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REVIEW

Nutrition during pregnancy: Influence on the gut microbiome and fetal development

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Abstract

Pregnancy is a finely tuned process, with the health and well-being of the developing fetus determined by the metabolic status and dietary intake of the mother. The maternal gut microbiome is remodeled during pregnancy, and this, coupled with the maternal nutrient intake during gestation shapes the production of metabolites that can cross the placenta and affect fetal development. As posited by the Developmental Origins of Health and Disease Hypothesis, such environmental influences can have major effects on the developing organ systems. When occurring at particularly sensitive gestational time points, these developmental programming events can have long lasting effects on offspring adaptation to the postnatal environment, and major health implications later in life. This review will summarize current knowledge on how pregnancy and maternal dietary intake intrinsically and extrinsically modify maternal gut microbiota composition and metabolite production. Further, we will assess how these factors shape the fetal landscape and ultimately contribute to offspring health.

DOHaD, fetal development, metabolites, microbiome, nutrition, pregnancy, short-chain fatty acids

KEYWORDS
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1 | INTRODUCTION

Maternal nutrition during pregnancy plays a profound role in the growth and development of the fetus, and is a critical factor determining the long-term health of the offspring. The effects of maternal diet on offspring health were first observed by David Barker et al. (1986)[1] who noted that though the incidence of cardiovascular disease tends to rise with increasing national prosperity, the poorest members of society had the highest disease incidence. In the most impoverished areas of England and Wales, a strong geographic correlation was observed between infant mortality (1921-1925) and ischemic heart disease mortality (1968-1971), leading to the proposal that "impaired growth and development in pre- and early post-natal life may be an important risk factor for ischaemic heart disease.[1]" Further work by Hales and Barker resulted in the Thrifty Phenotype hypothesis,[2] which argues that exposure to a poor maternal diet in utero combined with fetal growth restriction, developmentally programs the fetus as preparation for poor nutrient availability after birth. While these adaptations would likely confer a selective advantage to an offspring, exposure to a nutrient-rich postnatal environment could have deleterious effects.

Now, decades later, both epidemiological observations and proof-of-concept animal models have demonstrated the substantial effect that the early-life environment has on fetal and neonatal development.[3,4] In addition to nutrition, many studies have identified

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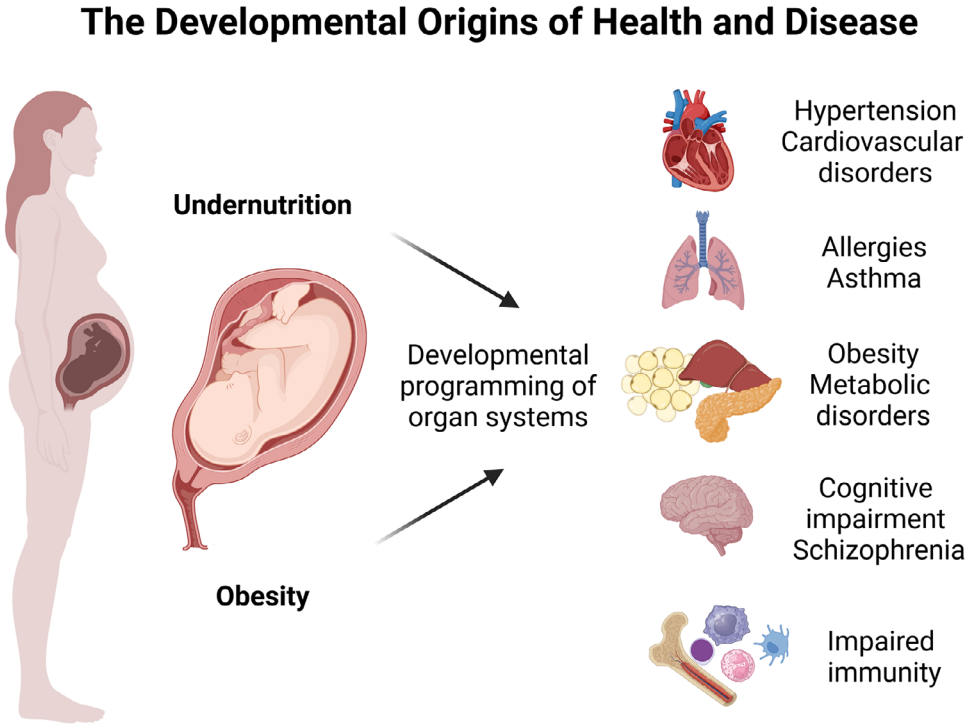

FIGURE 1 Fetal programming and the Developmental Origins of Health and Disease (DOHaD). Maternal metabolic status and dietary intake during pregnancy are intrinsic and extrinsic factors that play a major role in the fetal development of organ systems. Changes to these inputs can alter organ development at particular time points and increase the risk for developing diseases during early or later life.

other environmental influences during pregnancy that play a major role in offspring development and overall health including (but not exhaustive): antibiotic use during pregnancy,[5–7] maternal immune activation,[8–10] stress,[11,12] and vaginal microbiome exposure.[13] This research has provided a framework for the Developmental Origins of Health and Disease Hypothesis (DOHaD),[3,14,15] which states that environmental cues present during critical perinatal time points developmentally program offspring organ systems and subsequently influence individual health outcomes. These studies identify fetal development as a plastic process that is highly sensitive to environmental inputs during pregnancy, and highlight the important role that the maternal milieu plays in the developmental programming of disease susceptibility. For the purposes of this review, we will examine how maternal dietary intake and metabolic status during pregnancy influences the gut microbiome, metabolite production, and the developmental programming of organ systems in the offspring (Figure 1).

Crucial support for the Thrifty Phenotype and DOHaD hypotheses is provided by epidemiological studies on periods of famine, in particular the Dutch Hunger Winter. In a 4–5 month period from 1944 to 1945, food shortages led to a period of famine in which all residents of the western Netherlands, including pregnant women, received food rations of 400–800 calories per day.[16–18] Assessment of the children born during this time period revealed that in utero famine exposure was associated with both cognitive and metabolic disorders in later life, including: age-associated increase in cognitive decline,[19] addiction,[20] impaired glucose tolerance,[21] altered lipid profiles,[22] and obesity.[23] These findings were corroborated by studies of prenatal undernutrition during the 1950–1961 Chinese famine, which also demonstrated increased risk of cognitive morbidities such as schizophrenia[24,25] and cardiometabolic disorders such as hypertension,[26,27] dyslipidaemia,[28] and hospitalization for heart failure.[29] Studies examining periods of famine document the potent effects of undernutrition during pregnancy associated with adverse health conditions in the next generation.

On the other hand, maternal obesity during pregnancy also has major implications for the long-term health outcomes of both mother and child. Driven by convenient access to energy-dense, nutrient-poor foods, coupled with a sedentary lifestyle, obesity is a major global health problem occurring in over 300 million reproductive age women.[30,31] Obesity during pregnancy is associated with pregnancy morbidities such as preeclampsia,[32] preterm birth,[33,34] and caesarean delivery,[35] all of which have an indirect effect on fetal growth, development, and subsequent disease susceptibility.[36] As with undernutrition during pregnancy, infants born to obese mothers also have an increased risk for obesity,[37,38] diabetes,[39] asthma,[37] and cardiovascular disease,[40] as well as cognitive deficiencies such as altered brain development.[41] Furthermore, the maternal metabolic state associated with obesity modifies placental transport of nutrients and metabolites, often influencing fetal growth and metabolism and can result in large-for-gestational-age or small-for-gestational-age births.[31,42,43] Indeed, both maternal obesity and excessive weight gain are associated with a low-grade inflammatory state that can alter pregnancy equilibrium and have a substantial influence on the fetus during gestation.

Though undernutrition and obesity are both a consequence of dietary intake, it is important to highlight that these terms do not represent binary concepts, but rather, they describe a spectrum within

a larger framework. Both obesity and undernutrition are dietary-related disorders that fall under the World Health Organization definition of malnutrition.[44] In the context of this review, we will discuss studies on malnutrition during pregnancy and highlight the importance of having a metabolically stable maternal system that maintains a balanced mother-to-fetus nutrient supply for optimal fetal growth and development.

Considering how maternal nutrition contributes to fetal development and subsequent offspring health, the complex cross-talk between the intake of dietary components and the maternal microbiome must be considered.[45] The gut microbiome both produces, and is influenced by dietary metabolites, that when present at critical developmental time points, can participate in fetal programming events. In this regard, compounds of particular interest are: 1) The aryl hydrocarbon receptor (AhR) which is known to sense environmental toxins as well as dietary and microbiota-derived ligands[46]; 2) Fatty acids—such as immunoprotective short-chain fatty acids (SCFAs), that are produced via the digestion of dietary fiber by commensal bacteria[47]; and 3) Vitamin A and its retinoid derivative compounds, which contribute to secondary lymphoid organ development during embryogenesis.[48] Though human studies show a substantial correlation between maternal metabolic health during pregnancy and gut microbial composition,[36] there is still little information linking maternal nutritional status with changes to the gut microbiome and microbially produced metabolites, specifically with regard to fetal development and health outcomes in the next generation. The purpose of this review is to provide insight into how diet and the gut microbiome contribute to maternal metabolic status during pregnancy and how these processes steer fetal development and underpin a healthy start in life.

2 | INTRINSIC INFLUENCES: PREGNANCY-SPECIFIC REMODELING OF THE GUT MICROBIOME

Pregnancy is a unique biological process in which orchestrated hormonal, metabolic and immunological changes promote fetal nourishment and development within the maternal womb. These physiological adaptations interact dynamically with the microbiota resident in the gut, so that maternal hormonal and metabolic changes shape the structure and diversity of the bacterial community,[49,50] and conversely, microbial byproducts modulate pregnancy-associated processes including placental development[51,52] and feto-maternal tolerance.[53–56] Indeed, the bidirectional nature of these interactions is evidenced by the increasing amount of research demonstrating the direct link between imbalances of the microbiota and adverse pregnancy outcomes such as preeclampsia, fetal growth restriction, preterm birth, and gestational diabetes (reviewed in[57]).

The hormonal changes that drive pregnancy maintenance not only exert a direct influence on maternal immune responses but also affect gut function and hence bacterial composition. The high levels of estrogen and progesterone associated with pregnancy have a direct impact on bacterial metabolism, growth, and expression of virulence factors.[58] As an example, the increased susceptibility to *Listeria monocytogenes* infections in pregnancy is partly due to elevated estrogen and progesterone levels, leading to adverse outcomes including preterm delivery or stillbirth.[59] Of significance, mouse studies have shown that steroid nuclear receptor signaling (i.e., estrogen receptor beta, ER-β) can modulate gut microbial composition.[60] More recently, a direct effect of progesterone in driving the gut microbiome changes characteristic of late pregnancy was demonstrated in mice and humans, particularly in promoting the growth of *Bifidobacterium* species[49] (Figure 2). Besides these direct effects on bacterial composition, estrogen and progesterone can enhance the expression of tight junction components in the intestinal epithelium, thereby decreasing gut barrier permeability, bacterial translocation, and inflammation.[61–63] Progesterone-mediated effects on barrier function are most likely responsible for the amelioration of inflammatory bowel disease (IBD) manifestations observed in pregnant women.[63] Sex hormones are also involved in the inhibitory effects of pregnancy on gut transit and contractility,[64] which may represent an adaptive response to enhance energy extraction from the diet, thereby promoting maternal weight gain. Reciprocally, the microbiome itself may contribute to the production of sex hormones,[53] further adding to the complexity of host microbial interactions during pregnancy.

The gut microbiota is substantially remodeled throughout the progression of pregnancy, displaying a reduced individual richness (alpha-diversity) and increased inter-subject beta diversity towards term.[65] Importantly, although they may be influenced by factors extrinsic to pregnancy as will be discussed later, these changes occur regardless of maternal diet, antibiotic treatments or pre-pregnancy BMI and are vital for a healthy gestation. The gut microbiota profile during the first trimester resembles that of healthy non-pregnant women, showing a predominance of Firmicutes (i.e., Clostridiales) over Bacteroidetes.[65,66] As gestation progresses to the third trimester, there is a decline in the abundance of butyrate-producing species together with an increase of Bifidobacteria, Proteobacteria, and lactate producers so that the profile becomes more similar to that of a disease-associated dysbiosis and shows great variation among normal pregnant women[65] (Figure 2). Indeed, the third trimester gut microbiota shares striking similarities with the dysbiotic profiles reported in obesity and metabolic syndrome,[67,68] conditions associated with distinct metabolic alterations including hyperglycemia, insulin resistance, excess adiposity, and low-grade inflammation.[68,69] In normal pregnancy, however, these changes occur in a physiological context and are highly beneficial, as they provide adequate support for fetal growth as well as energy storage in preparation for lactation. It is likely that changes in the gut mucosal immune response together with hormonal adaptations during normal pregnancies drive the development of a low-grade inflammatory status at the intestinal mucosal epithelium, which may favor the diffusion of glucose towards the lumen and thus promote weight gain. This in turn would impact the composition of the gut microbiota, leading to the establishment of a positive feedback loop involving the microbial dysbiosis and the altered metabolic response of the host.[70,71]

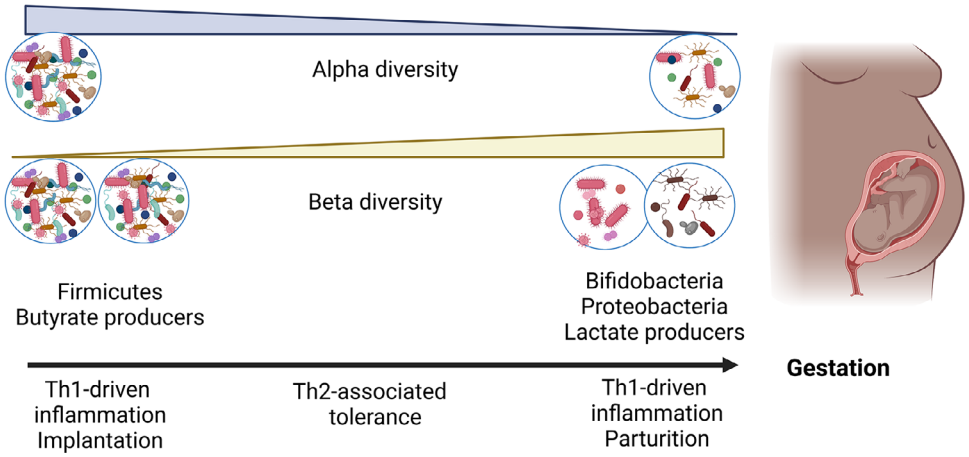

FIGURE 2 Intrinsic changes to the gut microbiome during pregnancy. As gestation progresses, a decrease in alpha diversity and an accompanying increase in inter-subject beta diversity is observed in the maternal gut microbiota. The gut in early pregnancy is rich in Firmicutes and SCFA-producing bacteria, which shifts throughout pregnancy toward increased Bifidobacteria, Proteobacteria, and lactate-producing bacteria at the end of gestation. This is accompanied by an initial Th1 inflammatory response during implantation, followed by tolerogenic Th2 immunity mid-pregnancy that shifts back to Th1-mediated inflammation at the end of gestation in preparation for parturition.

Finally, it is now recognized that successful pregnancy outcomes rely on a proper reciprocal interaction between the maternal immune system and the microbiome. Maternal immune function is tightly regulated during pregnancy so as to ensure effective protection from infections while also preventing rejection of the fetal allograft. A crucial aspect of the pregnancy immune response is the modulation of inflammation, with each trimester posing specific immunological needs. In general, early gestation is associated with a T helper (Th)−1-driven inflammatory milieu to support implantation and trophoblast invasion, followed by a tolerance-associated Th2 profile throughout the main duration of pregnancy and finally shifting again to a Th1 cytokine dominance that initiates parturition[72] (Figure 2). While it is still less clear how these local immunological shifts translate in the periphery, it appears that the course of pregnancy is associated with a progressive development of low-grade inflammation with rising levels of pro-inflammatory cytokines and immune cells in the gut and other mucosal sites.[65] Microbial components are important players in this regulation and are also themselves affected by the immunological changes of pregnancy. When such balanced inflammatory status is disrupted by maternal conditions like obesity, gestational diabetes, or impaired intestinal epithelial barrier function, vascular dysfunction of the placenta can ensue leading to deleterious effects such as fetal growth restriction and preeclampsia.[73,74] Indeed, cumulative evidence suggests that microbial translocation mechanisms, either by the direct systemic spread of microbes from a leaky gut or by bacterial byproducts such as lipopolysaccharide (LPS) that stimulate the production of inflammatory mediators, can have profound consequences on the immunological balance at the uteroplacental interface.[75] As an example, recent studies have shown that the dysbiotic microbiota of preeclampsia patients can alter the mucosal and systemic T regulatory (Treg) to Th17 cell balance and promote severe intestinal leakage and exaggerate inflammation in the placenta when transplanted to pregnant germ-free (GF) mice,[61] highlighting a possible role of bacterial translocation in the pathogenesis of this syndrome. Conversely, studies in rodent pregnancy models have shown multiple beneficial effects on maternal immune balance including the promotion of tolerogenic Th2 dominance upon treatment with a probiotic strain of *Enterococcus*,[76] and M2 macrophage polarization and reduced placental expression of inflammatory mediators following treatment with *Akkermansia*.[77]

Pregnancy is a highly dynamic process, and our knowledge on how host-microbial interactions change across temporal scales is only emerging. It must be acknowledged that most evidence regarding the interplay between the gut microbiome and maternal adaptations to pregnancy comes from descriptive work in animal models, which is often lacking a serial sampling or longitudinal approach, and hence limited to reporting associations or hypotheses that require formal testing. Collectively, the evidence presented in this section suggests that a better understanding of the dynamics of the host microbial interactions during a normal pregnancy may improve identification of populations at risk for adverse outcomes.

3 | EXTRINSIC FACTORS INFLUENCING GUT MICROBIOME CHANGES DURING PREGNANCY: THE ROLE OF MATERNAL DIET

In addition to internal cues, gut microbial changes during pregnancy are also modulated by environmental factors, with maternal diet playing a primary role. One of the most studied nutritional interventions in animal models is the consumption of a high-fat diet, which produces distinctive gestational-age dependent shifts in the maternal gut microbiota associated with a differential gene expression profile favoring lipid metabolism, glycolysis, and gluconeogenic metabolic pathways over the course of pregnancy.[78] More recent studies comparing mice fed a high-fat diet or subject to caloric restriction have shown that adaptations of the maternal gut during pregnancy in terms of barrier

function, inflammation, microbial composition, and expression of multidrug resistance transporters are differentially modulated depending on the nutritional insult.[79] Interestingly, these studies showed that pregnancy-induced changes in the female gut microbiome were more vulnerable to modulation by the diet, rather than by the maternal obesity status or weight gain trajectories during pregnancy.[78]

In pregnant women, most studies have demonstrated significant pregnancy-associated changes in microbial composition that correlate with maternal diet and initial weight, weight gain trajectories, inflammation and metabolic parameters. For instance, maternal overweight was correlated with alterations in gut microbial composition, namely, an increased abundance of *Bacteroides* and *Staphylococcus*.[80] Additionally, reinforcing the strong connection between microbiota alterations and maternal metabolic adaptations, insulin and adipokine levels in obese and overweight pregnant women were found to correlate with microbial changes in early gestation.[81] A main limitation in human studies is that most do not dissect the interactions between maternal body composition, gestational weight gain, and dietary quality in shaping gut microbial changes associated with pregnancy. As an exception, a recent longitudinal study examining gut microbial alterations throughout pregnancy, in a cohort stratified according to pre-pregnancy BMI and dietary macronutrient supply,[82] demonstrated not only that maternal obesity and diet influence distinct subsets of microbial taxa but also that the associations between specific dietary components and the microbiome differ in normal weight versus overweight mothers. For example, increased abundance of *Ruminococcus* correlating with dietary polyunsaturated fatty acid (PUFA) intake was observed only in normoweight pregnant women.[82] Although causal associations remain elusive, these observations show substantive evidence for pregnancy and maternal obesity-dependent interactions between dietary factors and the maternal gut microbiome.

Few studies have addressed the influence of specific dietary modifications on the maternal gut microbiome in pregnant women. Among macronutrients, carbohydrates and fats appear to exert the stronger influence on the gut microbiome during pregnancy. Indeed, fats and fat-soluble vitamins represent some of the most potent dietary modulators of the maternal gut microbiome, particularly with regards to their pro-inflammatory potential. Specifically, dietary intake of vitamin D, mono-unsaturated fatty acids, cholesterol, and retinol were associated with a reduced richness and relative increases in Proteobacteria, a phylum known to encompass multiple pathogenic genera with pro-inflammatory properties.[83] Similarly, a low-fiber dietary supply was associated with reduced diversity and an increased abundance of *Colinsella*,[84,85] a genus associated with type 2 diabetes mellitus. Maternal adherence to dietary reference values of fiber and fat intake, on the other hand, exerted a beneficial effect on bacterial richness during early pregnancy,[86] which was associated with an improved serum lipidomic profile and decreased systemic levels of low-grade inflammation markers. Women adhering to a vegetarian diet display a decreased beta diversity during early pregnancy and distinct microbial shifts favoring the production of immunoprotective SCFAs associated with an increased relative abundance of *Roseburia* and Lachnospiraceae.[84] In overweight pregnant women, dietary fiber and n-3 PUFA were associated with higher microbiota richness indexes and lower systemic levels of zonulin,[87] a marker of gut permeability. Interestingly, neither gestational age nor pre-pregnancy BMI were found to act as significant confounders in the associations reported in this study, suggesting an independent effect of dietary nutrients in the modulation of gut microbial composition during pregnancy. However, special caution should be taken when considering these associations due to the subjective nature of the data, as dietary composition was assessed using food frequency questionnaires or other types of patient's self-reports.[83,87]

4 | THE GUT-PLACENTA AXIS

Having discussed how intrinsic and extrinsic factors affect the intestinal commensals, we would also like to address the downstream effects on this crosstalk, highlighting the potential of the maternal microbiota to influence the development and immune functions of the offspring. In the last years, the presence of a microbiota at the level of the prenatal intrauterine environment (placenta and amniotic fluid) that could colonise the mammalian fetus before birth was under intense discussion. Recently, a critical review of the works done on this topic by several experts in the field emphasized the importance of controlling for contamination and bias in such studies and called for improved methods and standards for studying low-biomass microbial communities. The conclusion was that the presence of a living microbiota in both the fetus and placenta before birth, under physiological conditions, contradicts basic principles in immunology and clinical microbiology, as well as the development of GF animals.[88]

Despite the absence of a live placental microbiota, maternal microbial products and metabolites are soluble and are known to reach the fetus by passing the placenta. Microbial components (e.g., LPS or flagellin) can reach fetal tissues where they are recognized by innate pattern recognition receptors, such as toll-like receptors (TLRs) and therefore have the ability to affect fetal development.[89] TLR2 and TLR4 are also expressed by human extravillous cytotrophoblast cells in the first trimester suggesting that innate immunity could be activated first at this barrier level.[90] Additionally, comparison of the placental and fetal metabolome between GF mice and mice colonized with a diverse and undefined microbiota (specific-pathogen free, SPF) revealed significant differences.[91] The clearest differentiation was observed in the placenta, the fetal intestine and the brain with 168 molecular features more abundant in SPF compared to GF conditions. Among these, 24 annotated metabolites were detected in lower amounts in GF fetal organs, including 5-aminovaleric acid betaine (5-AVAB), trimethylamine N-oxide (TMAO), N,N,N-Trimethyl-5-aminovalerate (TMAVA), tryptophan derivatives [such as kynurenine and 3-indolepropionic acid (3-IPP)] and aminoisobutyric acid, alanine/β-alanine betaine, solanidine, catechol-O-sulphate, hippuric and pipecolic acid.[91]

Among these bacterially produced metabolites, 5-AVAB (which plays a role in fatty acid metabolism),[92,93] and TMAO an oxidized trimethylamine (TMA) product produced by gut microbes from dietary phosphatidylcholine, choline, and carnitine[94,95] have been detected in

the fetus. 5-AVAB was shown to be elevated in the cord plasma of preeclamptic human neonates[96,97] as well as in the fetal mouse brain[98] in a maternal microbe dependent manner. Maternal blood and fetal brain from both GF and antibiotic-treated mice had reduced levels of 5-AVAB and TMAO compared to SPF controls. This phenotype could be rescued by colonizing GF dams with Clostridia-dominant spore-forming bacteria.[98] TMAO is important in the fetal brain development, and its supplementation in vivo in microbiota-depleted dams promoted fetal thalamocortical axonogenesis similarly to animals with an intact maternal microbiota.[98] Dietary tryptophan can be metabolised by intestinal microbes either directly, into indole metabolites such as 3-IPP, or indirectly via the host metabolism (through the production of serotonin by enterochromaffin cells or kynurenine by immune and epithelial cells).[99] Kynurenine can act as ligand for AhR receptors expressed on gut epithelia and many types of immune cells, and may have a significant role in modifying the host mucosal immune system to promote the survival of commensal microbiota and provide protection against pathogens.[100,101] 3-IPP has antioxidant properties and binds the pregnane X receptor (PXR), regulating the intestinal barrier[102] and neuroprotective functions.[98,100] Finally, β-alanine betaine is a metabolite with unknown function in mammalian physiology; however, its production appears to depend on the gut microbiota as GF mice have lower concentrations in the intestine.[92] Altogether, these findings show that metabolites produced by both the host and the gut microbiome, can pass the placenta and reach the fetus, and thus could influence fetal development by educating the host enteral and central nervous systems, intestinal barrier function, and the mucosal immune system.[91]

Clear evidence that exposure to maternal microbiota during pregnancy has a strong effect on the offspring immune system comes from a study from colleagues,[103] which showed that by reversibly colonizing GF pregnant mice with a genetically modified auxotrophic strain of *E. coli*, significant alterations in the intestinal innate immune system of the offspring were induced. Small intestinal innate leukocytes such as NKp46$^+$RORγt$^+$ type 3 innate lymphoid cells (ILC3s) and F4/80$^+$CD11c$^+$ mononuclear cells were increased in numbers in the offspring of dams exposed only during pregnancy to the auxotrophic strain of *E. coli*, compared to animals born from GF dams. This difference was maintained until post-natal day 60 and also observed under defined conditions of colonisation with altered Schaedler flora. Only the treatment of pregnant GF dams with AhR ligands (indole-3-carbinol, I3C) induced the increase of intestinal NKp46$^+$ ILC3 in the offspring of the treated mothers; treatment with SCFAs, nucleotide-binding oligomerization domain (NOD) ligands or the retinoic acid–inducible gene I (RIG-I) ligands had no effect. Additionally, the small intestinal epithelial cells of the offspring born to mothers who underwent reversible colonization with *E. coli* during pregnancy showed changes in the expression of genes involved in epithelial cell division and differentiation, integrity, and homeostasis, such as ion channels/mucus secretion, mononuclear cell function and recruitment, and metabolic regulation (e.g., metabolism of dietary xenobiotics, bile acids, and sugar). Upon challenging the different offspring with a replicating strain of *E. coli* or LPS, mice born from gestational-colonised dams were more protected from *E. coli* translocation to the mesenteric lymph nodes and from systemic inflammation, via tumor necrosis factor–α and IL-6 proinflammatory cytokine production, respectively. This experimental approach showed the importance of maternal microbiota to prime the offspring host immune system to the environment to perhaps avoid inflammatory responses to microbial molecules and penetration of intestinal microbes into the systemic circulation.[103]

5 | HOW THE MATERNAL DIET AND MICROBIOME INFLUENCE FETAL DEVELOPMENT

As the maternal diet directly affects commensal composition and metabolite production, nutritional changes during gestation will have profound effects on the developing fetus, its immune system and capacity to adapt to the environment after birth. In this section, we discuss dietary impact on the maternal microbial metabolome and downstream effects on fetal development that promote offspring adaptation to the postnatal environment. In addition to AhR ligands, other maternal microbiota-derived metabolites such as fatty acids and retinoid compounds can reach the offspring during gestation (Figure 3). SCFAs are microbial metabolites derived from digestion of dietary fibers that have a strong influence on the offspring immune system. SCFAs signal through G-protein receptors (GPR), mainly GPR41, GPR43, and GPR109A, which are expressed on the uteroplacental interface, and are known to have a beneficial effect on fetal development, metabolism and the immune system. They modulate host lipid and glucose metabolism, control insulin levels and induce an anti-inflammatory effect by promoting proliferation and differentiation of Treg cells.[47,104] SCFAs influence offspring in terms of intestinal barrier integrity through the transcriptional regulation of tight junction proteins[105] and also participate in nervous system development through GPR41 signaling.[106] Feeding pregnant mice during gestation with high-fiber diet (with 10% inulin) led to a dramatic change in the maternal microbiota composition and an increase in plasma SCFA levels in the offspring already at day 1 of life, compared to the condition of feeding pregnant dams a low fiber diet. As the offspring microbiota at day 1 post birth is still very limited, the maternal microbiota during pregnancy and/or lactation would be responsible for the elevation of SCFA levels in the offspring plasma. Ultimately, the offspring born to high fiber diet-fed dams had increased frequencies of thymic and peripheral Tregs.[107]

Additional evidence showing how maternal diet-microbiota could affect offspring development and immunity showed that feeding pregnant mice either a high fiber diet, or supplementing the drinking water with acetate during pregnancy, protected against offspring asthma development. This protection was demonstrated by reductions in: inflammatory cells in the bronchoalveolar lavage, circulating IgE concentrations, lung tissue inflammation and eosinophil infiltration, and airway hyperreactivity.[108] The asthma-protective effect in the offspring was achieved when dams received high-fiber diet or acetate from G13 until delivery only, and not when high-fiber diet or acetate were given to the offspring exclusively after birth and during

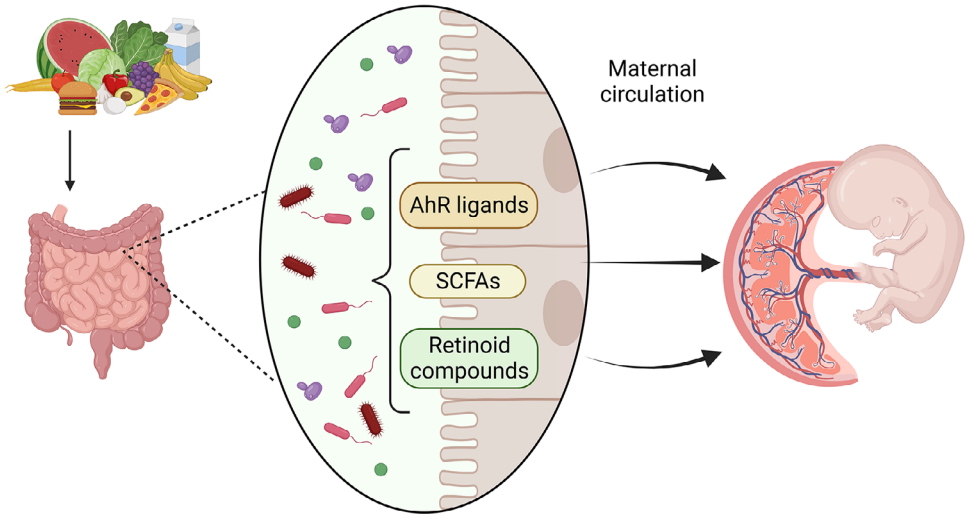

FIGURE 3 Metabolites produced by the maternal gut microbiota pass the placenta and alter fetal development. Nutrition during pregnancy can drastically influence maternal gut microbial composition, and digestion of dietary components by the gut bacterial produce metabolites such as AhR ligands, SCFAs, and retinoid compounds, among others. These compounds enter the maternal circulation and cross the placenta to play active roles in fetal development.

lactation.[108] Moreover, caesarean section experiments with cross-fostering showed that when offspring from high-fiber or acetate fed dams were transferred to control mothers, that pups exposed prenatally to the dietary changes were more protected from allergic asthma. However, offspring transferred from dams receiving the control diet or water to mothers fed high-fiber or acetate, continued to develop allergic airway disease, despite adopting a microbiota more similar to their foster mothers. Importantly, acetate (but not propionate or butyrate) levels in the serum of pregnant women correlated with a significant decrease in doctor visits for cough or wheeze and a trend toward reduced parent-reported wheeze.[108] These findings suggest that maternal microbiota-derived SCFAs, such as acetate, during gestation could be transferred across the placenta to the fetus and induce asthma protection in the offspring, in mice and potentially also in humans.[108]

Maternal vitamin A reaches the embryo through the placenta and the yolk sac and gets converted to retinoic acid (RA) within the embryonic tissues.[109] RA controls the development of different organs, such as the hindbrain, spinal cord, eye, heart, kidney, lung and limb buds,[110] therefore, any perturbation to RA levels during embryonic development leads to abnormal organ development. Animal studies show that moderate to severe maternal vitamin A deficiency can lead to early fetal developmental malformations or, in extreme cases fetal death.[110–112] RA has also an effect on the host immune system, in fact, maternal retinoid intake using a vitamin A-enriched diet only during gestation induced fetal ILC3s and lymphoid tissue inducer cells, which are fundamental for secondary lymphoid organ development during embryogenesis.[48] Commensal bacteria can also produce high concentrations of active retinoids [all-trans-retinoic acid (atRA), 13-cis-retinoic acid (13cisRA) and retinol], from conversion of dietary vitamin A. Therefore, the RA gut-microbiome-mediated metabolic pathways are essential for many mammalian biological processes.[113] In addition, RA affected the differentiation of fetal lymphoid organs as well as of ILC progenitors into mature lymphoid tissue inducer cells. Maternal exposure to retinoids from the diet had an impact also on the size of secondary lymphoid organs and the efficiency of immune responses in the adult offspring, all required to resist to infection later in life.[48]

Vitamin D is an essential fat-soluble vitamin and a key modulator of calcium metabolism in children and adults. There are two forms of vitamin D, D2 coming from plants and in supplements, whereas D3 is present in animal origin food such as egg yolks, sea fish, and liver. It can also be produced by the mammalian organism by itself via sun-light exposure. Because of its involvement in calcium metabolism, which is increased during the third trimester of pregnancy, vitamin D is crucial for maternal health, fetal skeletal growth, and pregnancy outcomes.[114–116] Vitamin D deficiency is common in pregnant women and has been linked to preeclampsia and low birth weight. In breastfed infants, maternal vitamin D deficiency is also associated with adverse childhood health outcomes such as neonatal hypocalcemia, poor postnatal growth, bone fragility, and increased incidence of autoimmune diseases.[116] Vitamin D3 (1,25-dihydroxyvitamin D3) also plays an important role in organ integrity, such as epithelial barrier integrity, and has an impact on host immune cells, such as in the T helper response. Prenatal high-dose vitamin D3 supplementation had balanced effects on cord blood Th1 and Th2 responses, but induced downregulation of *TLR-1*, *−2*, *−4*, *−6*, and *−9* on immune cells isolated from the cord blood.[117] Increased maternal and cord blood levels of 25-hydroxyvitamin D were associated with decreased diversity and richness of the neonatal microbiota at one-month post-birth in humans.[118] On the other hand, maternal vitamin D deficiency exacerbated the intestinal microbial dysbiosis in obese male offspring mice, in combination with high-fat diet consumption. Bacteroidetes and Verrucomicrobia (*Akkermansia*,

Alloprevotella, and *Bacteroides*) were decreased whereas Firmicutes (*Lactobacillus*, *Lachnoclostridium*, *Romboutsia*, and *Ruminoclostridium*) and Firmicutes/Bacteroidetes ratio were increased. The intestinal dysbiosis in offspring mice born from Vitamin-D deficient-high-fat diet fed dams correlated with increased levels of proinflammatory cytokines (Ccl2, Ccl4 and interleukin-1β) and lipid transportation molecules (Ffar3, Fabp4, and Fabp1), and decreased expression of markers of intestinal barrier function (Occludin, ZO-1, and Claudin-1), in the gastrointestinal tract, compared to pups coming from vitamin D-sufficient-high-fat diet fed dams.[119] Altogether, these findings show how diet during pregnancy plays a crucial role, not only influencing the host microbiota and metabolite production, but also to shape and educate the immune system and organs for healthy fetal and neonatal development and proper function of the host organism.

6 | CONCLUSION

In this review, we have addressed the complex interactions between the maternal nutritional status and intestinal microbiome during pregnancy and how they affect fetal developmental pathways ultimately contributing to disease susceptibility and offspring adaptation to the postnatal environment. Successful pregnancy is accompanied by specific hormonal, immunological and gut microbial alterations, but several challenges remain that limit our knowledge of the processes governing these changes. First, most evidence available on the local immunological changes and microbial patterns is derived from murine models or studies of pathological pregnancies and while it is increasingly evident that these changes fluctuate during the course of pregnancy, studies involving longitudinal samples from healthy human pregnancies are still lacking. Similarly, though the existence of these pregnancy-specific changes is undisputed, studies investigating microbial and immunological alterations have not all been consistent due to technical limitations that also preclude the identification of causal relationships between these parameters. Finally, adding a level of complexity, diet is arguably the key extrinsic factor determining maternal gut microbiome composition and how it interacts with the hormonal, metabolic and immunological adaptations to pregnancy. In this regard, one of the main limitations is that most studies conducted thus far fail to dissect the influence of specific dietary components in shaping gut microbial changes associated with pregnancy independently of other confounders such as body composition, gestational weight gain and metabolic disorders.

The emerging concept of the gut-placenta axis illustrates how the crosstalk between these intrinsic and extrinsic factors affecting microbial composition during pregnancy translates to the uteroplacental interface and is able to influence the development and immune functions of the offspring. Besides modulating maternal energy yield, the gut microbiota contributes to micronutrient supply and metabolism of xenobiotics. Furthermore, microbial derived components can trespass the placenta to reach the fetus and exert a wide range of long-lasting effects on immune and non-immune functions. The evidence discussed herein suggests that maternal diet is a crucial determinant of microbiota composition and metabolite production, which in turn shape and educate the fetal immune system and assists in the establishment of a healthy gut microbiota in early life for proper adaptation of the host organism to the environment. Thus, the dynamic remodelling of the maternal gut microbiota under dietary influences represents a major factor determining a healthy start in life.

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CONFLICT OF INTEREST STATEMENT

Authors have no conflict of interest to disclose.

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Not applicable.

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