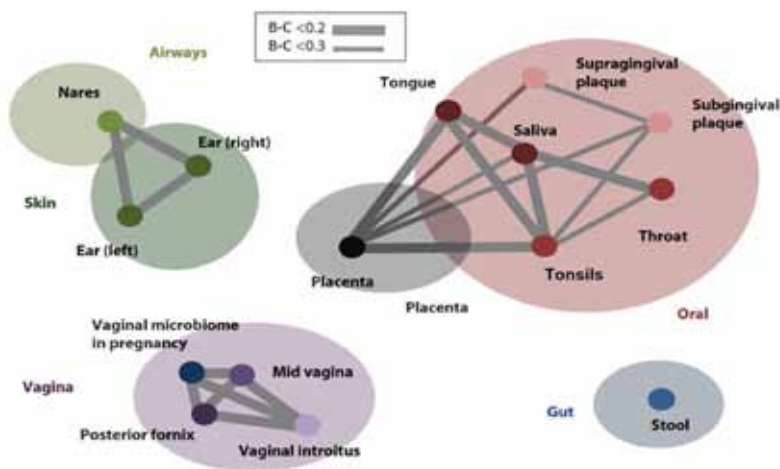
But in 2014, Kjersti Aagaard from Baylor College of Medicine challenged that dogma.

Contrary to the prevailing idea of a "sterile" intrauterine environment, Aagaard and coauthors demonstrated the consistent presence of a microbiome in placentas from healthy pregnancies.

This microbiome was consistently different from those reported in other parts of the body, including the skin and urogenital tract.

The placental microbiome was most similar to that of the oral cavity, but the clinical implications of this finding remain to be explored.

In addition, the authors identified associations between the composition of the pla-



**Fig. 2** The placental microbiome has a taxonomic profile that is similar to the oral microbiome (6) Strong phylum-level similarity was observed between the placenta and tongue, tonsils, saliva, and subgingival plaque taxonomic profiles. The colors of dots reflect the vicinity of the body sites.

central microbiome and a history of remote antenatal infection, as well as preterm birth, raising the possibility that the placental microbiome may play a role in these events.

The researchers also compared the placental microbiomes to those found in the vagina, gut, mouth and on the skin of non-pregnant women. They found that the placental microbiome was most similar to that of the mouth. The authors speculate that the microbes travel to the placenta from the mouth via the blood.

Investigations into reproductive-associated microbiomes began around 1885 by Theodor Escherich. He wrote that meconium from the newborn was free of bacteria. This was interpreted as the uterine environment was sterile.

Other investigations used sterile diapers for meconium collection. No bacteria were able to be cultured from the samples. Bacteria were detected and were directly proportional to the time between birth and the passage of meconium.

In 1982, Kovalovszki et al. were the first to describe the presence of aerobic bacteria in 16% of tested placenta samples using a culture-dependent approach, and concluded that bacteria can be detected in the placenta without any histological evidence of chorioamnionitis.

Since then, several additional reports described bacteria in the placenta.

A 1927 study demonstrated the presence of bacteria in the amniotic fluid of those that were in labor for longer than six hours.

The placenta contains a unique microbiome.

The placental microbiome is the nonpathogenic, commensal bacteria claimed to be present in a healthy human placenta and is distinct from bacteria that cause infection and preterm birth in chorioamnionitis. Until recently, the healthy placenta was considered to be a sterile organ but now genera and species have been identified that reside in the basal layer. It should be stressed that the evidence for a placental microbiome is controversial.

The placental microbiome more closely resembles that of the oral microbiome than either the vaginal or rectal microbiome. In a healthy placental microbiome, the diversity of the species and genera is extensive.

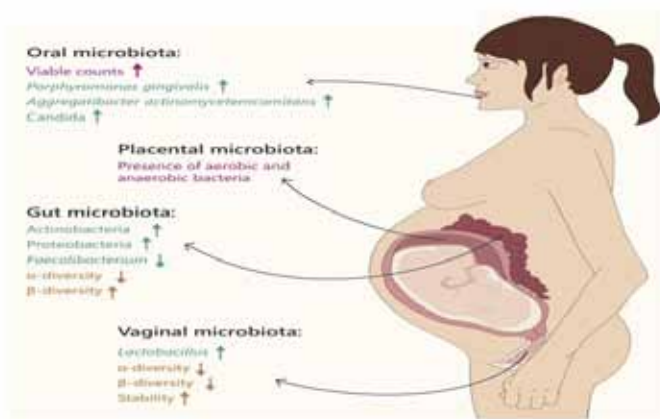
A change in the composition of the microbiota in the placenta is associated with excess gestational weight gain, and pre-term birth.

The placental microbiota varies (Fig.3), between low birth weight infants and those infants with normal birth weights.

While bacteria are often found in the amniotic fluid of failed pregnancies, they are also found in particulate matter that is found in about 1% of healthy pregnancies.

In animals, part of the microbiome is passed onto offspring even before the offspring are born. Bacteriologists assume that the same probably holds true for humans.

The microbes in the placenta comprise a wide spectrum, including Firmicutes, Tenericutes, Proteobacteria, Bacteroidetes, and Fusobacteria phyla. These are also found in the mouth.



**Fig. 3** Microbiome changes during pregnancy

A change in the composition of the microbiota in the placenta is associated with excess gestational weight gain, and pre-term birth.

Placental microbiome similar to that in the mouth may play a role in preventing preterm births.

The placental microbiome has not been robustly interrogated, despite recent demonstrations of intracellular bacteria with diverse metabolic and immune regulatory functions.

The placenta, long thought to be sterile, is home to a bacterial community similar to the one found in the mouth, researchers report today.

The microbes are generally non-pathogenic, but according to the authors of the study, variations in their composition could be at the root of common but poorly

understood pregnancy disorders such as pre-term birth, which occurs in one out of every ten pregnancies.

Healthy pregnancy is characterized by an increase in the bacterial load and profound alterations in the composition of gut microbiota.

Finally, it is intriguing to understand what are the consequences of maternal microbiome composition during pregnancy on the offspring in terms of weight gain, immunity, and infant health.

The postpartum period is also characterized by significant changes in the microbiota, and it has been reported that at least 1 month after birth the mothers' microbiotas do not yet return to their baseline.

The similarity between the oral and placental microbiota suggests that bacteria

may pass from the oral cavity to the placenta, possibly explaining the many observations of women with periodontal disease that have an increased risk of pregnancy complications.

Correlations between oral infections and pregnancy complications have been shown in various studies. Maternal periodontal disease has been shown to increase risk of preterm birth.

The development of the microbiome begins in utero, however factors related to the labor and birth environment have been shown to influence the initial colonization process of the newborn microbiome.

This “seeding” or transfer of microbes from the mother to newborn may serve as an early inoculation process with implications for the long-term health outcomes of newborns.

Vaginal microbes have also been isolated in intrauterine samples suggesting that organisms from the vagina may ascend into the intrauterine cavity from the vaginal canal.

It has become clear that the placenta is not a sterile organ, but rather has its own endogenous microbiome. Compared to the gut microbiome, the placental microbiome exhibits limited microbial diversity.

The interactions of host-microbe and microbial-microbe have existed before the birth.

However, the existence of placental microbiota and their regulatory effects on pregnancy are still controversial. It was found that placental microbes might be implanted into the placenta via urogenital-placental, gastrointestinal-placental, and oral-placental routes.

The placenta plays an important role in the modulation of pregnancy immunity; however, there is no consensus regarding the existence of a placental microbiome in healthy full-term pregnancies.

Also supporting the idea that the womb is sterile is the observation that germ-free mammals can be generated by sterile delivery of neonates into a sterile isolator, after which neonates remain germ-free, which would seem to provide strong data in support of sterility of the womb.

Our findings do not support the existence of a consistent placental microbiome, in either placenta from term deliveries or spontaneous preterm births.

Group B Streptococcus was detected in almost 5 percent of the samples collected before labor, but that does not make it a microbiome, it means that and other pathogens like *Listeria* can cross the placental barrier.

The placental microbiota varies between low birth weight infants and those infants with normal birth weights.

However, recent studies using molecular techniques suggest bacterial communities in the placenta, amniotic fluid, and meconium from healthy pregnancies.

The results support the existence of a low biomass placental microbiota in healthy pregnancies.

The human placenta has been traditionally viewed as sterile, and microbial invasion of this organ has been associated with adverse pregnancy outcomes.

A consistently significant difference in the abundance and/or presence of a micro-

biota between placental tissue and background technical controls could not be found.

This concept has become controversial as numerous studies suggest that the apparent placental microbiome is mostly, if not completely, comprised of contaminants.

Bacteria derived from the maternal circulation have been suggested to seed the human placenta during development leading to an intrinsic placental microbiome.

In a healthy placental microbiome, the diversity of the species and genera is extensive. A change in the composition of the microbiota in the placenta is associated with excess gestational weight gain, and pre-term birth.

Furthermore, commensal bacteria could be isolated from umbilical cord blood. Together, these studies underscore that there are microbial communities present in the placenta and that the fetus at term is not sterile.

Together these findings suggest that there is niche-specificity to the placental microbiota and placental microbiome studies should consider regional differences, which may affect maternal, fetal, and/or neonatal health and physiology.

Future research may find that the microbiota of the female reproductive tract may be related to pregnancy, conception, and birth.

## Conclusion

A bacterial presence already exists in the feto-placental unit.

The results support the existence of a low biomass placental microbiota in healthy pregnancies.

The placental microbiome more closely resembles that of the oral microbiome than either the vaginal or rectal microbiome. Some of the microbial taxa found in the placenta might have an oral origin.

The high risk of quality bias for the majority of the included studies indicates that the results of individual papers should be interpreted with caution.

Incidental findings of bacterial species could be due to contamination or to low-grade bacterial presence in some locations; such bacteria do not represent a placental microbiome per se.

These conclusions are largely based on the results derived from the sequencing of placental samples.

However, the existence of placental microbiota and their regulatory effects on pregnancy are still controversial.

## Conflicts of Interest

The author declare no conflict of interest.



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