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Sinha, Trishla; Brushett, Siobhan; Prins, Jelmer; Zhernakova, Alexandra

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The maternal gut microbiome during pregnancy and its role in maternal and infant health

Trishla Sinha[1], Siobhan Brushett[1,2], Jelmer Prins[3] and Alexandra Zhernakova[1]

There is growing knowledge that the maternal gut microbiome undergoes substantial changes during pregnancy. However, despite the recognition that the maternal gut microbiome influences maternal and infant health, we still have a limited understanding of the clinical and environmental factors that can impact the maternal gut microbiome during pregnancy and the consequences of these changes. Here, we review the current body of knowledge about factors shaping the maternal gut microbiome during pregnancy and its role in the development of pregnancy complications and infant health.

Addresses
[1] Department of Genetics, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
[2] Department of Health Sciences, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
[3] Department of Obstetrics and Gynecology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

Corresponding author: Zhernakova, Alexandra (a.zhernakova@umcg.nl)

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Introduction

During pregnancy, the body undergoes substantial hormonal, immunological, and metabolic changes that are needed for fetal growth and development. These include a rapid increase in the mother's cardiac output between the 9th and 14th week of gestation and immune adaptations such as higher levels of T-regulatory cells during early pregnancy that peaks in the second trimester [1,2]. Like almost every organ in the body, the gut microbiome also undergoes changes during pregnancy. Even in a nonpregnant state, changes in the gut microbiome have downstream effects on many organs and tissues and can subsequently affect other immune- and metabolic-related processes. For example, insulin sensitivity has been shown to be influenced by gut microbiome composition in both mice and humans [3–5]. Furthermore, functional and metabolic alterations of the gut microbiota have been observed in immune-mediated diseases such as type-1 diabetes in children [6]. Alterations in the gut microbiome during pregnancy are thus likely to have downstream effects that could play a role in the development of pregnancy-related diseases and lead to important consequences for maternal and infant health. Being modifiable, the gut microbiome is also an attractive target for interventions to prevent such diseases.

Gut microbial changes during pregnancy

The number of studies investigating changes in the gut microbiome during pregnancy is rather limited. Data on gut microbiomes in early pregnancy thus remain sparse, and most studies have relatively small sample sizes ($n < 50$) and used 16S rRNA sequencing, which limits them to species-level resolution, at best. Despite these issues, several studies report gestational differences in both mice and humans [7,8], although it is important to note that there are studies that report no, or limited, differences in the gut microbiome during gestation [9–11]. This highlights the critical need for large longitudinal human studies that consider relevant confounding factors such as pregnancy outcomes and changes in maternal weight and diet.

In 2012, Koren et al showed that the first-trimester gut microbiota is similar in many aspects to that of healthy nonpregnant males and female controls but that, by the third trimester, the structure and composition of the gut microbiota resembled a disease-associated dysbiosis and varied greatly among pregnant women [8]. The authors speculated that low-grade inflammation at intestinal mucosal surfaces could lead to these changes in the gut microbiota, although they also proposed that pregnancy-related hormonal changes could play a role. Hormonal modulation of the gut microbiota during pregnancy can be considered crucial for both mother and infant. Nuriel-Ohayon et al showed that increased intrinsic progesterone levels in late pregnancy directly increased *Bifidobacterium* levels in both women and mice [7]. *Bifidobacterium* is crucial for infants in the neonatal period as it degrades host-indigestible human milk oligosaccharides (HMOs) coming from maternal milk [12].

One can speculate that the increase in *Bifidobacterium* in mothers increases the chances of gut–gut transmission of this genus to infants for the purpose of degradation of HMOs and for training and development of the infant gut microbiota and immune system [13]. This demonstrates that remodeling of the gut microbiota during pregnancy could be extremely important for infant health. Knowledge about which factors influence the maternal gut microbiota during pregnancy is important, as modifying these factors could have short- and long-term health implications for both mother and infant.

Factors shaping the maternal gut microbiome before and during pregnancy

Prepregnancy factors

In general population cohorts, we and others have shown that up to 20% of the interindividual variation in the gut microbiome can be explained by various intrinsic and exogenous factors [14–16]. It has been consistently observed in humans and mice that environmental factors dominate over host genetics in shaping the overall structure of the gut microbiome [15,17–19]. Important factors shaping the adult gut microbiome include anthropometric factors (e.g. Body Mass Index (BMI)), medications (e.g. antibiotics and proton-pump inhibitors), diseases (e.g. type-2 diabetes), environment (e.g. smoking), and diet (e.g. Mediterranean diet) [14,15,18,20,21]. Interestingly, some early-life factors have long-lasting effects on the gut microbiome, for example, diet, lifestyle, physical activity, urban living, and pet exposure [15,22]. Similarly, past exposures, such as smoking at any point in life, can influence the gut microbiome long after the exposure ends [15]. Many of these factors also continue to influence the gut microbiome during pregnancy. A study of 1479 pregnant women using 16S rRNA gene sequencing of fecal samples showed that prepregnancy BMI influenced 20 core operational taxonomic units (OTUs) [9]. Additionally, diseases before pregnancy (e.g. hyperthyroidism) were shown to be associated with OTUs during pregnancy [9]. Diseases such as inflammatory bowel disease (IBD) are characterized by a massive dysbiosis in the gut ecosystem [23]. Van der Giessen et al analyzed fecal (16S rRNA sequencing) and serum samples from 46 IBD patients (31 Crohn's disease and 15 ulcerative colitis) and 179 healthy controls during the first, second, and third trimester of pregnancy, and prepregnancy and postpartum samples for IBD patients [24]. The authors concluded that serum proinflammatory cytokine levels decreased upon conception in pregnant patients with IBD, and, while the gut microbiome diversity of patients with IBD was reduced in comparison to healthy controls in early pregnancy, these differences were no longer observed by middle and late pregnancy. These findings suggest that pregnancy is safe and possibly even beneficial for patients with IBD. It is thus important to remember that the gut microbiome during pregnancy is not only influenced by factors occurring in and around pregnancy, but also by factors long before pregnancy, which could have important consequences for both maternal and infant health.

During pregnancy

In mice, it was demonstrated that pregnancy-associated shifts in the maternal gut microbiota are associated with maternal diet before and during pregnancy [11]. Not only does diet during pregnancy have important consequences on the maternal microbiome, maternal macronutrient intake was significantly associated with the neonatal gut microbiome in a human cohort of 86 mother–neonate pairs [25].

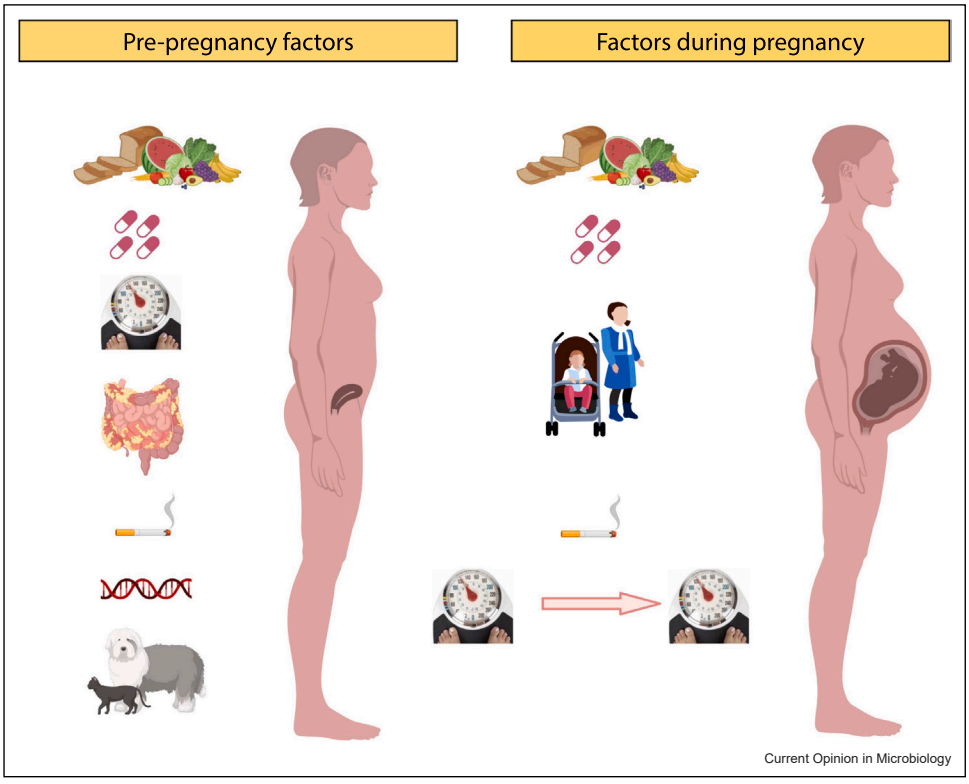
Additionally, prepregnancy weight and pregnancy weight gain have been shown to be associated with maternal changes in gut microbiota. In a cohort of 169 women, prepregnancy overweight/obese status was associated with lower alpha diversity and differences in microbial composition and excess gestational weight gain was associated with compositional differences in the gut microbiome [26]. It remains unclear whether prepregnancy maternal BMI and gestational weight gain also have an impact on the infant gut microbiome, with some studies reporting differences [27,28] while others do not [26,29]. Interestingly, some studies also show evidence of birth-mode-dependent associations of maternal weight with the infant gut microbiota where the influence is largely in vaginally delivered infants in contrast to infants delivered by c-section, perhaps due to hampered transfer of microbes during birth in infants delivered by c-section [30–32].

Functional studies in mice have also shown that exposures during pregnancy, such as smoking, influence the maternal gut microbiome. Using a mouse model, Zubcevic et al. examined alterations in the maternal gut microbiome in response to nicotine exposure during pregnancy [33]. They concluded that changes in the maternal gut microbiota were an important intermediary that may mediate the effects of prenatal nicotine exposure, affect gene expression, and alter fetal exposure to circulating short-chain fatty acids (SCFAs) and leptin during in utero development.

Furthermore, pregnancy history may also influence the maternal gut microbiota during pregnancy. A longitudinal study in pregnant pigs demonstrated that increasing maternal parity (the number of previous pregnancies) was associated with more rapid gut microbiome changes during pregnancy, with increasing parity leading to more rapid changes during pregnancy [34].

Lastly, consumption of medications such as antibiotics, proton-pump inhibitors, laxatives, and metformin and

Figure 1



Factors shaping the maternal gut microbiome before and during pregnancy.

use of pre- and probiotics have also been shown to influence the microbiome during pregnancy [35,36]. Overall, we conclude that numerous factors modulate the gut microbiome during pregnancy (Figure 1). These factors may be related and/or interact with each other, making comprehensive longitudinal studies with large sample sizes necessary to study all these factors, their associations to the pregnancy-related gut microbiome, and their implications for maternal and infant health.

Maternal gut microbiome and pregnancy complications

As several factors are involved in shaping the pregnancy-related gut microbiome, there is a lot of curiosity as to whether these gut microbiome changes are also associated with pregnancy complications and outcomes. Of the studies investigating these relationships, most have focused on gestational diabetes mellitus (GDM) and hypertensive disorders of pregnancy such as preeclampsia (PE) (Figure 2), although there is also some evidence for associations to other pregnancy complications such as preterm birth. Factors such as excessive gestational weight gain and obesity, for example, have been shown to be associated with the gut microbiome of mothers in a few human studies [26,37]. Additionally, in a small human cohort, 41 mothers who delivered preterm showed an increase in commensal oral bacteria in their gut microbiome compared with gestational-age-matched controls who delivered at term [38]. Lastly, gut microbial features have also been associated with pregnancy loss [39].

Gestational diabetes mellitus

GDM is characterized by pancreatic β-cell dysfunction, increased insulin resistance, and spontaneous hyperglycemia during pregnancy. Its prevalence ranges between 5.4% and 14% globally [40]. Most studies exploring the link between gut microbiome and GDM report differences in the gut microbiota composition of GDM women compared with healthy pregnant controls, although there is very little consistency between studies, possibly due to differences in methodology, sampling time, and sampling frequency during gestation [41–43]. Additionally, many of these studies do not adjust for relevant covariates/confounders (e.g. prepregnancy BMI, treatment of GDM, diet, maternal age, or parity). Nonetheless, the consensus seems to be that GDM is associated with a decreased abundance of *Bifidobacterium* and *Faecalibacterium species* and an increased abundance of *Bacteroides*, *Lachnospiraceae*, *Enterobacteriaceae*, *Ruminococcaceae*, *Collinsella*, and *Eggerthella* [42]. The changes in bacterial composition could also be long-lasting; Crusell et al found that, even at 8 months postpartum,

the gut microbiota of former GDM women was still different from that of women who had a pregnancy without complications [41]. In one of the few studies to use metagenomic sequencing (MGS), Kuang et al showed a greater abundance of membrane transport, energy metabolism, lipopolysaccharide, and phosphotransferase system pathways in the microbiome of GDM patients, whereas the microbiome of controls was enriched in amino acid metabolic pathways [44]. In another study with 147 cases, GDM was also shown to alter the serum metabolome of mothers, including alterations in pathways involved in taurine and hypotaurine metabolism, pyrimidine metabolism, beta-alanine metabolism, and bile acid biosynthesis [45]. Lastly, in a human cohort with 50 women with GDM, Ye et al used a combination of MGS and serum metabolomics to identify gut-microbiome-derived circulating dopamine insufficiency, imbalanced production of SCFAs, and excessive metabolic inflammation linked to GDM development [46].

There is also some evidence for a mechanistic link between the gut microbiome and development of GDM. Fecal microbiota transplantation (FMT) from GDM women into germ-free mice showed that the GDM microbiome contributed to the induction of the hyperglycemia, insulin resistance, and inflammation seen in GDM women [43]. A recent study combining data from a human prospective cohort (with 44 GDM cases) with FMT in mice showed that future GDM onset could already be accurately predicted in the first trimester using a combination of clinical records, cytokine profiles, and gut microbial features [47]. The transfer of the first-trimester gut microbiome to mice drove inflammation and insulin resistance, although the authors acknowledge that this could also be a consequence of transfer of metabolites or viruses rather than of bacteria [47]. These results provide evidence for the role of the gut microbiota in GDM pathogenesis and indicate that the gut microbiome could be a biomarker for early detection of GDM and a potential target to reduce the risk of GDM.

Preeclampsia

PE is mostly characterized by new-onset hypertension, proteinuria, and end-organ dysfunction of organ systems, including the liver and central nervous system [48]. Recent studies have shown that gut microbiome composition is altered in PE. However, these studies are limited, performed with 16S rRNA sequencing and relatively small. Nevertheless, Wang et al showed gut microbiota dysbiosis and increased plasma lipopolysaccharide and trimethylamine N-oxide levels in 48 PE patients compared with 48 healthy controls matched in age, gestational week, and prepregnancy BMI [49]. Recently, when comparing 67 PE patients with normotensive women, Chen et al showed that PE was associated with reduced bacterial diversity and distinct gut microbiome changes [50]. In the PE group, opportunistic pathogens were enriched, particularly *Fusobacterium* and *Veillonella*, whereas beneficial bacteria, including *Faecalibacterium* and *Akkermansia*, were markedly depleted. Additionally, the authors showed that FMT from PE women into antibiotic-treated mice triggered an increase in blood pressure and proteinuria in recipient mice. They also demonstrated that the dysbiotic gut microbiome induced immune imbalances related to T lymphocytes and intestinal barrier dysfunction, facilitating translocation of bacteria to the intrauterine cavity, which elicited inflammation in the placenta and contributed to poor placentation, thus contributing to disease pathology.

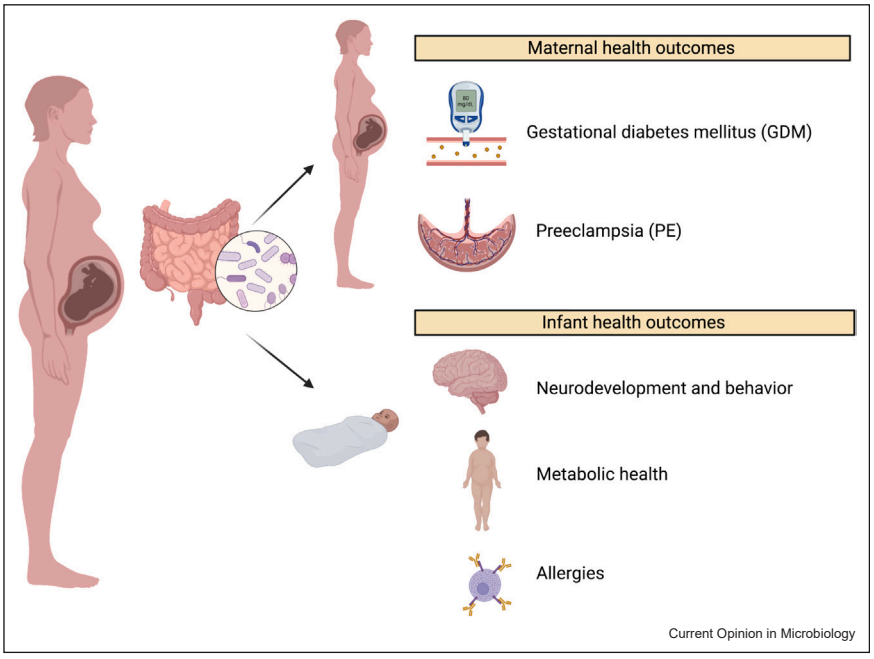
Maternal gut microbiome and infant health

While the maternal gut microbiome has been associated with maternal health, it has also been associated with infant health outcomes such as fetal neurodevelopment [51]. In a mouse study, Vuong et al showed that the maternal gut microbiome promotes fetal thalamocortical axonogenesis, most likely via signaling of microbially modulated metabolites to neurons in the developing brain of the embryo [51]. Such changes could have long-lasting effects on infant behavior. Additionally, in a longitudinal human cohort of 213 mothers and 215 children, it was shown that the alpha diversity of the maternal fecal microbiota during the third trimester of pregnancy was associated with child-internalizing behavior at two years of age, however, case samples were relatively small (n = 20) [52]. The effects of the maternal microbiome on infant health are not limited to neurodevelopment. It was shown in a mouse study that the maternal microbiota shapes the offspring's metabolic system through metabolites such as SCFA [53]. Lastly, there is some evidence linking maternal gut microbiota and allergic disease in human offspring. Using 16S rRNA sequencing, Vuillermin et al demonstrated that *Prevotella copri* presence in the maternal gut during pregnancy predicted decreased IgE-mediated food allergy in their children [54]. These studies emphasize the need to systematically investigate the associations of maternal gut microbiome composition with infant health given the short- and potentially long-term consequences these associations may have on infant health (Figure 2).

Modulation of the gut microbiome

Given the increasing number of associations found between the maternal gut microbiome and maternal and infant outcomes, gut microbiome modulation poses an appealing target for disease prevention. This has led to a growing number of pre- and probiotic interventions aimed at the prevention of various pregnancy complications and the optimization of infant health outcomes, with probiotics currently being the most well-studied. Owing to the large heterogeneity in intervention studies in terms of the probiotics used, the duration of use, and

Figure 2



Key maternal and infant health outcomes linked with maternal gut microbiome described in this review.

the complications studied, there is a need for systematic assessment of the effects of probiotic supplements, either used alone or in combination with pharmacological and nonpharmacological interventions, on the prevention of pregnancy complications. A systematic review by Cochrane in 2021 urged caution in using probiotics during pregnancy. In their analysis, they included six studies with a total of 1440 participants and concluded that it was uncertain if probiotics had any effect on the risk of GDM [55]. Probiotics were further found to increase the risk of PE, and they did not influence maternal weight gain during pregnancy. Additionally, Jarde et al. conducted a systematic review of 19 studies (n = 4098) and found no definitive link between probiotic supplementation and better clinical outcomes in women and their infants [56]. It is important to note that the benefit of probiotic supplementation for the gut microbiome of nonpregnant healthy adults is also highly debated, even though larger numbers of individuals have been studied [57,58]. Hence, well-designed adequately powered trials are needed to identify whether probiotics and prebiotics can improve maternal or infant outcomes.

Future perspectives

A key observation about the studies we have reviewed is that there is great variation in the timing of stool sample collection during gestation, the microbiome isolation, and sequencing methods and the analysis methodologies, which limits comparability across studies and results in the absence of firm conclusions. Standardization of microbiome methodology and collaboration between groups are imperative to enhance future understanding in this complex and rapidly evolving research area.

This review focuses on the pregnancy gut microbiome without touching upon other niches such as the oral or vaginal microbiome. Changes in these niches during pregnancy have also been associated with maternal and infant health [10,59], and it will be important to also study interactions between these niches and the gut microbiome to better understand their relationship with pregnancy outcomes. Additionally, while much of the attention in studies involving pregnancy complications has focused on investigating gut bacteria, the gut viral and fungal ecosystems also warrant attention.

Besides the use of pro- and prebiotics, other means to modulate the gut microbiome, such as dietary interventions, are also gaining interest. Zeevi et al showed that personalized postprandial glycemic response was highly individual-specific and dependent on the gut microbiome [60]. Additionally, in 225 adults with prediabetes, a Personalized Postprandial Targeting diet improved glycemic control significantly more than a Mediterranean diet [61]. For complications such as GDM, personalized dietary recommendations based on integrating clinical variables with an individual's gut

microbiome composition could thus be an exciting avenue for future research.

Currently, most human studies regarding the pregnancy gut microbiome are observational, and very few include early pregnancy time points or longitudinal follow-up. Furthermore, while some studies focus on changes in the microbiome during pregnancy, few look at the recovery of the gut microbiome after pregnancy, even though this may have important consequences for the future development of diseases. There is thus much need for large longitudinal studies, ideally starting from preconception and continuing to after pregnancy recovery, and an integrated multiomics approach is vital in such studies to fully encompass the complexity of disease pathology. Using the findings from these studies, we may be better able to predict disease or design interventions that prevent pregnancy complications and negative infant health outcomes.

Data Availability

The data that have been used are confidential.

Declaration of Competing Interest

The authors disclose no conflict of interest

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