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REVIEWS

Review

Maternal Microbiome and Metabolic Health Program Microbiome Development and Health of the Offspring

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Maternal nutritional, metabolic, and physiological states, as well as exposure to various environmental factors during conception, gestation, and lactation, have a fundamental role in the health programming of the offspring. Therefore, alterations affecting the maternal microbiota might indirectly influence fetal development. In addition, such alterations could be transmitted to the progeny at different stages of infant development (e.g., preconception, prenatal, or postnatal), thereby favoring the development of an altered microbiota in the neonate. Microbial changes of this kind have been linked to an increased risk of non-communicable diseases (NCDs), including obesity and metabolic syndrome, allergy-related problems, and diabetes. In this review, we summarize the relevance of the maternal microbiota to fetal–neonatal health programming, with a focus on maternal nutritional and metabolic states.

Highlights

Shifts in the maternal microbiota could influence fetal development, in addition to being transmitted to the newborn during birth and lactation.

Alterations in microbial colonization patterns are linked to an increased risk of NCDs, such as obesity, diabetes, and allergies.

The delivery mode, nutritional status of the mother, and perinatal environmental exposures all impact the gut microbiota, thereby affecting the nutritional and metabolic status of the host.

Maternal metabolic status and diet during pregnancy have a key impact on both the maternal and infant microbiota, although the detailed effects remain obscure.

The Relevance of Nutrition in Health Programming

The intimate interrelationship that exists between an individual's diet, microbiome, and health has been widely recognized in studies explaining susceptibility to disease, including allergic, autoimmune, and inflammatory diseases, as well as to obesity [1].

Epidemiological studies have highlighted the relevance of perinatal nutrition to the physiology and structural biology of fetal and neonatal development, with an impact on 'health programming' [2,3]. Both the maternal and paternal nutritional states before conception have pivotal implications for the growth and development of offspring, as well as for the health outcomes of the progeny in both the short and long term [4,5]. Nevertheless, preconception and perinatal interventions intended to improve outcomes for both mothers and neonates remain limited, and additional evidence is required in this regard [6].

Developmental programming *in utero* may be affected by prenatal exposure to environmental factors. Fetal development requires an adaptation to the *in utero* environment, which affects fetal physiology and metabolism. Alterations of homeostasis during embryonic and fetal development may result in an increased risk of non-communicable diseases (NCDs) later in life [3]. Adaptation to the maternal nutritional status (both under- and overnutrition) occurs through changes in the fetal–placental physiology, hormonal alterations, and metabolic modifications [3,7]. In fact, the perinatal period is considered the most critical time span in terms of the risk of developing NCDs [8,9]. Recent studies have provided strong evidence that prenatal exposure to unhealthy dietary patterns, xenobiotics or stress may increase the risk of adverse health outcomes, such as obesity, diabetes, and allergy/asthma, among other diseases, reviewed in [10]. These environmental conditions may act through diverse mechanisms that include epigenetic mechanisms as well as cellular and physiological routes that affect neonatal development and metabolism, thereby leading to an increased risk of NCDs [9]. Detailed mechanisms on epigenetic links between maternal diet, microbiome, and offspring are outside the scope of this review and readers are referred to [11] for further details.

The Human Microbiota and Its Impact on Health

The human body harbors complex communities of microorganisms comprising bacteria, yeast, and fungi, as well as viruses, and Archaea, which perform essential functions in terms of human physiology, metabolism, nutrition, and immunity throughout the human life span [12]. The development of the human microbiota is a complex and step-wise process, which is thought to be initiated at birth, when the infant first encounters maternal microbes during delivery, and then supported by breastfeeding [12]. Historically, the

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human uterus was considered sterile in healthy pregnancies; however, recent data suggest prenatal colonization of the fetal gut [13]. This hypothesis is based on the presence of microbial DNA in amniotic fluid, meconium, and placenta; however, the role of prenatal microbial colonization remains open to debate [14]. Microbial contact before birth may be a possible mechanism of NCDs programming, because the most critical time for the establishment of genome-wide epigenetic profiles occurs during early embryogenesis [11,15]. Microbial colonization not only has a decisive role in relation to both gut physiology and homeostatic balance, but also shapes the maturation of the immune system and cognitive development [16–18]. The immune systems of fetuses, newborns, and infants evolve in a dynamic and complex fashion to adapt to the different challenges and requirements occurring during specific developmental periods [19]. The links between nutrition, maternal microbiota, and neonatal immune system have previously been described elsewhere [20].

The order and timing of species arrival in the neonatal host (priority effects) may influence the early stages of community assembly and development, which in turn would have long-lasting consequences for the human gut microbiota and host health, but these consequences remain poorly understood [21]. These critical processes can be adversely affected by several factors, including the mode of birth [caesarean (C)-section], antibiotic use, prematurity, and formula feeding, which have all been linked to an increased risk of NCDs [12,22].

During birth, the neonate first encounters an immense quantity and diversity of maternal microbes from the maternal reproductive tract, gut, and skin, in addition to those from the environment. Vaginally delivered infants are exposed to maternal vaginal and fecal microbiota, resulting in neonatal gut colonization by vagina-associated microbes (e.g., *Lactobacillus* and *Prevotella*), significantly differing from C-section infants, especially during the first week after birth [23]. The effects of maternal diet and metabolic parameters during pregnancy and prebirth on the vaginal microbiome and the possible consequences for infant gut colonization warrant further research.

During breastfeeding, the neonate's microbiome evolves and becomes more diverse and complex; following the introduction of food, it shifts to an adult-type microbiome at between 2 and 4 years of age [24]. The key factor shaping neonatal microbiota development is the mother's breastfeeding status, whether exclusive or partial [25]. Furthermore, the mode of birth, as well as the adopted breastfeeding practices and antibiotic treatment during the first 2 years of life, have been found to be associated with a distinct oral and gut bacterial composition at a later age [26,27].

Maternal influence on infant microbiota is well recognized, but the role of paternal impact on the health of the progeny remains to be appreciated. Environmental factors, such as paternal diet, nutritional status, xenobiotics exposure, or physical activity, are key in shaping both sperm and seminal plasma composition, which transmit paternal modulatory signals to influence the developmental programming of the offspring [28,29].

In summary, a growing body of evidence suggests that the early life period, that is, from conception through the first 2 years of life, is pivotal for microbial colonization, immune system maturation, cognitive development, and metabolic stimulation (Figure 1). Hence, this period is considered to be a window of opportunity during which dietary, among other changes, will have a strong impact on the metabolic, immunological, and microbiological programming of a child, thereby affecting the health, physical, and intellectual development [12,16,18].

Maternal Adaptation during Pregnancy: Impact on the Microbiota

The physiology, metabolism, and immunity of women alter during pregnancy to allow for an optimal intrauterine environment that favors fetal development and growth [30]. Physiological changes during gestation, including shifts in endocrine, immunological, and metabolic levels, favor a proinflammatory status, analogous to the alterations reported in relation to diabetes, obesity, and metabolic syndrome, which are reflected in the maternal microbiota, including the oral cavity, gut, and vaginal microbiota [31]. However, this proinflammatory status is also implicated in metabolic alterations during pregnancy that

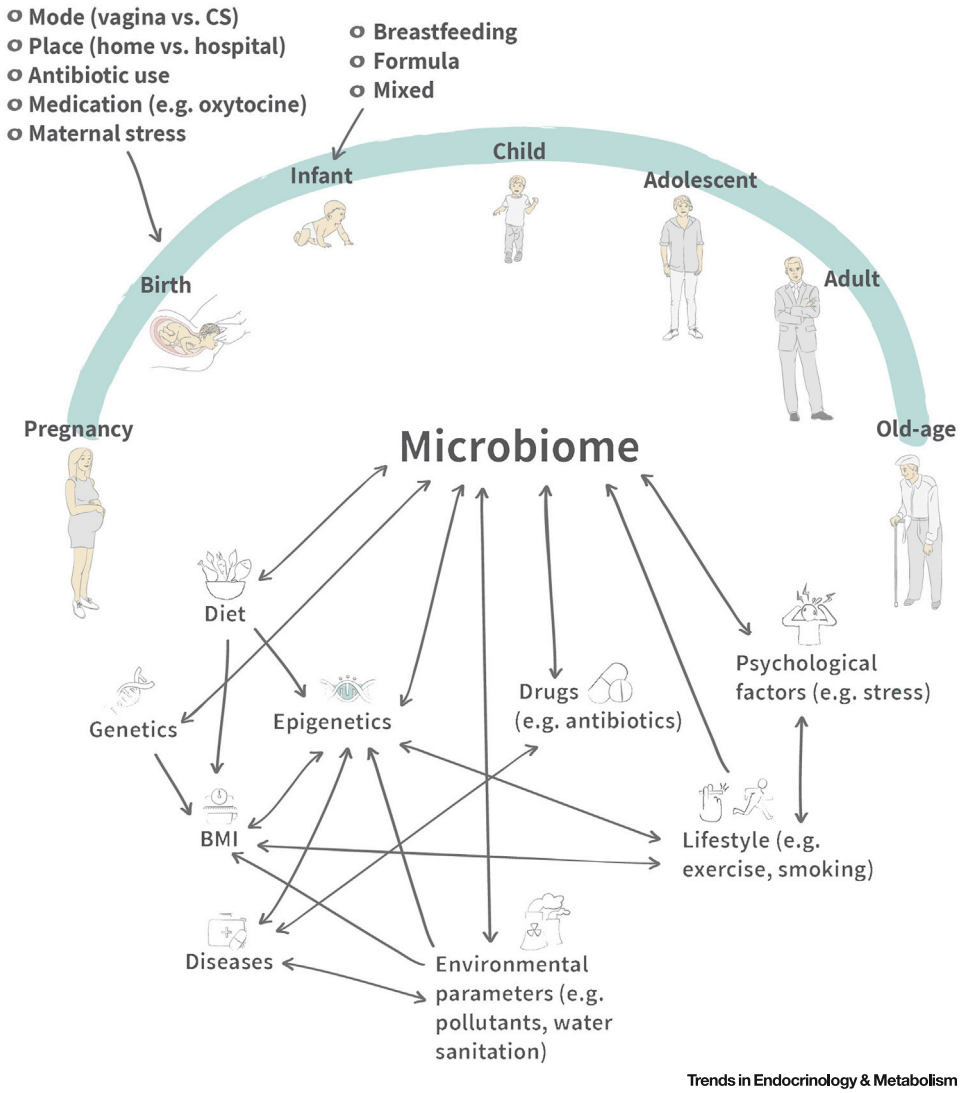

Figure 1. Maternal Microbiota Contribute Significantly to the Initial Microbial Colonization of the Neonate, with Both Short- and Long-Term impact

Different factors shape and alter the maternal microbiota and maternal dysbiosis is transferred to the neonate. The early-life period, from conception through the first 2 years of life, is pivotal for microbial colonization, immune system maturation, cognitive development, and metabolic stimulation. Abbreviations: BMI, body mass index; CS, cesarean section.

contribute to ensuring a healthy pregnancy. The microbial changes in the gut mainly manifest as an increase in Actinobacteria and Proteobacteria, alongside a reduction in microbial diversity and butyrate-producing bacteria [32]. Some studies have identified shifts in the gut microbiota during pregnancy [33,34], while others have failed to identify any microbial changes, reviewed in [35].

Correlations between the gestational metabolic variables and the gut microbiota during pregnancy have previously been described, including direct relationships between the levels of *Collinsella* and circulating insulin, triglycerides, and very-low-density lipoproteins; *Sutterella* and C-reactive protein; Ruminococcaceae and/or Lachnospiraceae and leptin; Bacteroidaceae and ghrelin; and *Coprococcus* and gastrointestinal polypeptide (GIP). Moreover, inverse relationships have been reported

between *Blautia* and insulin values; *Faecalibacterium*:*Fusobacterium* ratios and the blood glucose level; *Odoribacter* and arterial blood pressure; Ruminococcaceae and GIP; and Prevotellaceae and ghrelin level [36]. Recently, it was also shown that progesterone, a major hormone during pregnancy, influences the composition of the gut bacteria in pregnant women, and more specifically, increases the relative abundance of *Bifidobacterium* [34].

Therefore, the gut microbiota may contribute to gestational metabolic changes, although the exact mechanisms behind this contribution remain unknown. Moreover, it has been suggested that multiple childhood difficulties (e.g., chronic stress or abuse) program an exaggerated adult inflammatory response to stress, thereby driving changes in the gut microbiota during pregnancy [37].

Does the Maternal Diet during Pregnancy Affect the Maternal–Neonatal Microbiota and Metabolism?

Evidence from animal models and epidemiological data show that maternal obesity during pregnancy, as well as a high-fat diet, imprint a long-lasting metabolic signature on the neonatal microbiota and immune system, which predisposes the offspring to both obesity and metabolic diseases [38]. Limited data are currently available concerning the impact of the maternal diet during gestation on the maternal microbiota [39–41], with some of the available studies having focused on the relationship between maternal overweight and obesity and gestational diabetes (GDM) [36,42,43] (Table 1). Interestingly, it has been reported that stress and adverse childhood experiences (ACEs) affect the maternal microbiota during pregnancy [37]. In rodents, the consumption of dietary omega-3 fatty acids [including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)] during adulthood modulated the shifts caused by ACE in the maternal gut microbiota [44]. These data also emphasize the relevance of the maternal diet to both maternal and fetal health, as well as its influence on the gut–brain axis. However, additional studies are needed to identify which foods, macro- and micronutrients, and specific dietary compounds influence the perinatal microbiota in both the mother and her offspring [45]. Yet, Savage and collaborators [46] did not find an association between the maternal diet during gestation and the infant's microbiota, which suggests that the infant's diet has a stronger influence on the composition of the microbiome.

Impact of Metabolic Complications on the Maternal Microbiota during Pregnancy

Evidence obtained from human studies suggests that shifts in the gut microbiota during pregnancy are sensitive to the maternal pregestational body mass index (BMI), as well as to weight gain during pregnancy [51,52] (Table 2). Reduced levels of *Bifidobacterium* spp. have been reported in the obese maternal gut, as well as in women with excessive weight gain during pregnancy, compared with levels reported in lean mothers and those with appropriate weight gain during pregnancy [51]. Higher levels of *Staphylococcus* and Enterobacteriaceae (mainly *Escherichia coli*), as well as lower levels of *Bacteroides* spp., were observed in Spanish obese pregnant women compared with levels observed in lean pregnant women [45,52]. Maternal obesity and excessive weight gain were found to be associated with lower microbial diversity, in addition to shifts in Christensenellaceae and the levels of *Lachnospira*, *Parabacteroides*, *Bifidobacterium*, and *Blautia*; however, such shifts were not correlated with the infant gut microbiota composition during the first 2 years of life [53].

Moreover, GDM has a significant impact on the gut microbiota during both gestation and lactation [54,55], and also on breastmilk microbiota and composition [56]. In fact, GDM was found to modify the gut microbiota of pregnant women during the third trimester of pregnancy, and the identified differences were maintained for 8 months after delivery [54]. A higher increase in levels of Ruminococcaceae early during pregnancy (12 weeks) has been found to be associated with GDM [57]. Changes in the gut microbiota have been reported in pregnant mothers with GDM between the second and third trimesters, leading to increased microbial richness, an increase in the levels of Firmicutes, and a reduction in Bacteroidetes and Actinobacteria [43]. It was previously reported that the levels of *Faecalibacterium* spp. are associated with fasting glucose levels, that higher levels of *Collinsella* and lower levels of *Blautia* are associated with insulin levels and the homeostasis model assessment of insulin resistance, and that *Sutterella* is linked to C-reactive protein levels [43]. Pregnant mothers

Study population	Volunteers	Diet record	Effects[b]	Refs
Pregnancy microbiota; Norwegian NoMIC cohort	*N* = 60; dietary records during second trimester; microbiota 4 days after birth	FFQ covering 255 food items	↑ MUFAs; ↑ Firmicutes, Proteobacteria, and Bacteroidetes; ↑ vitamin E intake; ↓ Proteobacteria; ↓ fiber intake; ↓ reduced gut microbiota diversity and richness; ↑ *Sutterella*; ↑ vitamin D, monounsaturated fat, cholesterol, and retinol; ↑ Proteobacteria	[41]
Pregnancy microbiota; OW and/or OB women	*N* = 100; OW and/or OB women (BMI ~30); early pregnancy (≤17 weeks)	3-Day food record	↑ Dietary fiber and PUFAs; ↑ microbiota richness ↓ serum zonulin level	[47]
Pregnancy microbiota; Study of Probiotics IN Gestational diabetes (SPRING)	*N* = 57 OW; *N* = 73 OB; 16 weeks' gestation	Victoria Cancer Council FFQ (Version DQES V2.0)	↓ Fiber intake; ↓ gut microbiota diversity and richness; ↑ *Collinsella*	[42]
Pregnancy microbiota; GDM	*N* = 41; second and third trimester	3-Day food record and Minnesota Leisure-Time Physical Activity Questionnaire	↑ Adherence to dietary recommendations; ↓ metabolic and inflammatory pattern; ↓ *Bacteroides*	[43]
Pregnancy microbiota; SPRING	*N* = 9 vegetarian; *N* = 18 omnivorous; 16 weeks' gestation	Victoria Cancer Council FFQ (Version DQES V2.0)	Vegetarian diet: ↑ *Roseburia* and *Lachnospiraceae*; ↓ *Collinsella* and *Holdemania*; no difference in α-diversity compared with omnivorous diet	[39]
Mother–infant dietary intervention trial (NCT01922791); pregnancy microbiota; OW and/or OB women	*N* = 100; OW and/or OB women (BMI ~30); early pregnancy (≤17 weeks)	3-Day food record	↑ High fat; ↓ fiber intake; ↓ gut microbiota diversity and richness and ↓ Bacteroidaceae; ↑ microbiota richness; ↓ low-grade inflammation marker GlycA	[48]
Pregnancy microbiota; OW and/or OB women	*N* = 84; OW and/or OB women (BMI ~30); early pregnancy (≤17 weeks)	Dietary quality measured by validated index of diet quality (IDQ)	↑ IDQ score; ↑ microbial diversity (Shannon index); ↑ *Coprococcus* (Lachonspiraceae); ↑ *Faecalibacterium prausnitzii* (Ruminococcaceae) ↓ *Sutterella*	[49]
Vitamin D Antenatal Asthma Reduction Trial	*N* = 323	FFQ	Marginal associations between maternal diet during pregnancy and infant gut microbiome: high maternal intake of vegetables and low intake of processed meats and deep-fried foods; ↑ *Lactobacillus* spp. in infant stool; solid food introduction: ↑*Clostridium* spp.	[46]
Infant gut microbiome 6 weeks post-delivery; New Hampshire Birth Cohort Study	*N* = 145	FFQ	↑ Maternal fruit intake associated with infant gut microbial community structure; a) in vaginally delivered infants: ↑ fruit intake; ↑ odds of infants belonging to high *Streptococcus/ Clostridium* group; b) in C-section infants: maternal dairy intake ↑ odds of infants belonging to high *Clostridium* cluster	[50]

Table 1. Evidence of Effect of Maternal Diet during Pregnancy on Maternal and/or Neonatal microbiota[a]

[a]Abbreviations: FFQ, Food Frequency Questionnaire; GDM, gestational diabetes; GlycA, glycoprotein acetylation; GWG, gestational weight gain; MUFA, monounsaturated fatty acid; OW, overweight; OB, obese; PUFA, *N*-3 polyunsaturated fatty acid.

[b]Effects are related to the mothers, unless otherwise stated.

with GDM harbor a higher abundance of Actinobacteria and certain specific bacteria, including *Rothia*, *Collinsella*, *Clostridium* (sensu stricto), *Veillonella*, and *Desulfovibrio,* as well as a reduced abundance of *Faecalibacterium* and *Anaerotruncus*. A lower α-diversity and a lower relative abundance of *Prevotella* and *Lactobacillus* in the meconium of the progeny of mothers with GDM have also been reported [58]. Moreover, maternal GDM status has a significant impact on the neonatal microbiota, resulting in an increased viral load and altered microbial metabolism [59]. This suggests that

Study population	Factor of study	Effects	Refs
Canadian Healthy Infant Longitudinal Development (CHILD birth cohort); *N* = 935	Effect of birth mode and maternal BMI on infant gut microbiota and offspring; BMI z-score at 1 and 3 years	Infants from OW or OB mothers had threefold (vaginal delivery) or fivefold risk (C-section delivery) of becoming OW at the age of 1 year with a similar risk at the age of 3 years; abundance of Lachnospiraceae in microbiota of infant gut directly associated with child obesity in early infancy	[73]
New Hampshire Birth Cohort; *N* = 335 mother–infant pairs	Effect of birth mode and maternal BMI and weight gain	In vaginal-delivery group, ↑ maternal OW or OB associated with ↑ infant microbial diversity and ↑ relative abundance of *Bacteroides fragilis*, *Escherichia coli*, *Veillonella dispar*, *Staphylococcus*, and *Enterococcus*; no associations in the C-section group	[60]
FinnBrain Birth Cohort; *N* = 46	BMI and gestational weight gain during midpregnancy	↑ Gestational weight gain and ↓ α-diversity in midpregnancy associated with Bacteroidetes-dominated gut microbiota in offspring	[74]
EPOCH study; *N* = 107	Associations among gut microbiota, diet, and HFF in adolescents	↑ HFF associated with ↓ α-diversity; 32% of variation in HFF explained by combination of *Bilophila* and *Paraprevotella* abundance, dietary intake of monounsaturated fatty acids, and BMI z-scores	[75]
Finnish Gestational Diabetes Prevention Study (RADIEL); *N* = 109	GDM	↑ *Anaerotruncus* in children of women with GDM ($P < 0.001$)	[76]
Norwegian birth cohort (NoMIC); *N* = 165	Maternal OW/OB or GWG, infant early life microbiota, BMI at age 12	Gut microbiota composition at 2 years explained 53% of variability in BMI z-scores at 12 y; overlap between maternal gut microbiota associated with OW/OB, or excessive GWG and infant gut microbiota associated with elevated BMI in children (e.g., *Bifidobacterium bifidum* and *Blautia* spp.)	[53]
Norwegian birth cohort (NoMIC); *N* = 267 mother–child pairs	Effect of environmental toxins in breastmilk on gut microbiome of infants (1 month)	Exposure to PBDE-28 and PFOS from milk reduced microbiome diversity; *Lactobacillus* had lower abundance in infants with high exposure to toxins (>80th percentile); breast milk toxins affected acetic and propionic SCFA production	[77]
$ARCH_{GUT}$ or $BABY_{GUT}$ cohorts; *N* = 42	Prepregnancy BMI	OW mothers had lower α-diversity and higher abundance of *Bacteroides*, *Acidaminococcus*, and *Dialister*, and lower *Phascolarctobacterium*; infants from NW and OW women had lower abundance of *Meghaspera*; *Staphylococcus* was lowest in infants of OB women	[78]
PREOBE study cohort; *N* = 39	Effect of prepregnancy BMI on microbiome functions of infants at 18 months (transition to solid food)	Infants from OB mothers had higher abundance of Bacteroidetes, and gut microbiota functional shifts: enrichment in streptomycin biosynthesis, sulfur, taurine, and hypotaurine metabolism, and lipopolysaccharide biosynthesis pathways	[79]
KOALA Birth Cohort Study; *N* = 281	Effect of early diet and breastfeeding duration on microbiota and metabolic phenotype in children at school age	Children with a bacterial gene number < 600 000 exhibited ↑ BMI z-score; no pattern observed in lean children; children dominated by *Bifidobacterium* showed lowest gene number and lowest diversity compared with children enriched with *Bacteroides* or *Prevotella*; ↓ breast-feeding duration in the *Bifidobacterium*-dominated enterotype in school-age children	[80]
Bibo (*N* = 87) and Flora (*N* = 75) cohorts	Effect of early-life microbiota composition and antibiotic exposure on infant BMI	Children minimally exposed to antibiotics: positive association between BMI and Bacteroidetes (*Bacteroides ovatus*, *Bacteroides vulgatus*, and *Prevotella tannerae*); multiple antibiotic courses: positive association of Firmicutes (streptococci) and BMI. Actinobacteria (particularly *Bifidobacterium infantis*, *Bifidobacterium pseudocatenulatum*, *Bifidobacterium longum*, *and Bifidobacterium thermophilum*) negatively associated with BMI	[81]

Table 2. Selected Studies Describing Factors Affecting Microbiota Profiles of Offspring, with Emphasis on Influence of Parental Diet on Infant Weight Gain and Metabolic Parameters[a]

(Continued on next page)

Study population	Factor of study	Effects	Refs
New Hampshire Birth Cohort *N* = 81 maternal (oral, intestinal, and vaginal) and *N* = 248 neonatal (oral, pharyngeal, meconium, and amniotic fluid)	Maternal GDM in maternal–neonatal microbiota	*Prevotella, Streptococcus, Bacteroides*, and *Lactobacillus* prevalent in multiple sample types of maternal and neonatal microbiota, reflecting their possible significance to GDM	[59]

Table 2. Continued

[a]Abbreviations: BMI, body mass index; GWG, gestational weight gain; HFD, high-fat diet; HFF, hepatic fat fraction; NW, normal weight; OW, overweight; OB, obese; SCFA, short-chain fatty acid.

metabolic abnormalities on the part of the mother have an indirect effect (e.g., through lactation) on the infant's microbiota. Long-term and mechanistic studies focused on assessing the effect of microbial change on infant or adult health are warranted.

It was previously demonstrated that the maternal prepregnancy BMI and the level of weight gain during pregnancy impact the gut microbiota of 6-week-old infants [60]. In vaginally delivered infants, higher infant gut microbial diversity, as well as higher levels of *Bacteroides fragilis, E. coli*, and *Veillonella dispar*, were associated with maternal obesity, while no associations were observed in infants delivered by C-section [60].

However, a pilot study (*N* = 16) showed that the identified shifts in the composition and diversity of maternal vaginal *Lactobacillus spp.* were linked to a higher prevalence of type 1 diabetes mellitus in children [61].

Furthermore, maternal gut microbiota can shape the development of the central and peripheral nervous system of the fetus by modulating neurotransmitters or host biosynthesis pathways, secreting short-chain fatty acids or other bioactive metabolites, stimulating vagal nerve responses, affecting the permeability of the blood–brain barrier, or shaping the response to stress via the hypothalamic–pituitary–adrenal (HPA) axis [62]. Accordingly, a higher maternal BMI during gestation has been linked to lower levels of salivary cortisol in the offspring during adulthood [63]. Likewise, maternal obesity alters the HPA axis activity toward lower maternal cortisol, which has been linked to an increased birthweight and a prolonged pregnancy [64]. Maternal obesity during pregnancy has also been linked to an increased risk of neurodevelopmental disorders in the offspring, including autism spectrum disorder (ASD) [65].

Impact of Gestational and Early-Life Antibiotic Use

Antibiotics are widely used during pregnancy, and are often administered during a C-section, thereby impacting the maternal microbiota [66]. Perinatal antibiotics administered to the mother shape the infant's microbiota for up to 3 months [67], an increased abundance of Enterobacteriaceae [68]. Furthermore, intrapartum antibiotics shape the early neonatal gut microbiota toward an increase in levels of Proteobacteria and Firmicutes and a reduction in Actinobacteria [69,70]. In fact, antibiotics administered during delivery shape the neonatal oral microbiome, thereby resulting in higher levels of Proteobacteria following antibiotic treatment [71]. This could have important consequences in terms of child development. Relatedly, it has been observed that children who were exposed to antibiotic treatment during the second and third trimesters exhibited an 84% higher risk of developing obesity [72]. Additionally, *Neisseria, Streptococcus mitis,* and *Streptococcus dentisani* were found to be present in significantly higher levels in 7-year old children who did not take antibiotics early in life [26].

Maternal Metabolic Impact on Breast Milk Composition

Human milk is considered to be the 'gold standard' for infant nutrition due to its many epidemiologically demonstrated advantages for both mothers and infants, most notably the decreased risk of NCDs, including obesity and other metabolic-related problems [82]. In addition to its nutritional

components, breast milk contains a complex and varied mixture of bioactive compounds, including proteins, peptides, lipids, micronutrients, nucleotides, hormones, growth factors, immunomodulatory agents, human milk oligosaccharides (HMO), and microbes [83].

The maternal pregestational BMI shapes the milk microbiota [84]. The mother's BMI was positively associated with colostrum *Lactobacillus* and *Staphylococcus* levels, as well as being negatively associated with *Bifidobacterium* levels, in milk samples. These findings were confirmed by mixed model analyses, which also identified an increase in the total number of bacteria in milk with an increasing maternal BMI [84]. Similarly, an association between gestational weight gain and the human milk microbiota has been reported, with the microbiome being less diverse with increased gestational weight gain [84]. A recent study involving 393 breast milk samples obtained 3–4 months postpartum [85] demonstrated that the composition and diversity of the milk microbiota were associated with maternal BMI, parity, mode of delivery, breastfeeding practices, and sex of the offspring. Furthermore, several studies have highlighted the impact of the maternal BMI on human milk components, such as the leptin and insulin hormones, fatty acids, and some cytokines [86–88]. Modulation of breastmilk composition through dietary, pre-, pro-, and postbiotic interventions aiming to beneficially steer the establishment of the gut microbiome and infant metabolic homeostasis in early life is an area that remains to be explored (see Outstanding Questions).

Breastfeeding and the Gut Microbiota: A Key Interaction to Reduce Obesity and Metabolic Diseases

A recent meta-analysis [89], which included seven studies conducted in different locations (>1825 gut samples obtained from 684 infants), reported that exclusive breastfeeding practices shaped the gut microbiota by promoting higher relative abundances of Bacteroidetes and Firmicutes. This change in bacterial composition was accompanied by increases in predicted microbial pathways related to carbohydrate, lipid, and vitamin metabolism, as well as detoxification pathways, compared with nonexclusively breastfed neonates. The identified differences in the predicted microbial pathways were higher in the nonbreastfed neonates delivered by C-section compared with vaginally delivered neonates. Recently, it was demonstrated that the shifts induced by C-section delivery on infant gut microbiome may be partially re-established by exclusive breastfeeding to a microbiota similar to that resulting from vaginal birth [90]. Furthermore, exclusive breastfeeding practices of a longer duration were associated with lower gut microbiota dysbiosis related to diarrhea. The gut microbiota differences between the exclusively and nonexclusively breastfed neonates persisted until 6 months of age, suggesting both short- and long-term benefits of exclusive breastfeeding in terms of the gut microbiota across different populations [89].

Concluding Remarks

The maternal metabolic status both before and during gestation exerts a significant influence on the infant microbiota at the beginning of life. Although the maternal diet influences the infant microbiota, it appears that early-life nutritional patterns (e.g., breastfed or formula fed) have a stronger effect on the microbiota.

Outstanding Questions

Can infant risk for NCDs be controlled by changing the maternal diet during gestation?

What are the effects of the changes described in the infant microbiota on NCDs during early and late adulthood? For example, is the increased risk for C-section babies to be allergic later in life due to the aberrant gut colonization pattern?

How does maternal and/or paternal epigenetic programming relate to progeny microbiome? Can maternal interventions during pregnancy alter the epigenetic programming during early developmental stage? Does the maternal–fetal or maternal–infant microbiome have a role in progeny epigenetic programming?

What is the consequence of primary effects on infant microbiome development and immune programming? How important is the first colonization or do the effects of further environmental parameters mask the primary events?

Do antibiotic administration protocols during pregnancy and birth need to be revisited? Is it possible to balance the effect of C-sections, antibiotic intake, preterm deliveries, or other negative factors affecting the microbiome, by promoting exclusive breastfeeding?

What are the economic consequences of exclusive breastfeeding for governments (in terms of the improvement in infant and maternal health)? Would it be possible to create educational programs to promote exclusive breastfeeding, especially in C-section delivery cases?

Can pro-, pre-, and postbiotic supplementation in mothers benefit infant health?

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