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The Maternal Microbiome and Pregnancy Outcomes that Impact Infant Health: A Review

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Abstract

The maternal microbiome is recognized as a key determinant of a range of important maternal and child health outcomes, and together with perinatal factors influences the infant microbiome. This manuscript provides a summary review of research investigating: (1) the role of the maternal microbiome in pregnancy outcomes known to adversely influence neonatal and infant health, including preterm birth, cardiometabolic complications of pregnancy such as preeclampsia and gestational diabetes, and excessive gestational weight gain; (2) factors with an established link to adverse pregnancy outcomes that are known to influence the composition of the maternal microbiome; and (3) strategies for promoting a healthy maternal microbiome, recognizing that much more research is needed in this area.

Keywords

Microbiota; Pregnancy Complications; Premature Birth; Women's health

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Introduction

The human microbiome – that is the community of microorganisms that live on and in the human body – consists of upwards of 100 trillion cells,[1,2] which outnumber human cells by a factor of ten and collectively contain 27 times more genes than the human genome.[3-5] Different sites within and upon the human body harbor discrete populations of microbes. For example, the skin, mouth, nasal cavity, gut, reproductive tract, and possibly the placenta host unique microbial communities.[6,7] Until recently, information about the microbes inhabiting the human body was obtained via conventional culture-based microbiology techniques,[8] where fluid or epithelial swabs from a given body site are placed in culture media and the organisms that grow are phenotypically and genetically characterized. However, perhaps as many as 50% of the species that are common components of the human microbiome cannot be grown in culture.[9-11] Culture-independent methods were initially developed in 1985,[12] when polymerase chain reaction (PCR) technology was used to exploit characteristics of the 16S ribosomal gene, a section of DNA found in all bacteria but not eukaryotic cells, that is comprised of regions that are highly conserved and regions that are highly variable. PCR primers could be designed to anneal to the conserved regions and amplify through the variable regions; the amplicon could then be sequenced and the variable region used for taxonomic identification of microbes. The potential of this method was realized when combined with next-generation sequencing methods, a mixture of amplicons from a microbiome could all be sequenced simultaneously, and all the taxa present in one microbiome could be identified in a single experiment.[13] Next-generation sequencing strategies have decreased costs of sequencing while increasing throughput, and have precipitated a revolution in the detection of new microbial species. Another major scientific advantage of sequenced-based analysis is that phylogenetic relationships can be readily inferred from DNA-based comparisons, whereas older approaches to classification of bacterial species, which relied on phenotypic characteristics such as gross morphology (*e.g.*, rods vs. cocci) or nutritional requirements for growth in culture, did not provide systematic information on evolutionary relationships among species. These recent technological advances have led to an explosion of information about the human microbiome.[7] As such, it is becoming increasingly clear that the human microbiome plays a role in maintaining health, and may also serve to attenuate or exacerbate both genetic and environmental risks for poor health outcomes.[8] The exciting potential of human microbiome research lies in understanding how this recently recognized “organ” functions to establish and maintain a healthy state, and whether it is possible to promote “healthy” microbiome configurations that protect from negative health outcomes.[9]

The Human Microbiome and Pregnancy Outcomes

A growing body of research demonstrates that the human microbiome, as characterized by new sequencing technologies methods, plays a role in maternal and child health outcomes. In the sections that follow, this manuscript will review research investigating the role of the maternal microbiome in pregnancy outcomes known to impact neonatal and infant health, including preterm birth, including preterm birth, cardiometabolic complications of pregnancy such as preeclampsia and gestational hypertension, and gestational weight gain.

Finally, the manuscript will review research delineating the mechanisms by which the human microbiome may exert its effects upon pregnancy outcomes.

Preterm Birth

Overview of the Problem—Preterm birth (birth prior to 37 weeks' gestation) affects nearly 500,000 – or 1 of every 9 – infants born in the United States.[14] Preterm birth is a leading cause of infant mortality, accounting for ∼35% of infant deaths, and substantially contributes to severe morbidity (involving many organ systems) and disability among survivors.[15] Of the known risk factors for preterm birth, among the strongest is African American race. Compared to Caucasian women, African American women have more than 1.5 times the risk of preterm birth (16.8% vs. 10.5%), and more than double the risk of early preterm birth < 32 weeks'.[14] While low socioenonomic status is a risk factor for preterm birth, less than half of the black-white disparity is explained by socioeconomic status and other known risk factors for preterm birth, such as age of the mother (< 20 or >35 years), sexually transmitted infections, underweight, obesity, chronic health conditions, short interpregnancy intervals, and tobacco and substance use.[16-18]

Vaginal Microbiome and Preterm Birth—The vaginal tract is home to > 50 microbial species considered non-pathogenic.[19-21] Among asymptomatic women of reproductive age, the vaginal microbiome varies widely.[22,23] There is growing evidence that the vaginal microbiome influences risk for preterm birth. The healthy vaginal microbiome plays a role in preventing bacterial vaginosis, sexually transmitted infections, urinary tract infections,[24-27] and HIV.[28,29] Protection is attributed to lactic acid-producing bacteria, mainly *Lactobacillus* sp.,[30,31] and by competitive exclusion such that when *Lactobacillus* sp. are present other more virulent microbes are disadvantaged.[32,33] Bacterial vaginosis is characterized by a reduction in *Lactobacillus* sp. The CDC estimates 30% of US women suffer from bacterial vaginosis, with prevalence surpassing 60% for AA women. The vaginal microbiome that accompanies bacterial vaginosis is associated with increased risks of sexually transmitted infections [27,29,34,35] which increase the risk for preterm birth[36] and occur with increased incidence among African American women compared to other US women.[37] Bacterial vaginosis is also a risk factor for preterm birth itself,[38] although a systematic review found no significant reduction in preterm birth risk even with eradication of bacterial vaginosis.[39]

Characterization of the vaginal microbiome among 396 asymptomatic women from four ethnic groups (white, black, Hispanic, and Asian) reveals clustering of microbial communities into five groups, with lactobacilli predominant in four, with the proportion of each microbial group and the vaginal pH varying significantly by ethnicity.[22] Notably, vaginal communities in which lactobacilli are not dominant are significantly more common in African American (33%) compared to Caucasian (7%) women.[40] These studies suggest that varying levels of protective vaginal microbiota may partly explain observed racial disparities in bacterial vaginosis and sexually transmitted infections.[40] Moreover, characterization of the vaginal microbiome of pregnant women reveals a substantial reduction in taxonomic diversity as pregnancy advances.[41] Among Caucasian women a

greater diversity of the vaginal microbiome was found for those with term compared with preterm births.[42]

Oral Microbiome and Preterm Birth—The oral cavity has a characteristic microbiome, with > 700 microbial taxa present.[43,44] Microbial species commensal in the oral cavity but not found in the urogenital tract cause intrauterine infection.[45-47] Interestingly, characterization of the microbiome of 48 term placentae reveals microbes more similar to the oral than the vaginal microbiota.[48] The primary route theorized for oral microbes to cause intrauterine infection is hematogenous dissemination, particularly with periodontal disease,[49] however, colonization of the vaginal tract with microbes from the oral cavity during receptive oral sex is also proposed.[50] Studies show that periodontal disease is associated with a 2-to 7-fold increase in preterm birth[51,52] and another links maternal periodontal disease to preeclampsia.[53] A large US multicenter trial comparing women treated for periodontal disease at < 21 weeks' vs. post-delivery found no reduction in preterm birth but a trend for reduced early preterm birth < 32 weeks'.[54]

Gut Microbiome and Preterm Birth—The gastrointestinal tract is populated by a vast and diverse array of microbes that participates in host metabolism, protects from invading microbes, and facilitates immune system function.[55] The gut microbiome is also proposed as a possible source of intrauterine infection after finding gut-associated taxa in amniotic fluid of women with preterm premature rupture of membranes.[56] Gut-associated microbes could colonize the vagina and ascend;[21,57] hematogenous spread by translocation from the gut lumen into the bloodstream also could occur.[58]

Cardiometabolic Complications of Pregnancy

Overview of the Problem—Gestational diabetes mellitus and gestational hypertension are the two most common cardiometabolic complications of pregnancy, affecting 7-14% and 10% of pregnancies, respectively.[59,60] Gestational diabetes and gestational hypertension are associated with adverse pregnancy and perinatal outcomes as well as future cardiometabolic disease for both the offspring and the mother.[61]

Gestational diabetes increases the risk of maternal complications, such as gestational hypertension, that in turn, increase the risk of Cesarean delivery and indicated preterm birth. In addition, the resulting maternal hyperglycemia is associated with fetal hyperinsulinemia, which is linked to unbalanced fetal growth and macrosomia, increasing the risk for Cesarean delivery, shoulder dystocia, and birth trauma. Hyperinsulinemia is also linked to neonatal metabolic complications that impact the well-being of the neonate, including hypoglycemia, hyperbilirubinemia, polycythemia, hypomagnesemia, hypocalcemia, and respiratory distress syndrome.[62-64] Also, children born to mothers affected by gestational hypertension have been found to have higher body mass index (BMI), systolic blood pressure, glucose and insulin levels;[65] this risk extends into adulthood, with an 8-fold increased risk of type 2 diabetes among young adults exposed to gestational diabetes during fetal life.[66]

Pregnancies complicated by severe gestational hypertension and preeclampsia, experience an increased risk of maternal and perinatal morbidity, with higher rates of abruption placentae, small-for-gestational-age, and preterm birth.[67,68] Preeclampsia also poses

significant risk for the offspring later in life, with a 2-fold increase risk for stroke.[69] This elevated risk has been previously explained both by the "fetal origins of adult disease hypothesis"[70] and by the shared genetic risk factors between mother and fetus. However, an emerging hypothesis suggests that shifts in the maternal gut microbiome that are associated with preeclampsia may alter fetal gut development and lead to future disease.[71]

Gut Microbiome and Cardiometabolic Complications of Pregnancy—There is mounting evidence supporting the role of the gut microbiome in cardiometabolic diseases.[72,73] Influenced by dietary intake, the gut microbiome interacts with the host to alter energy harvest, energy expenditure and fat storage.[74] Differences in gut microbiome composition, and its related metabolic activities, distinguish lean versus obese individuals, and those with type 2 diabetes mellitus versus those without,[73,75] suggesting that imbalance in the gut microbiome contributes to the development of cardiometabolic disease.[75] Moreover, a dysbiotic microbiome is implicated in the diffusion of gut bacterial endotoxin into systemic circulation, inducing a low-grade inflammatory response,[76] which is a common feature of cardiometabolic diseases. Combined with insulin resistance, chronic subclinical inflammation characterizes the hallmark pathway to the development of both gestational diabetes and gestational hypertension.[77-79]

The gut microbiome of pregnant women has been associated with prepregnancy body weight and excessive weight gain during pregnancy.[80] A recent study that examined the composition of gut microbiome during pregnancy found significant remodeling of the gut microbiome from the first through the third trimester.[81] First trimester composition most resembled that of the non-pregnant state; whereas the changes from the first to the third trimester included a greater between-subject diversity, but a reduced within-subject diversity, with the majority of women demonstrating increasing abundance of Proteobacteria, a microorganism observed in inflammation-associated shifts in the gut microbiome.[82] Women who developed gestational diabetes had the least diversity in their gut microbiome during the first trimester.[81]

While few studies have examined the role of the gut or vaginal microbiome in association with gestational hypertension and preeclampsia, the contribution of periodontal disease and the oral microbiome to the incidence of preeclampsia is established.[83,84] Despite the significant association between periodontal disease and preeclampsia, periodontal therapy during pregnancy has not been effective in reducing the rate of preeclampsia.[85] Furthermore, one study has examined the presence of microbes in amniotic fluid in preeclamptic women and concluded that the low presence of microbes and intra-amniotic infection plays a limited role in the incidence of preeclampsia.[84]

Gestational Weight Gain

Overview of the Problem—Prepregnancy obesity and excessive maternal weight gain increases the risk of fetal macrosomia, which in turn increases the risk of cesarean delivery, hyperinsulinemia in infancy, and metabolic syndrome in childhood. Among women who are overweight or obese, a healthy gestational weight gain is associated with a significantly lower risk of preeclampsia, cesarean delivery, and large for gestational age birth.[86] Also, as

maternal BMI increases, folate intake decreases, contributing to an increased incidence of fetal neural tube and other birth defects.[87-89] Maternal weight exceeding 200 pounds and gestational weight gain of over 40 pounds have each been found to be associated with increased risk of autism and other intellectual/developmental disabilities in the child.[90]

Nearly two-thirds of American women of childbearing age are classified as overweight or obese and nearly half of women, once pregnant, gain excess gestational weight.[91] African American women are the most likely to enter pregnancy overweight or obese.[92-100] In 2009, the Institute of Medicine published their latest recommendations for weight gain during pregnancy.[91] Obese women are to gain only 11-20 pounds compared with the previous recommendation of “at least a 15 pound weight gain”.[91,92] Among women in all BMI categories, only half of pregnant women achieve weight gain within the recommended range. Women who are overweight prior to becoming pregnant are six times more likely than normal weight women to gain more than the recommended amount of weight.[91]

While most women experience declining weight retention as time extends postpartum, weight retention remains a problem for a large proportion of women even at a year postpartum.[95,101,102] Sixty percent of women retain 10-20 pounds at six months postpartum or later, regardless of prepregnant BMI.[102-105] If women retain weight, their subsequent pregnancies are then subject to both the rise in maternal BMI and advancing age, further multiplying obstetrical risks.[106,107]

Gut Microbiome and Maternal Weight—A number of genetic and environmental factors are linked to obesity, including diet quality and quantity, cultural behaviors, and socio-economic factors.[108] Also linked to obesity is the composition of the gut microbiome, which affects health by extracting nutrients and energy from ingested food, producing essential metabolites, serving as a barrier against harmful microbes, and promoting immune function. Those who are obese have a gut microbiome that varies compared to those who are not obese.[109] Lean individuals have more Bacteroidetes, while obese individuals harbor more Firmicutes, including Clostridium clusters, in their gut.[110-114] Differences in gut microbiota between normal versus obese pregnant women suggests the microbiome may be important in weight management during pregnancy, as in other populations.[111,112,115] Among pregnant women, those who have greater numbers of Lactobacillus appear protected against the highest degrees of excessive gestational weight gain; likewise, their infants also appear less likely to be large for gestational age at birth.[116-118]

The Maternal Microbiome Sets the Neonatal Microbiome

The birth process plays an important role in the microbial colonization of the infant gut, and is influenced by the composition of the mother's microbiome, the mode of delivery, genetic, and other perinatal factors.[119,120] Vaginally delivered infants acquire microbes resembling mother's vaginal microbiome, while caesarean delivered infants acquire those found on maternal skin.[119,120] The size and gestational age of the neonate also affects the composition of the infant microbiome. Preterm infants lack two of the main bacterial genera of healthy term infants (Bifidobacterium and Lactobacillus) instead displaying a dominance of Proteobacteria.[121] Further, the abundance of Proteobacteria is higher in neonates born large-

for-gestational age whereas Firmicutes is more abundant in those appropriate-for-gestational age.[122] As infants develop over the first month of life, they begin to develop body site-specific microbiomes, with feeding patterns heavily influencing gut microbiome composition. The microbiome of breastfed infants is characterized by substantially higher abundance of Bifidobacteria, believed to be beneficial to immune functioning.[123,124] The type and timing of introduction of complementary foods in the first year influences microbiome composition, with their earlier introduction being associated with important microbiome shifts linked with risk for gastrointestinal infection. In fact, during the first 2-3 years the microbiome is a dynamic entity with each dietary juncture.[125] Hospitalization and antibiotics also affect gut microbiome composition, being associated with substantial loss of diversity.[126] Recent findings suggest that the fetal microbiome may even begin to be colonized in utero, further underscoring the important role of the maternal microbiome in neonatal and infant health.[127]

Factors that Influence the Maternal Microbiome and Pregnancy Outcomes

A variety of modifiable and non-modifiable factors are known to affect the human microbiome.[128,129] In fact, the development of the microbiome begins in utero and is further influenced by factors at or soon after birth, such as gestational age at birth, mode of delivery, antibiotic use, and breastfeeding.[130] Breastmilk is rich in viable skin and non-skin bacteria, suggesting a critical role of the maternal transfer of microbes, which may be enhanced further with skin to skin measures such as kangaroo care.[131] The microbiome is thereafter influenced throughout life by environmental exposures, diet and nutrition, clinical infections and disease states, antibiotic and anti-inflammatory medication, the inflammatory-immune response, and myriad health behaviors.[129] Dietary and weight status, health behaviors, and stress are a subset of biobehavioral factors with great potential to impact the human microbiome, and are theorized to contribute to the high and disparate rates of preterm birth and cardiovascular complications of pregnancy observed in the United States.[132]

Diet and Probiotics—Both low and high BMI are linked to risk of preterm birth and gestational hypertension and are known to influence the composition of the maternal microbiome. Low BMI (< 18.5 kg/m^2) is linked to spontaneous preterm birth.[133] There is conflicting evidence regarding the association between obesity (BMI ≥ 30 kg/m^2) and preterm birth, with growing clarity that the association may be mediated by obesity's impact on indicated preterm birth due to preeclampsia, rather than spontaneous preterm birth.[134]

In addition to body weight status (discussed above), other aspects of the diet are key factors in determining the composition of the gut microbiome. The Western diet, high in simple carbohydrates, fats, and animal proteins, is linked with an imbalance of the gut microbiome, in which there are increased numbers of *Clostridium innocuum, Eubacterium dolichum, Catenibacterium mitsuokai* and *Enterococcus spp.* and decreasing Bifidobacteria and Bacteroidetes.[135] Research supports that placing obese individuals on calorie-restricted diets and increasing physical activity changes the gut microbiome composition toward a pattern that is typical of non-obese individuals.[136]

Consumption of probiotic-rich food during pregnancy has been associated with lower rates of preterm birth and preeclampsia,[137] which could be attributed to the beneficial effect of probiotic supplementation on placental inflammatory responses.[138] While randomized trials of probiotic supplementation in pregnancy are few, there have been some investigating the role of probiotic supplementation on the occurrence of preterm birth, gestational hypertension, and excessive gestational weight gain. The two trials investigating the role of probiotics on preterm birth were small and could not conclude that the probiotic supplementation decreased preterm birth, however, they did find that probiotics shift the composition of the vaginal microbiome in a manner that inhibits pathogens and modulates the inflammation commonly associated with preterm birth.[139,140] A single randomized controlled trial on gestational weight gain reports that probiotic supplementation did not significantly alter gestational weight gain or postpartum weight retention, but significantly decreased postpartum weight circumference.[141] Another trial reports that the incidence of gestational diabetes was significantly reduced among those supplemented with probiotics vs. dietary alteration alone.[142]

There is some evidence that probiotics might have a role in preventing severe gestational hypertension and preeclampsia. In an observational Norwegian cohort, high maternal intake of dairy products containing Lactobacilli (>200 ml/day) was associated with reduced risk of overall preeclampsia and severe preeclampsia, controlling for maternal age, smoking, BMI, smoking, socioeconomic status, and diet;[143] this study did not assess for changes in the composition of the vaginal and/or gut microbiome with the probiotic supplementation to establish if probiotics.

Health behaviors—A range of behaviors – including smoking and substance use and hygiene practices (*e.g.*, douching, poor oral hygiene) – are linked with preterm birth and are known to impact the vaginal, oral, or gut microbiome.[128,129,144] For most of these health behaviors, a mechanistic link with preterm birth remains to be elucidated, highlighting the microbiome as a potential connection. For example, many studies show a dose-response in risk of preterm birth and number of cigarettes smoked daily. Smoking also affects the composition of the oral microbiome. Periodontal pathogens are more common and persistent in smokers, and smokers demonstrate a pro-inflammatory response to colonization by these microbes.[145]

Oral hygiene practices alter the oral microbiome and also initiate imbalance in the gut microbiome.[146] Poor oral hygiene is greatly responsible for the accumulation of bacteria within biofilms. Failure to detach accumulating plaque will lead to overgrowth of bacteria that may become pathogenic, reduce biodiversity of the oral cavity, and ultimately cause diseases such as dental caries or periodontal disease.[147]

A variety of health behaviors are also known to contribute to shifts in the composition of the vaginal microbiome. For example, frequent sexual intercourse, multiple sex partners, frequent episodes of receptive oral sex, douching and use of spermicides all contribute to destabilization of vaginal microbial bacterial communities and thereby increase the chance of pathogenic bacteria to colonize the reproductive tract and contribute to infection and inflammation.[148]

Stress—With mental or physical stress, a complex neuroendocrine-immune response is initiated,[149] leading to increased pro-inflammatory cytokines and cortisol.[150,151] Although protective against infection, acute inflammation increases the risk of preterm birth.[152-154] Chronic inflammation increases risks for preterm birth,[155] gestational hypertension,[156-158] and diabetes, [159-161] each of which are associated with adverse maternal and infant consequences. Among low-income African American women, stressful exposures are associated with bacterial vaginosis during pregnancy, and stressors explain a significant proportion of the racial disparity in rates of bacterial vaginosis.[162] Among non-pregnant women, there is also an association between stress and bacterial vaginosis.[163]

Chronic stress also affects gut microbiota and increases translocation of bacterial cell components from the gut into the blood stream.[128] Animal models suggest that stress-induced shifts in gut microbiota increase circulating inflammatory cytokines and activate the HPA axis.[164] Gut microbiota can also influence depression symptoms and psychological responses to stress, which are in turn associated with poor pregnancy outcomes such as preterm birth.[128]

Summary

Perinatally the maternal microbiome serves as the source for the infant microbiome, and within the context of pregnancy, the maternal microbiome is being shown to play an important role in the occurrence of adverse pregnancy outcomes that greatly influences the health of the neonate and infant. Further characterization of the maternal microbiome and identification of various factors that facilitate changes in microbial profiles preconceptionally and during pregnancy may elucidate preconception and prenatal strategies for improving pregnancy outcomes and, thereby, neonatal and infant health. Neonatal nurses who care for and investigate medical conditions and pregnancy outcomes that influence the well-being of neonates will be critical for advancing the research in this field and for drawing attention to the consequences of this knowledge gap on neonatal and infant health.

Furthermore, neonatal nurses are critical to the health and development of newborns and are well positioned to influence factors that are involved in the establishment of the microbiome. Key target areas for nursing intervention include promotion of breastfeeding, and encouragement of kangaroo care, and the appropriate selection and use of antibiotics, since nurses are key agents involved in breastfeeding initiation, skin to skin care, and medication administration.

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What we know about this topic: The maternal oral, vaginal, and gut microbiome influence the risk of pregnancy outcomes that have profound impacts upon the health of the neonate and infant, including preterm birth, preeclampsia, gestational diabetes, and excessive gestational weight gain. Although incompletely elucidated, there are a number of modifiable factors that shape the composition of the maternal microbiome, including maternal diet, prepregnancy weight and gestational weight gain, and hygiene practices. The maternal microbiome and perinatal factors establish the fetal and infant microbiome.

What needs to be studied: There is a need for research to further elucidate maternal microbiome patterns that protect against and elevate the risk for adverse pregnancy outcomes that impact neonatal and infant health and, thereafter, to identify modifiable factors that influence the composition of the maternal and infant microbiome to support the targeting of health strategies to improve pregnancy outcomes and infant health.

What we can do today: As a strategy for reducing the risk of adverse pregnancy outcomes that negatively impact neonatal and infant health, practitioners can further women's attainment of a healthy maternal microbiome before and during pregnancy (via preconception and prenatal care) through the promotion of a healthy diet, attainment of a healthy weight status and weight gain during pregnancy, and oral hygiene (such as regular brushing, flossing, and dental care). In the perinatal period, key target for promoting a healthy infant microbiome include the promotion of breastfeeding and kangaroo care along with the judicious use and appropriate selection of antibiotics.