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Maternal microbiomes in preterm birth: Recent progress and analytical pipelines

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ABSTRACT

Worldwide, 10% of babies are born preterm, defined as birth before 37 weeks' gestation. We have had little success in developing strategies to prevent preterm births, the majority of which are due to infection or are idiopathic. An emerging hypothesis is that the maternal microbiome—the bacteria that inhabit the mother's body and play vital functions in normal health—contributes to the etiology of preterm birth. Here, we highlight the latest data revealing correlations between preterm birth and maternal intestinal, vaginal, cervical, and placental microbiomes. Additionally, we describe the most commonly used comparative microbiome analysis methods and highlight important issues to consider when conducting such studies.

Introduction

The World Health Organization estimates that each year, 15 million infants are born preterm, putting them at increased risk of morbidity and mortality.[1] Simplistically, preterm birth (PTB) occurs when normal term labor events—uterine contractions and cervical remodeling—occur early.[2] However, PTB is challenging to explain, predict, and prevent because up to 40–45% of cases are idiopathic (spontaneous), and numerous risk factors are known, including maternal history, demographics, nutritional status, stress, and infection.[2]

Approximately 30% of PTB cases are caused by infection and inflammation.[2] Traditionally, infection-related PTB was thought to ensue from foreign microbes reaching the uterus via ascending infection or hematogenous transfer. During ascending infections, microbes from the vagina travel upward through the cervix to reach the fetal membranes. For example, the presence of *Mycoplasma* spp., Ureaplasma spp., and Candida spp. and *Candida* spp., in the vagina is associated with PTB.[3] Hematogenous infection occurs when bacteria travel through the blood stream from another site in the body and then traverse the placenta at the maternal–fetal interface.[2]

Although foreign bacteria are important causes of PTB, current research in this area is building on the observation that, far from being sterile, the human body is home to millions of microorganisms.[4] Collectively, all of the bacterial genomes present in or on our body surfaces are known as the human microbiome, and each body niche has its own resident microbes. These bacteria contribute to human health in many ways, such as providing resistance to pathologic infection, breaking down nutrients, and educating the immune system.[4,5] In addition to contributing to physiology, microbiome communities respond to physiology. Pregnancy

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is a period of major physiological changes,[6] such as immunological shifts and the vascular remodeling and metabolic changes needed to promote exchange of nutrients, gases, and wastes with the developing fetus.[7] Thus, the microbial community structure in various maternal niches has the potential to shift during pregnancy.[6] Although many of these changes may benefit or cause no harm to the mother and fetus, we are beginning to learn that dysbiosis of the maternal microbiomes is associated with adverse pregnancy outcomes such as PTB.

Here, we review human microbiome studies that define the microbiomes in key maternal niches and identify associations with both term and preterm birth. Additionally, we describe common technical, analytical, and statistical approaches used to conduct maternal microbiome studies. Rigorous studies together with curated microbiome data will provide an in-depth understanding of the maternal microbiomes and their impact on pregnancy and, hopefully, identify new therapeutic strategies to decrease the incidence and burden of PTB.

Maternal intestinal microbiome changes during pregnancy

A healthy gastrointestinal tract, dominated by *Bacteroidetes* and *Firmicutes*, contains numerous beneficial microbes that generate vitamins, break down complex foods, and synthesize products that can keep potentially harmful microbes at bay[8] (Fig.). Because the intestinal microbiome regulates critical metabolic processes, diseases, such as obesity and allergy, may arise when the community structure is abnormal.[9]

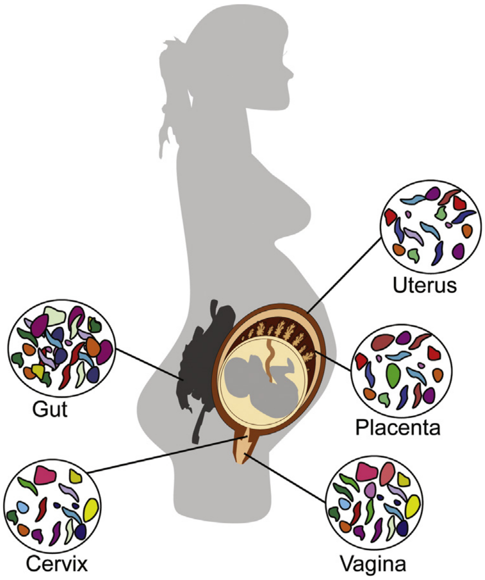

Fig. – Schematic depicting the intestinal and reproductive tract microbial communities during pregnancy. Adverse pregnancy outcomes may be associated with microbes that originate from reproductive tract (vaginal and cervical) and ascend to colonize the gestational compartment. However, mounting evidence suggests that other microbial communities including those in the gut and placenta may also impact pregnancy health.

Koren et al.[10] used stool samples to characterize the maternal gut microbiome during the 1st and 3rd trimesters of pregnancy and post-partum. They found that Proteobacteria was more abundant and *Faecalibacterium* was less abundant in the 3rd trimester compared to the other two stages of pregnancy. Although the underlying mechanisms and implications of this shift are not fully understood, the authors suggested that types of taxa present during these stages may be related to both anti-inflammatory and pro-inflammatory-related diseases.[10] The maternal gut microbiota may change as a result of shifts in the environment during pregnancy as a result the demand for the transfer of nutrients to the fetus.[11] Future work will hopefully reveal the role of the gut microbiome during pregnancy and neonatal outcomes, which impact neonatal birth weight and infant gut colonization.[12,13]

Vaginal microbiome and preterm birth

The hallmark of a healthy vaginal microbiome in non-pregnant, reproductive age (12–45 years old) women of multiple ethnic groups is a preponderance of the *Lactobacillus* genera.[14] These bacteria thrive in anaerobic niches and contribute to the acidic vaginal environment by producing lactic acid.[14–16] Lactic acid-producing species, like *Lactobacillus*, are thought to help protect the uterus from ascending infections such as sexually transmitted infection and urinary tract infections.[17,18] For example, diminished lactic acid-producing bacteria is associated with greater susceptibility to human immunodeficiency virus.[15,19]

The normal vaginal microbiome differs between pregnant and non-pregnant women.[20] Romero et al. found that whereas the community structure of the vaginal microbiota remained consistent across multiple gestational ages (and included species such as *Lactobacillus vaginalis*, *Lactobacillus crispatus*, *Lactobacillus gasseri*, and *Lactobacillus jensenii*), the vaginal microbiota of non-pregnant women was more variable across different time points, with differences in the dominating *Lactobacillus* species.[20] Similarly, another study revealed that the vaginal microbiome 6 weeks post-delivery was more diverse than the vaginal microbiome during pregnancy, regardless of ethnic background.[21] However, the dominating *Lactobacillus* species in the vagina differed depending on the region from which the women originated,[21] suggesting that region-specific factors such as diet affect the community structure of the vaginal microbiome. One possibility to explain the shifts before, during, and after pregnancy is that hormonal, nutritional, and immunological pressures alter the vaginal microbiota during pregnancy. Alternatively, these shifts in the vaginal microbiome may help maintain maternal and fetal health during pregnancy.[20]

Thus far, evidence that the community structure of the vaginal microbiota plays a role in PTB is limited. Nonetheless, a number of studies found that PTB correlates with bacterial vaginosis, a dysbiosis of the vaginal microbiome characterized by the emergence of pathogens such as *Fusobacterium nucleatum*, *Mycoplasma hominis*, and *Bacteriodetes urealyticus* and the loss of *Lactobacillus*.[22] Prematurity in association with