Educational Gaps

1. The placenta is one of the least understood human organs, especially when considering its effect on fetal outcomes.
2. Recent work has revealed that the placenta is not sterile.
3. Many unexplored questions remain regarding microbial colonization in the placenta and the effect on pregnancy and fetal outcomes.

Abstract

Despite the well-known fact that the placenta has long-term effects on maternal and fetal health, the placenta remains a poorly understood and understudied organ. Not only is the placenta a site of exchange of nutrients and blood and gases between the fetal and maternal systems, but it also performs critical metabolic functions for supporting fetal development and maintaining maternal-fetal tolerance. It is also abundantly clear that impairment of placental function leads to severe pregnancy complications, including preterm birth (PTB), a significant cause of perinatal mortality and morbidity worldwide. Understanding the causes of PTB and other adverse outcomes is clearly essential for the development of effective methods of prevention and treatment. We focus our review of one major known cause of PTB, namely, infection. We also introduce a new and somewhat unexpected factor(s) that may well affect PTB and every aspect of placental biology and function: the placental microbiome. We discuss the implications of the placenta housing a microbial biomass for PTB and the effect of maternal microbiomes at various niches for fetal colonization and health outcomes. We suggest that the placenta is an integral part of the pipeline for microbe-powered driver of fetal destiny.

Objectives

After completing this article, readers should be able to:

1. Summarize the types of microbes found in placetas.
2. Describe the effect of vaginal microbiome on pregnancy outcomes.
3. Recognize the effect and association of maternal-fetal microbiomes on long-term fetal outcomes.

Placenta, the Microbiome, and Preterm Birth

The conventional paradigm is that the placenta is a sterile organ and any intrauterine infection would be caused by ascending infection from the lower genital tract. Indeed, there is abundant evidence that links infection and inflammation with preterm birth (PTB), including associations with subclinical intrauterine infections, intra-amniotic infection, and extrauterine maternal infections, such as pyelonephritis and periodontal disease. The most common microorganisms associated with PTB are genital Mycoplasma species, in particular Ureaplasma urealyticum and Ureaplasma parvum. Others include Leptotrichia/Sneathia, Atopobium vaginae, and bacterial vaginosis (BV)–associated bacteria types 1, 2, and 3, which are bacteria associated with BV, a condition in which the normal vaginal flora of lactobacilli are replaced by other low- and high-grade pathogens. Other studies have identified the intrauterine bacterial species using culture-dependent or culture-independent methods. We refer the reader to an excellent review by Jefferson for a full description of the many microbial species associated with PTB.
PTB-causing infections have been postulated to originate in the reproductive or genitourinary tract, ascend upward through the cervix, and possibly breach the placental barrier. However, although there are undoubtedly strong associations, these species have not been definitely found to be causative agents of PTB, suggesting that there was more to the findings than hitherto understood.

The Human Microbiome Project consortium characterized the microbiome in multiple human organs and helped establish the link between changes in the microbiome and human health. (13) The advent of culture-independent microbiome analyses and the pioneering investigations of the Human Microbiome Project have provided important insights into human physiology and pathophysiology in multiple fields of medicine, such as gastrointestinal disorders, endocrine diseases, and cardiovascular disorders, to name a few. Traditional consideration of microbes as pathogens has shifted instead to an understanding of the complex and necessary interactions between the human host and the microbial communities in various body habitats. Of importance, microbial communities demonstrate relationships of mutualism with the human host, providing resistance to acquisition of pathologic infections, immune system education, nutrient breakdown in the gut, and many other processes that are beneficial to the human host.

In line with this, bacterial colonization of the human placenta has been found not only in patients with clinical infections or in preterm births but also in normal pregnancy and term placentas. Our group provided morphologic evidence that both gram-positive and gram-negative bacteria of diverse morphologic origins were present in a third of all placentas from preterm and term pregnancies. (12) Of interest, these microbes were found to be intracellular, within extravillous trophoblast (EVT) cells in the maternal decidua (Figure). EVT cells are fetally derived and directly contact maternal stromal and immune cells. EVT cells have unique immune-privileged status because they are coated with self-antigens, including the major histocompatibility antigen HLA-G, which is implicated in the maintenance of immune tolerance of the fetus. (14) A new study supports the existence of such a placental microbiome. Aagaard et al (15) recently identified a low-abundance but metabolically rich microbiome in the human placenta using culture-independent whole-genome shotgun technology on genomic DNA isolated from human placentas (preterm and term). Of particular interest was the cataloguing of commensal bacterial species in the normal and term placenta, including *Escherichia coli*, *Prevotella tannerae*, *Bacteroides* species, *Fusobacterium* species, and *Neisseria lactamica* among others. Among the bacterial species found in placenta, *E. coli* was surprisingly identified as the species of highest abundance.

Pregnancy is a unique state with profound physiologic changes. During pregnancy, the body undergoes substantial changes in anatomy, immunology, endocrinology, and metabolism, which can lead to fluctuations of physical function in different organs. Not surprisingly, the placental microbiome studies support that such temporal alterations are accompanied by remodeling of this microbiome during pregnancy. For example, the study by Stout et al found that the number of placentas harboring intracellular bacteria increased by half in placentas before 28 weeks of gestation. Moreover, when the study by Aagaard et al compared the placental microbiome of term relative to preterm placentas, they found preterm placentas had changes in abundance of certain bacteria taxa, such as *Burkholderia* species, whereas term placenta had an increase in paenibacilli. Whether the alterations in microbial patterns are a feature of gestational age or indicative of specific functions or physiologic stages of placental and fetal development remains unknown.
The bacterial type, functions, and host responses at maternal-fetal interface may also collectively determine the outcome of the presence of a placental microbiome. The aforementioned EVT cells have been found to be preferred sites of entry for placental pathogens, such as *Listeria monocytogenes* (16) and *Toxoplasma gondii* (17), as well as *E coli* (18), in primary human placenta cultures, suggesting that EVTs embedded in the maternal basal plate may serve as a protective environment for placental microbes. Whether this is true of commensal organisms has not yet been tested. Stout et al (19) recently found that placentas had an increase in HLA-G positivity in preterm births compared with those from term births, implying the contribution of maternal (host) factors in etiology of preterm birth. Whether and how changes in HLA-G levels affect the placental microbiome remains to be determined.

**The Vaginal Microbiome and Preterm Birth**

Traditional teaching is that normal vaginal ecology is dominated by lactobacilli and the local production of lactic acid contributes to an environment that restricts survival of pathogenic bacteria. BV has been broadly defined as alterations in bacterial composition of the vagina and more specifically as a relative decrease in the number of lactobacilli. Such shifts away from the normal vaginal flora have been linked to an increased risk of sexually transmitted infections, suggesting that the normal vaginal bacterial communities serve important functions in preventing survival of pathogenic species. (20)(21) Culture-independent sequencing techniques have refined this traditional understanding of the normal vaginal microbiome. A large study of asymptomatic, nonpregnant, reproductive age women found that the vaginal microbiota could be categorized into 5 discrete groups based on the type and abundance of microbial communities present. (22) Four of the 5 communities had the *Lactobacillus* genus as the predominant community present (*iners, cispatus, jensenii, and gasseri* species), but one community type was not dominated by *Lactobacillus*. This unique heterogeneous community had increased evenness (ecologically defined as multiple species present in relatively equal proportions in contrast to *Lactobacillus* dominance) with communities of anaerobic bacteria, such as *Prevotella, Atopobium, Gardnerella*, and others. The findings of Ravel et al suggest that normal vaginal flora is not required to have *Lactobacillus* predominance, there may be racial differences in normal vaginal microbiota, and the traditional diagnosis of BV may not be consistent with current culture-independent evidence of vaginal bacterial ecology.

There is ample evidence that abnormal vaginal flora (albeit broadly and heterogeneously defined) is associated with PTB. (23)(24)(25)(26)(27)(28)(29) Despite the clear correlation, well-designed randomized trials that treated BV have not realized a significant reduction in PTB. (30)(31) Molecular-based investigations have examined not only who is present in the vaginal microbiota but also the metabolic functions of normal vaginal communities and how this information will shed light on understanding the pathogenesis of PTB. One could speculate that immune system and hormonal changes that occur in pregnancy might alter vaginal microbiome communities compared with the nonpregnant state. Using 16S microbial census analysis, Aagaard and colleagues (32) examined the vaginal microbiome community in pregnant patients (*n* = 24) compared with a nonpregnant population (*n* = 301) and found that pregnancy confers a unique microbiome signature compared with the nonpregnant state. The pregnant microbiome was characterized by decreased species richness and diversity. Furthermore, richness decreased with increasing proximity to the cervix. Hyman et al (33) hypothesized that differences in the vaginal microbiome may be associated with PTB. In a prospective cohort study, these investigators sampled the posterior fornix in 46 patients classified as high risk for preterm birth and 42 low-risk controls and then followed the pregnancy forward for gestational age delivery outcome. The Shannon Diversity Index (a measure of number and abundance of species present) was decreased in pregnancies that ultimately resulted in a preterm birth. Taken together, Aagaard et al describe depressed species richness and diversity of the pregnancy-related vaginal microbiome compared with the nonpregnant state, and the findings of Hyman et al suggest that oversuppression of the vaginal microbial communities may be associated with adverse obstetric outcomes. Romero and colleagues (34) sampled the vaginal microbiome every 2 to 4 weeks in a prospective cohort of 22 women who delivered full term without complication. Consistent with the findings by Ravel et al in nonpregnant patients, they document that there is no single core vaginal microbiome in pregnancy. Rather, multiple community states are dominated by *Lactobacillus* species. In addition, in pregnant women who delivered at term, a heterogeneous non-*Lactobacillus*-dominated community is found rarely. Using measures of community stability, the researchers examined whether pregnant women change from one community type to another. Their findings suggest that vaginal bacterial communities are significantly more stable (fewer community changes over time) in pregnancy than in the nonpregnant state. In pregnant women who change community states, the change most commonly
occurs from one *Lactobacillus*-dominant community to another *Lactobacillus*-dominant community and rarely to the heterogeneous community type of microorganisms.

As current and future studies carefully classify the census of vaginal microbial communities and answer who are there, we must then turn our attention to questions regarding what they are doing and how do they do it. How the vaginal microbiome may affect metabolic functions, genomic redundancy, interactions with host, and beneficial or harmful pathways in pregnancy remains to be elucidated.

**Oral Microbiome and PTB**

Epidemiologic studies have established a firm link among oral flora, periodontal disease, and PTB. This finding suggests that a bloodborne route is involved in microbial colonization of the placenta. (6)(35) Consistent with this idea, periodontal pathogens have been detected in placentas of women with preeclampsia and in the amniotic fluid of pregnant women with preterm labor. In support of this concept, state-of-the-art next-generation sequencing and metagenomic analyses conducted by Aagaard et al revealed that the placental microbiome is most homologous with oral flora and not vaginal flora. Future studies determining the extent that the oral flora community is capable of oral-uterine transmission during pregnancy are needed to provide new knowledge of the diversity of oral bacteria involved in PTB. Multiple other questions remain unanswered, such as how the oral flora evade systemic immune defenses as they possibly traverse the circulatory system to arrive at the uterine-placental interface. Deeper characterization of both microbial biomasses will determine whether the homology findings are a concrete observation or whether the placental microbes have originated from yet unknown habitats. Table 1 summarizes a few recent studies on placental, vaginal, and oral microbes that may be associated with prematurity and which may influence the establishment of the fetal microbiome.

**Fetal Microbiome and PTB**

The existence of a placental microbiome has major implications for fetal colonization in utero and much earlier than has been suspected. The implications of prenatal microbial exposure are currently unknown, with outcomes ranging from immune tolerance to intestinal inflammation and uncontrolled systemic inflammatory response syndrome (36)(37) that may even contribute to PTB. (38) Evolving non–culture-based sequencing techniques have suggested the presence of bacteria in the amniotic fluid and in the absence of a history of rupture of membranes. This microbial colonization of the amniotic fluid may allow for prenatal development of a fetal microbiota and affect fetal outcomes. For example, Kacerovsky et al (39) evaluated microbial colonization of the amniotic cavity and found increased levels of fetal inflammatory cytokines in pregnancies complicated by premature rupture of membranes. Several studies from the Extremely Low Gestational Age Newborns study investigators revealed that fetoplacental inflammation is strongly associated with early PTB, suggesting that microorganisms colonizing the placenta might provoke distinctive newborn inflammatory responses, depending on the type of microbes.

Many potential sources for a prenatal microbiome exist. A recent study, which analyzed the microbiota of meconium samples obtained within 48 hours of birth, compared organisms identified in the meconium with previously published literature on maternal microbiomes from various sites. Ardissone and colleagues (38) found that meconium fluid accounted for a greater relative abundance of bacteria found in meconium than either the oral or vaginal cavities of pregnant women. A previous study was also able to isolate *Enterococcus, Streptococcus, Staphylococcus*, and *Propionibacterium* from umbilical cord blood, suggesting a homogeneous mechanism by which microorganisms from distal locations in the mother can be transmitted to the fetus. (40)

In normal gut development, the interaction between Toll-like receptors and commensal bacteria help to down-regulate inflammatory cascade. However, the premature infant has a gastrointestinal tract with highly immunoreactive intestinal epithelial cells and submucosa. The delayed colonization of the preterm infant’s gut by commensal bacteria results in upregulation of genes involved in inflammation and other proinflammatory molecules that could potentially contribute to preterm birth. (37) The prevalence of several bacteria associated with inflammatory responses in prematurely born infants (including *Enterococcus* and *Enterobacter*) was greater in infants born at 33 weeks or less compared with infants born at more than 33 weeks of estimated gestational age. (38) The preterm gut also experiences abnormal bacterial colonization with a decreased rate of diversification (41) and altered microbiome composition with an increased number of pathogenic bacteria. (42)

Beyond the interaction with PTB, this fundamental alteration in the development and qualitative characteristics of the preterm gut microbiota (43) results in an increased risk of necrotizing enterocolitis and other gastrointestinal, as well as immunologic issues later in life. (44)(45) One recent study observed that low intestinal microbial diversity at age 1 month was associated with IgE-associated eczema. Furthermore, the gastrointestinal
tracts of adults and children with Crohn disease have altered microbial composition. Other studies have noted an association with late-onset sepsis. (44)(46) Tarr and colleagues matched bloodstream pathogens from episodes of late-onset sepsis to pathogens identified in stools of 7 of 11 children.

Not only do these diseases have significant rates of mortality, but the growth and neurodevelopmental outcomes of these children are also affected. (47)(48)(49) Prenatal and neonatal infections have been associated with a variety of adverse neurologic outcomes in the literature. Lee et al (50) examined the association between perinatal infection and brain structure (injury, size, and white matter tract development) and neurobehavioral outcomes in premature infants born at less than 30 weeks’ gestation. They found an association between both maternal genitourinary tract infections and histologic chorioamnionitis and changes in neurobehavioral outcomes at age 2 years (cognitive and language abilities for maternal infection and language abilities for histologic chorioamnionitis). Although maternal infection was not associated with changes in the frequency of brain

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Table. Recent Studies on Microbes in Placenta, Vagina, and Oral Mucosae That Stimulate Preterm Labor and Birth and Influence the Composition of the Fetal Microbiome

<table>
<thead>
<tr>
<th>Study</th>
<th>Site</th>
<th>Technique</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMP consortium (13)</td>
<td>Vagina</td>
<td>Sequencing</td>
<td>Characterized healthy, nonpregnant women vaginal microbiome</td>
</tr>
<tr>
<td>Ravel et al (22)</td>
<td>Vagina</td>
<td>Sequencing</td>
<td>Vaginal microbiome of nonpregnant, reproductive age women</td>
</tr>
<tr>
<td>Romero et al (34)</td>
<td>Vagina</td>
<td>Sequencing</td>
<td>The composition and stability of the vaginal microbiota of normal pregnant women is different from those of nonpregnant women</td>
</tr>
<tr>
<td>Aagaard et al (32)</td>
<td>Vagina</td>
<td>Sequencing</td>
<td>Characterization of the vaginal microbiome signature in pregnancy</td>
</tr>
<tr>
<td>Aagaard et al (15)</td>
<td>Placenta</td>
<td>Sequencing</td>
<td>Identified a unique low-abundance but metabolically rich placental microbiome with greatest homology to human oral microbiome and associated with a remote history of antenatal infection</td>
</tr>
<tr>
<td>Stout et al (12)</td>
<td>Placental basal plate</td>
<td>Histopathologic analysis</td>
<td>Intracellular microbes of diverse morphologic findings were present in 27% of placentas from term and preterm pregnancies</td>
</tr>
<tr>
<td>Wang et al (8)</td>
<td>Amniotic fluid and cord blood</td>
<td>Sequencing</td>
<td>Microbial species in paired amniotic fluid and cord blood likely share the same infectious origin</td>
</tr>
<tr>
<td>DiGiulio et al (9)</td>
<td>Amniotic fluid</td>
<td>16s PCR and colonic assay</td>
<td>Characterized the microbes in amniotic cavity of women in preterm birth</td>
</tr>
<tr>
<td>Han et al (10)</td>
<td>Amniotic fluid</td>
<td>Sequencing</td>
<td>Bergeyella strain identified in the patient’s intrauterine infection originated from the oral cavity, providing direct evidence of oral-utero microbial transmission</td>
</tr>
<tr>
<td>Carl et al (46)</td>
<td>Stools from premature infants</td>
<td>Sequencing</td>
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<tr>
<td>Ardissone et al (38)</td>
<td>Meconium</td>
<td>Sequencing</td>
<td>Fetal intestinal microbiome derived from swallowed amniotic fluid is associated with premature birth</td>
</tr>
</tbody>
</table>

PCR = polymerase chain reaction.

*Next-generation or deep sequencing of whole microbial genomes.
injury, brain size, or white matter development, histologic chorioamnionitis was additionally associated with changes in white matter development in the corpus callosum. On the other hand, neonatal infections were associated with brain structural changes but not neurobehavioral differences at age 2 years. Not only do these diseases have significant rates of mortality, but infections affect growth and neurodevelopmental outcomes of these children. Thus, systemic inflammation adds considerably to the increased risk.

**Clinical Implications**

The long-term implications of neonatal microbial environments for patient management are enormous but challenging to quantify during a short-term evaluation. It is essential to understand the microbial diversity and composition at various epidermal and mucosal sites in the human newborn body. We have now added the placenta as the home for microbes that result in adverse neurologic outcomes during infancy and childhood. In many ways, the observation that the placenta harbors a microbiome is not surprising because it is the first organ to aid in nourishing and maintaining the fetus. Yet microbes in our adult microbiome exceed our human genome by 11-fold. However, we must be mindful that progress has allowed a better understanding of the metabolic effect of the gut microbiome on all aspects of human biology: from obesity, to diabetes, to cardiovascular diseases, to autism. These findings have resulted in new treatment strategies to prevent disease in adults. Understanding who the placental microbes are and how they may or may not be shaped by those that reside in the maternal genital tract or oral mucosa during pregnancy is essential for determining maternal and fetal outcomes. We need to know when a pregnant woman is considered to have an infection with in the placental site. Determining microbial infection and preterm delivery. *N Engl J Med*. 2000;342(20):1500–1507


**American Board of Pediatrics Neonatal-Perinatal Content Specification**

- Know the risk factors, including the effects of chorioamnionitis and inflammation as contributing factors, for preterm labor.


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1. A woman who is receiving prenatal care at the community clinic is in her 20th week of gestation. She has heard from a friend that one reason for spontaneous preterm birth is placental infection. Which of the following statements about microorganisms and the placenta is true?
   A. The most common microorganism found associated with preterm birth is group B *Streptococcus*.
   B. The organisms that are associated with bacterial vaginosis have been found to actually protect against preterm birth.
   C. *Ureaplasma urealyticum* and *ureaplasma parvum* have both been found in association with preterm birth.
   D. Although it has been suggested by animal studies, no human studies link any microorganism growth to very preterm birth (<34 weeks’ gestation).
   E. Bacterial vaginosis is a condition in which there is overproliferation of normal vaginal flora, such as lactobacilli.

2. The placenta of a newborn infant is sent to the laboratory after informed consent for studies on the microbiome. Preliminary analysis reveals bacterial colonization. Which of the following statements is correct?
   A. This is almost certainly a placenta associated with preterm birth (<37 weeks’ gestation) because bacteria are present in less than 1% of placentas of term births.
   B. Microbes found in placentas are found to be intracellular and present in extravillous trophoblast cells in the maternal decidua.
   C. Gram-positive bacteria in the placenta have been found to produce large quantities of progesterone, causing signaling that may lead to preterm birth.
   D. In studies using whole-genome shotgun technology, *Mycobacterium tuberculosis* is the bacterial species that has been found in highest abundance in human placentas.
   E. Current studies using routine pathologic methods can reveal bacterial growth in more than 95% of placentas of infants born preterm (<37 weeks’ gestation).

3. A woman who is in the 24th week of gestation during pregnancy presents with a diagnosis of bacterial vaginosis. Which of the following is consistent with current understanding of vaginal bacterial composition?
   A. After several large, multicenter randomized trials, there is a clear recognition that proper diagnosis and treatment of bacterial vaginosis would prevent approximately 50% of all preterm births.
   B. Studies comparing the vaginal microbiome in pregnant vs nonpregnant women have found that the 2 groups are remarkably similar, although there tends to be higher species richness and diversity during pregnancy.
   C. On the basis of the type and abundance of microbial communities present, there have been 10 discrete community groups identified, of which 6 are dominated by *Lactobacillus*, 2 by *Prevotella*, and 2 by *Gardnerella* species.
   D. In pregnant women who change vaginal microbial community states, the change most commonly occurs from one *Lactobacillus*-dominant community to another *Lactobacillus*-dominant community.
   E. *Lactobacillus* has been implicated in premature rupture of membranes and is the most common organism to cause severe early-onset sepsis in preterm newborns.

4. A female infant is born at 31 weeks’ gestational age after premature rupture of membranes, followed by spontaneous preterm labor and cesarean delivery for fetal distress. Which of the following is true regarding the microbiome of this patient before and after delivery?
   A. If this patient’s meconium were to be tested, the microbiome would more likely reflect the bacteria present in the mother’s oral and vaginal cavities and not have any relationship to the amniotic fluid.
B. Contrary to normal fetal gut development where the interaction between Toll-like receptors and commensal bacteria upregulates the inflammatory cascade, this premature infant is likely to have a gastrointestinal tract with decreased immunoreactivity.

C. The preterm gastrointestinal tract tends to have abnormal bacterial colonization with a decreased rate of diversification and increased numbers of pathogenic bacteria.

D. High intestinal microbial diversity has been associated with IgE-associated eczema later in life.

E. In pregnancies with premature rupture of membranes of extremely low gestational age newborns (<25 weeks' gestation), studies have found microbial colonization of both the placenta and fetus in 80% of cases, which was associated with decreased levels of fetal inflammatory cytokines.

5. The placenta associated with the patient born at 31 weeks' gestational age is being studied by researchers in the laboratory who are focused on extravillous trophoblast cells. Which of the following statements about these cells and the placenta is correct?

A. These cells appear to be preferred sites of entry for placental pathogens, such as *Listeria monocytogenes* and *Escherichia coli*.

B. These cells grow and differentiate from stem cells derived from the maternal uterus and ovaries.

C. Although part of the placenta, these cells do not have any direct contact with maternal stromal or immune cells.

D. Placentas appear to have decreased HLA–G positivity in preterm births compared with term births.

E. Studies on bacterial colonization of the human placenta have found that only very specific gram-positive organisms that secrete membrane-disrupting enzymes have the ability to enter into these cells.
Placental Microbiome and Its Role in Preterm Birth
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*NeoReviews* 2014;15:e537
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