

Review

# The Maternal–Fetal Gut Microbiota Axis: Physiological Changes, Dietary Influence, and Modulation Possibilities

Eva Miko <sup>1,2,3,\*</sup>, Andras Csaszar <sup>2,4</sup>, Jozsef Bodis <sup>2,4</sup> and Kalman Kovacs <sup>2,4</sup>

<sup>1</sup> Department of Medical Microbiology and Immunology, Medical School, University of Pécs, 12 Szigeti Street, 7624 Pécs, Hungary

<sup>2</sup> National Laboratory for Human Reproduction, University of Pécs, 7624 Pécs, Hungary; csaszar.andras@pte.hu (A.C.); bodis.jozsef@pte.hu (J.B.); kovacs.kalman@pte.hu (K.K.)

<sup>3</sup> Janos Szentagothai Research Centre, 20 Ifjusag Street, 7624 Pécs, Hungary

<sup>4</sup> Department of Obstetrics and Gynaecology, Medical School, University of Pécs, 17 Edesanyak Street, 7624 Pécs, Hungary

\* Correspondence: miko.eva@pte.hu; Tel.: +36-(72)-536001 (ext. 31907)

**Abstract:** The prenatal period and the first years of life have a significant impact on the health issues and life quality of an individual. The appropriate development of the immune system and the central nervous system are thought to be major critical determining events. In parallel to these, establishing an early intestinal microbiota community is another important factor for future well-being interfering with prenatal and postnatal developmental processes. This review aims at summarizing the main characteristics of maternal gut microbiota and its possible transmission to the offspring, thereby affecting fetal and/or neonatal development and health. Since maternal dietary factors are potential modulators of the maternal–fetal microbiota axis, we will outline current knowledge on the impact of certain diets, nutritional factors, and nutritional modulators during pregnancy on offspring’s microbiota and health.

**Keywords:** gut microbiota; pregnancy; fetal development; maternal nutrition; probiotics



**Citation:** Miko, E.; Csaszar, A.; Bodis, J.; Kovacs, K. The Maternal–Fetal Gut Microbiota Axis: Physiological Changes, Dietary Influence, and Modulation Possibilities. *Life* **2022**, *12*, 424. <https://doi.org/10.3390/life12030424>

Academic Editor: Einar Ringø

Received: 28 January 2022

Accepted: 9 March 2022

Published: 15 March 2022

**Publisher’s Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Copyright:** © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).


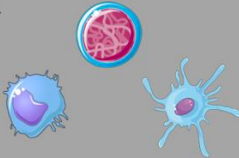

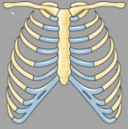

## 1. Introduction

The term “microbiota” defines the entirety of microorganisms that reside in the organs and tissues of an individual acting mostly commensal or symbiotic [1]. The microbiota includes bacteria, archaea, fungi, and viruses, from which bacterial microbiota is the best characterized and most intensively studied component. While the human body hosts many trillions of bacteria, the gastrointestinal tract is the most densely colonized area, with bacterial concentrations ranging from  $10^1$ – $10^3$  bacteria/gram tissue in the upper intestine to  $10^{11}$ – $10^{12}$  bacteria/gram tissue in the colon [2,3]. Analyzing the ratio of intestinal bacterial phyla, *Firmicutes* (species, e.g., *Clostridiales*, *Lactobacillus*, *Enterococcus*) and *Bacteroidetes* (species, e.g., *Bacteroides*) make up the majority, with less dominance of the other phyla *Actinobacteria* (*Bifidobacteria*), *Proteobacteria* (*Escherichia coli*), *Fusobacteria*, and *Verrucomicrobiota* [4–6]. In recent years, the human microbiota, especially the intestinal microbiota, has been recognized as having a major impact on human health, contributing to different physiological processes. The intestinal bacterial community is thought to participate in the metabolic, biochemical, and immunological balance of the host organism (summarized in Figure 1) [7–10].

Since the development of the human gut microbiota begins probably already before birth, it can be assumed that maternal and gestational factors and environmental exposures during pregnancy could affect healthy development and composition of fetal/neonatal/infant gut microbiota and thereby offspring’s health issues [11–13].

The focus of this review, therefore, is to summarize the main characteristics of maternal gut microbiota and its possible consequences on fetal development and offspring’s health.

Besides genetic and environmental factors, nutrition is a key determinant factor affecting the composition and function of gut microbiota; therefore, we will discuss the effects of maternal dietary factors and modulation possibilities on pregnancy microbiota [14,15].

Main beneficial effects of gut microbiota in the host	
<b>Gastrointestinal tract</b> 	colonization resistance mucosa integrity reduction of inflammation breakdown of non-digestible food compounds promotion of angiogenesis
<b>Immune system</b> 	development, education, and training of innate and adaptive immunity promotion of self-tolerance prevention of autoimmunity and allergies
<b>Central nervous system</b> 	bidirectional communication via gut-brain axis control of mood and happiness restoring neurocognitive functions prevention of neurodegeneration
<b>Skeletal system</b> 	calcium absorption bone growth and development bone remodeling
<b>Metabolism</b> 	biotransformation of bile acids biosynthesis of vitamins and amino acids production of short chain fatty acids (SCFAs) production of antioxidants control of fat storage maintenance of insulin sensitivity metabolism of therapeutics

**Figure 1.** Suggested functional effects of gut microbiota in host organism.

## 2. Maternal Gut Microbiota

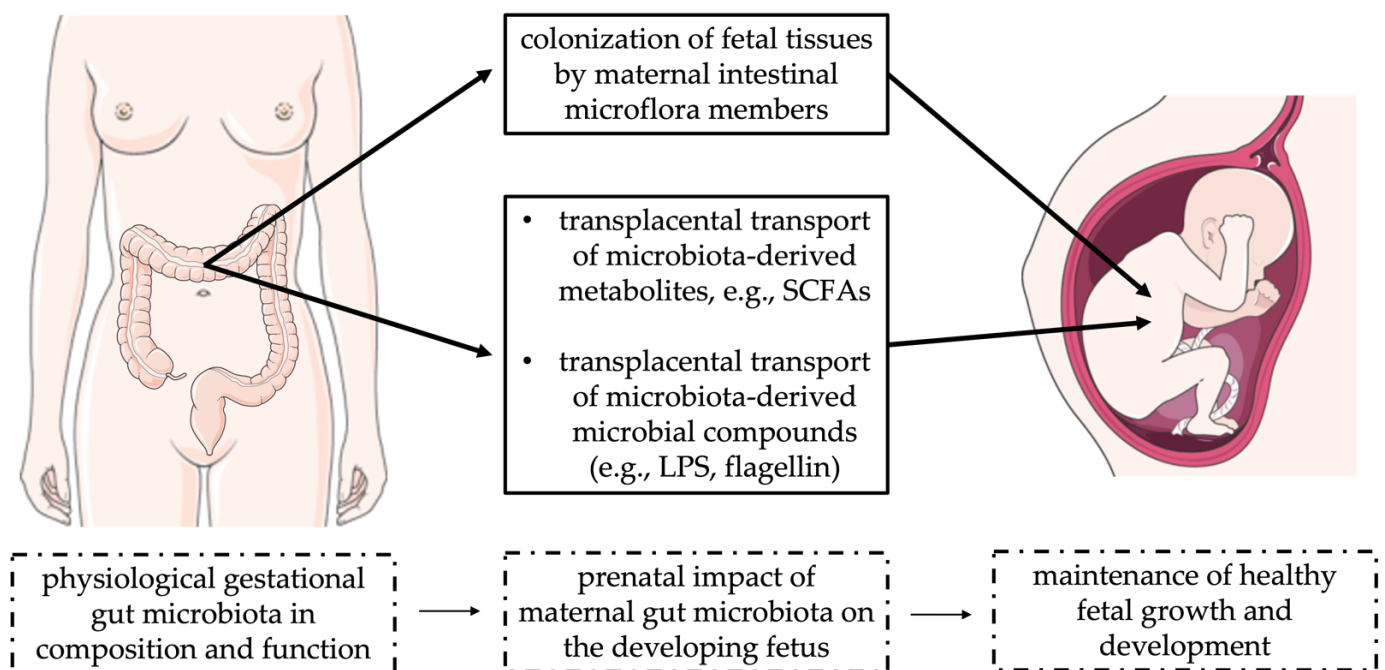
Pregnancy represents a challenging condition for the maternal organism. To meet fetal requirements and thereby ensure self-integrity, it must undergo several profound physiological changes. Maternal adaptation involves primarily endocrine, metabolic, and immunological changes. During pregnancy, the notable rise of progesterone, estrogen, and thyroid hormone levels is well known. Metabolic alterations focus on the expanding neonatal nutrient and energy demand: food intake, insulin secretion, and lipogenesis will increase significantly, resulting in a metabolic syndrome-like condition [16]. Immunological changes are referred to as maternal–fetal immune tolerance: very special and tight regulation of tolerogenic and proinflammatory immune responses. These immune mechanisms enable successful implantation, along with sufficient placentation on the one hand and restoration of maternal antimicrobial immunity on the other [17,18]. In the periphery, healthy human pregnancy is characterized by a mild systemic inflammatory response [19,20].

In the last decade, it has become obvious that pregnancy affects the composition of the maternal gut microbiota, indicating another major pregnancy-related maternal change with possible consequences for fetal/neonatal development. While in the first trimester of

pregnancy, the intestinal microbiota is comparable to that of healthy, nonpregnant women, the composition of the gut microbial community changes significantly from the first to the third trimester [21,22]. From the second trimester onwards, *Proteobacteria*, *Bifidobacteria*, and lactic-acid-producing bacteria (some specific *Lactobacillus* strains) increase parallel with the reduction of the number of butyrate-producing bacteria [7]. Overall, the gestational gut microbiota is characterized by a low alpha diversity index (intraindividual bacterial diversity) and a high beta diversity index (interindividual bacterial diversity), with the most prominent changes occurring mainly in the third trimester [11,23–25]. Intestinal microbiota transfer from pregnant women to germ-free mice revealed functional consequences of changes in gut microbiota during pregnancy [22]. Microbiota-transplanted mice gained weight and showed impaired glucose tolerance associated with insulin resistance [22]. These data suggest that the described changes in the intestinal microbiota during pregnancy might contribute to the well-known metabolic changes observed in pregnant women. Moreover, an increased *Proteobacteria* ratio is thought to stimulate the immune system, leading to enhanced local inflammatory responses. Inflammation, in turn, increases gut mucosa permeability and enables bacterial translocation [22]. This, at least in part, provides a possible reason for the mild systemic inflammation observed in the peripheral blood of healthy pregnant women [19,20]. It should be mentioned that changes in maternal microbiota composition could be influenced by many patient-related factors (maternal diet, maternal BMI before conception, weight gain during pregnancy, and metabolic diseases) and also by population level (ethnicity, geographic, and environmental factors) [7,12–14,19,25–35].

### 3. Establishment of the Maternal–Fetal Gut Microbiota Axis

The impact of maternal gut microbiota on fetal growth and development represents a major field of investigations and theories. Two main distinct pathways were proposed on how gestational intestinal microbiota could exert significant effects on the fetal side (summarized in Figure 2).



**Figure 2.** Possible action of maternal gut microbiota on the developing embryo during pregnancy.

#### 3.1. Placental Microbiota

One of the theories suggests direct and beneficial effects of bacterial presence assuming colonization of fetal tissues by maternal microbes in utero, long before birth [11]. Prenatal

microbial transport from the maternal gastrointestinal tract to the fetus is only a hypothetical consideration requiring direct evidence in the future. According to actual presumptions, microbes at the maternal site are translocated somehow from the intestinal epithelium into the bloodstream and then delivered to the placenta. The bacterial transition could be facilitated through alteration of maternal gut microbiota composition during pregnancy. The increasing abundance of the phylum *Proteobacteria* during pregnancy is thought to be associated with proinflammatory changes (increased serum endotoxin and zonulin concentrations, as well as increased fecal calprotectin levels) in the bacterial environment, enhancing mucosal permeability and microbiota translocation (cellular uptake and occurrence of intestinal microbiota members in extraintestinal tissues and maternal circulation probably resulting in colonization of fetal gut in utero) [36,37].

Regarding the origin of neonatal gut microbiota, there was a consensus about its postnatal establishment until the last two decades. The uteroplacental unit was considered as being sterile. Bacterial occurrence was thought to be associated with colonization and subsequent infection mostly through the ascending way, leading to chorioamnionitis in most cases. The dogma of the “sterile womb” was widely accepted with the consideration that this sterile environment would protect the fetus from infections [13,38,39].

Over the last two decades, noncultivational, PCR, and DNA sequencing-based data have emerged, supporting new theories about maternal–fetal transmission of microbes in utero [13,40–48]. Convincing animal studies have further supported this route of transmission. Increased bacterial translocation from the gut to extraintestinal tissues was observed in pregnant and lactating mice [49]. Orally administered, foreign bacteriophage DNA to mice was shown to persist in the gastrointestinal tract to penetrate the intestinal epithelium and could be discovered in fetuses and newborn animals through the transplacental pathway [50,51]. Moreover, orally inoculated pregnant mice with genetically labeled *E. faecium* strain transmitted labeled bacteria to the amniotic fluid and to the fetal gut during pregnancy [52,53]. Interestingly, the murine fetus seems to be exposed to viable and cultivable bacteria in midgestation and to noncultivable bacteria in late gestation [47].

The human placental microbial community was found to be dominated by the major phylum *Proteobacteria*. The composition was comparable to the oral microbiota, with the species of *Prevotella* and *Neisseria* suggesting the hematogenic route of seeding from the oral cavity to the placenta [46]. It is of note that during pregnancy, the viable oral microbiota increases in number with the parallel rise of the parodontopathogenic strains *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* in the subgingival plaque [54,55]. In pregnant mice, oral infections with *Campylobacter rectus* and *Porphyromonas gingivalis* or *Fusobacterium nucleatum* resulted in inflammatory placental and fetal complications [56–58]. In humans, pregnant women diagnosed with periodontal disease showed an increased risk of pregnancy complications. This observation could be interpreted as the result of an enhanced bacterial transition from the inflamed oral mucosa with increased permeability to the uteroplacental unit [59–62].

Microbiota studies were not only limited to the investigation of the placenta but reported physiological bacterial presence in the amniotic fluid, in the umbilical cord, fetal gut, and also in the meconium [13,21,39,43,63–65]. So far, all of them were considered sterile before.

With the increasing number of conducted studies suggesting in utero fetal exposure to maternal microbiota, concerns have been raised regarding the interpretation of their obtained results [66]. Possible contamination of samples with low microbiota density is a major issue with data distortion potential. Avoiding contamination is very challenging since multiple sources exist. For example, laboratory reagents (nucleic acid extraction kits and PCR reagents) can harbor low concentrations of bacterial DNA, and samples may be contaminated at the time of or even before collection [67–69]. Using the most appropriate analysis platform is also another important issue [70]. Whether in utero exposure of fetal tissues to maternal microbiota members exists is still controversial, and there is disagreement even among the experts in the field.

Another argument against the in utero colonization hypothesis is the fact that germ-free animals are usually generated from non-germ-free pregnancies by embryo transfer following hysterectomy. This could not be the case if mammalian fetuses were already contacted by maternal microbiota members during pregnancy [39].

Usually, the intestinal epithelial barrier itself acts as a physiological barrier, even for the entry of members of the harmless microbiota. Dendritic cells (DCs) can take up bacteria intracellularly from the gut lumen and transport them first to the lymph nodes locally. From here, the bacterial spread can also continue widely, e.g., into the bloodstream, resulting finally in transplacental trafficking [71–73]. This concept of hematogenic maternal intestinal microbiota translocation to the fetus was strengthened by mouse experiments, where increased bacterial sequestering in murine mesenteric lymph nodes was demonstrated [49].

Once bacteria arrive at the fetal site, they probably get noticed. One of the most possible ways of recognizing foreign structures is through toll-like receptors (TLRs). Human TLRs represent a family of 10 transmembrane proteins. They are located either on the cell surface or in intracellular vesicles of primary sentinel cells of innate immunity (macrophages, dendritic cells, and mast cells) in most human tissues [74]. TLRs function as conserved innate immune receptors, recognizing pathogen-associated molecular patterns (PAMPs) that are broadly shared by microbes but not by the host itself. There are different types of TLRs for the recognition of distinct bacterial structures resulting in classical immune activation and inflammatory response directed against the pathogen [75–77].

Despite comparable expression levels of TLRs on neonatal monocytes, the extent of activation of the TLR pathway is considerably reduced compared to adults [77]. Reduced levels of proinflammatory cytokines produced by neonatal monocytes, limited expression of TLR-associated intracellular signaling proteins, and impaired phosphorylation activity of TLR-induced protein kinases suggest immature innate immunity and ongoing immune development in the perinatal period [78,79]. Within this immune milieu, fetal recognition of maternally derived microbiota members exposed in utero would likely result in inadequate immune response favoring immune tolerance of the translocated bacteria. Supporting this concept, recent studies revealed the presence of effector memory T cells in second-trimester fetal tissues [68,80]. However, it should be mentioned again that the concept of existing prenatal microbiota before birth is a matter of debate, and it is not widely accepted. Further studies are needed in the future to clarify the possibility of maternal–fetal microbiota exchange.

### 3.2. Effects of Microbiota-Derived Molecules

The second possible pathway of regulating fetal growth and development through the maternal intestinal microbiota is indirect. It is thought to be mediated by microbiota-derived metabolites that are transmitted transplacentally to the fetus [81–84]. These soluble factors are either synthesized endogenously by members of the microbiota or are metabolites of compounds that are taken up from the intestinal lumen.

One of the most convincing proofs of this concept comes from animal studies. Reversible colonization of germ-free murine pregnant females with a nonpathogenic *E. coli* strain resulted in changes in the intestinal innate immune system development of the offspring [85,86]. Proliferation of innate lymphoid cells type 3 (ILC3s), an innate cell population critical for intestinal barrier functions and host defense, was observed, suggesting maternal microbiota-derived aryl hydrocarbon receptor (AhR) ligands [87]. Moreover, maternal colonization alters the gene expression profile of the offspring's gut epithelium. Expression of genes encoding homeostasis, integrity, and differentiation (upregulated gene networks for cell division and differentiation, mucus and ion channels, metabolism of xenobiotics, bile acids, complex lipids, and sugars) was modulated in small intestinal epithelial cells of offspring born to mothers who had experienced reversible colonization during pregnancy [86].

SCFAs are considered to be the main soluble end product of bacterial metabolism, with a major impact on an individual's health issues. They are taken up by the gut epithelium

and transported to the tissues via circulation [88]. During pregnancy, SCFA concentrations (e.g., levels of acetic acid, propionic acid, butyric and caproic acid) in the cecum increase significantly [89]. The dominant SCFA in both pregnant women and their babies is acetic acid [90]. SCFAs act as signaling molecules through G-protein receptors (GPR), mainly through GPR41 and GPR43 [88]. SCFAs from the maternal gut microbiota can be sensed through uteroplacental GPR41 and GPR43 receptors [91,92]. A series of murine studies demonstrated the beneficial effects of SCFAs during embryo development [91–94]. SCFAs are responsible for increasing free fatty acids' oxidation and mitochondrial activity in muscle and brown adipose tissue [95]. Their beneficial effect on metabolism, mainly through the control of insulin levels, was also observed in the fetus [93]. SCFAs have a major impact on the developing immune system, especially on immune regulatory mechanisms. They may control and balance immune responses, thereby preventing exaggerated inflammation but also autoimmunity. Regulatory T-cell (Treg) proliferation, differentiation, cytokine synthesis, Foxp3 expression, and anti-inflammatory activities were found to be promoted by SCFAs [88,94,96].

Another suggested major function of SCFAs in the fetus is the influence of the development of the nervous system through GPR41 signaling [93]. Enhanced maternal gut microbiota occurs at the third trimester of pregnancy, and this is also a critical period for brain development, such as synaptogenesis, myelination, and development of some specific areas [97–99]. Increased microbiota-derived metabolites, such as SCFAs, could have a beneficial effect on neuronal development [99].

The integrity of the intestinal barrier can also be regulated by SCFAs, mainly through the transcriptional regulation of tight junction-related proteins [100].

Although there is no scientific consensus about whether the developing fetus and the placenta are sterile, besides alive bacteria, many endogenous microbial compounds (e.g., lipopolysaccharide (LPS) or flagellin) can reach fetal tissues and get recognized by innate pattern recognition receptors, such as TLRs, mentioned above. Murine experiments revealed continuous penetration of different tissues by bacterial structural elements required for host immune system maturation. In mice, activated T cells can be detected already in the fetal gut, activation is supposed to be the result of antigen recognition from the maternal gut microbiota ([101–105]. Therefore, it can be hypothesized that even without bacterial trafficking, maternal gut microbiota compounds can reach fetal compartments and provoke recognition. The primitive immune system requires interaction with bacteria or at least bacterium-derived molecules in order to learn to distinguish the microbiota from pathogen types in the future [106–109].

#### 4. Effects of Maternal Nutritional Factors on Gut Microbiota and Offspring's Health

According to epidemiological, clinical, and basic science studies, the offspring's later health issues can be linked, at least partly, to adverse preconceptional, gestational, and post-natal factors, mainly of maternal origin [110]. Regarding the gut microbiota composition and function, dietary factors could have the most determining potential (Table 1) [111].

##### 4.1. High-Fat Diet and Maternal Obesity

Maternal diet type, weight, and nutritional status have an important effect on the developing embryo [112]. Maternal influence on the child's well-being could be exerted via the intestinal microbiota during pregnancy. This is thought to be regulated at least partly by nutritional factors [113]. The typical Western diet consists of excessive processed foods, dietary fat, and sugars. Such a diet promotes excess weight gain and a dysbiotic gut and is associated with adverse maternal and child health outcomes [113–115]. There are numerous fetal developmental characteristics associated with maternal obesity: fetal overgrowth, macrosomia, congenital defects, stillbirth, decreased neonatal Apgar score, preterm delivery, child morbidity, respiratory complications, and neonatal mortality [116–120].

It is well known that the intestinal microbiota is altered profoundly in obese individuals. First, there is an increased abundance of the phylum *Firmicutes* over *Bacteroidetes*, with

a reduced microbial diversity [121,122]. Similar findings were observed in rats when diet-induced obesity modulated gut microbiota composition with a lower relative abundance of fecal *Bifidobacterium* spp. and higher relative abundance of *Clostridium* Clusters XI and I [123]. Moreover, murine experiments revealed that the obese phenotype can be transferred to lean germ-free mice via fecal microbiota transplantation [122]. Pregnancy itself further alters the gut microbiota. Reduced numbers of *Bifidobacterium* and *Bacteroides* and increased numbers of *Staphylococcus*, *Enterobacteriaceae*, and *Escherichia coli* were detected in overweight compared with normal-weight pregnant women [28,35,120,122]. These changes in microbiota are thought to be associated with a reduction in butyrate production, a reduction in hydrogen and methane production, and an increase in mucus degradation and local inflammation [124]. Maternal adherence to the dietary reference intake of fat and fiber during pregnancy is thought to be associated with beneficial gut microbiota composition changes, such as higher gut microbiota richness [125]. Maternal microbiota alterations may be transferred to the infant already in utero and during birth. Infants born to obese mothers display a different bacterial microbiota pattern than those born to lean mothers. These differences last at least one year, showing the long-term impact of maternal obesity on offspring's intestinal microbiota [30,41,120,126]. Similar findings were observed in a primate model, where a high-fat maternal diet (consisting of 36% fat from lard, butter, animal fat, and safflower oil) modulated the offspring's intestinal microbiome in Japanese macaques [127]. The main changes in humans are differences in the abundances of *Bacteroides* spp., *Enterococcus* spp., *Acinetobacter* spp., *Pseudomonas* spp., *Blautia* spp., *Eubacterium* spp., *Oscillibacter* spp., and *Faecalibacterium* spp. [43,120,126,128–130]. There are suggestions that a higher abundance of *Lactobacillus* spp. and a lower abundance of *Bacteroides* spp. The early infant gut microbiota may predict the risk of obesity and overweight in childhood [131]. All these findings support the concept of a vicious intergenerational circle of transferring microbiota patterns related to excessive weight gain and associated unfavorable metabolic development [102].

#### Gestational Diabetes Mellitus: A Special Case

Gestational diabetes mellitus (GDM) is a disease of abnormal glucose tolerance resulting from insulin resistance and showing its first occurrence during pregnancy. Diagnosis of the disease primarily based on the oral glucose tolerance test (OGTT) carried out between 24 and 28 weeks is the gold standard [132].

Obesity and gestational GDM share similar metabolic disorder phenotypes. One of the main suggested mechanisms that could explain insulin resistance and the development of GDM in pregnancy is an unhealthy diet with high fat, high sugar, and low fiber intake characteristics [88,133–135]

GDM contributes to changes in the composition of intestinal microorganisms, their diversity, and disturbed SCFA proportions. Distinct microbiota changes can be observed in each trimester. There are some investigations focusing on the dynamic changes of maternal gut microbiota during pregnancy and progression to GDM [136]. The microbiota profile during pregnancy could be a biomarker for early detection of GDM and predict progression of the disease [136,137]. A positive correlation was found between the *Ruminococcaceae* family and glucose level, with a higher odds ratio for diagnosis of GDM [137]. The main findings regarding microbiota changes were: increased relative abundance of the families *Ruminococcaceae*, *Lachnospiraceae*, and *Enterococcaeae*; enrichment of *Bacteroides*, *Blautia*, *Collinsella*, and *Eggerthella* bacteria; decrease in the levels of *Faecalibacterium*; and decrease in alpha diversity in the GDM groups compared to healthy pregnancy [136]. The functional capacity of the GDM gut microbiota revealed an association with enhancement of membrane transport of sugars, oxidative stress responses, branched-chain amino acid transport, and decreased butyrate biosynthesis [136,138]. A possible influence of GDM on fetal/neonatal microbiota was also studied. The placental microbiota from women with GDM harbor lower levels of *Pseudomonadales* order and *Acinetobacter* genus. Moreover, decreased placental *Acinetobacter* was associated with a more adverse metabolic and

inflammatory phenotype [44]. The meconium microbiota of offspring of women with GDM showed lower alpha diversity and increased *E. coli* and *Lactobacillus* abundance [139]. Meconium microbiota of infants born to mothers with diabetes is enriched for the same bacterial taxa as those reported in the intestinal microbiota of adult patients [140]. Analyzing microbiota from different body sites immediately after birth varied by the same trend between the maternal and neonatal microbiota, suggesting the intergenerational concordance of microbial variations observed in GDM [140].

#### 4.2. Vegetarian Diet

Plant-based and vegetarian eating patterns are very popular nowadays. This diet type is thought to lower the risk for obesity, cardiovascular disease, cerebrovascular disease, diabetes mellitus, and chronic kidney disease [141]. Vegetarian dietary patterns are thought to alter gut microbiota, with beneficial changes for the host (increased SCFAs synthesis, higher abundance of *Bifidobacteria*, *Lactobacilli*, *Roseburia*, *Ruminococcus*, decrease in *Proteobacteria* and *Firmicutes* for instance) [142,143]. Limited information is available regarding gut microbiota of vegetarian pregnant women. One study found no difference in alpha diversity but reduced beta diversity of intestinal microbiota in pregnant vegetarians compared to omnivorous pregnant women [144]. There were also differences in the relative frequency of several genera in those on a vegetarian diet (decrease in *Collinsella* and *Holdemania* and increases in *Roseburia* and *Lachnospiraceae*) [144]. These changes could result in higher SCFA levels associated with healthier gut mucosa and a lower degree of inflammation. No data exist about the impact of gut microbiota of pregnant vegetarian women on the health issues of their offspring [144].

#### 4.3. Artificial Sweeteners

In the United States, non-nutritive sweeteners (e.g., sucralose, aspartame, acesulfame-K) are very popular in the daily diet. This is probably due to the growing awareness of sugar's negative impact on health effects [33,145]. Although several artificial sweeteners almost do not contact the colonic microbiota itself, they seem to change the composition of the gut bacterial community [33]. Based mainly on animal experiments, artificial sweeteners have been shown to alter gut microbiota composition, affecting certain bacterial taxa of adults, as well as their offspring (increase in *Bacteroides*, *Lactobacillus*, and *Clostridiales*, depletion of *Akkermansia muciniphila*). Furthermore, they increase body weight in parallel with activation of energy metabolism bacterial genes involved in carbohydrate absorption, glycolysis, and sugar transport [146–151]. Bacterial proinflammatory mediator genes were also shown to increase [147]. *Akkermansia muciniphila*, found depleted in the microbiota after sweetener administration, is a useful bacterium associated with normal weight, balanced serum glucose levels, and intestinal anti-inflammatory effects [33,152–154]. Meanwhile, human results also support the concept of adverse effects of artificial sweeteners on offspring's gut microbiota. Regular intake of artificial sweeteners of women resulted in a higher BMI of one-year-old infants, suggesting that an altered infant gut microbiota could partly account for it since differences of some microbiota-associated metabolites could favor weight gain [155].

#### 4.4. Alcohol

Alcohol consumption during pregnancy and its possible consequences on the establishment of intestinal microbiota is, besides artificial sweeteners, another less studied factor. It is well known that regular gestational alcohol use during pregnancy has also been associated with various disorders in neonates [156,157]. Chronic and significant alcohol consumption affects gastrointestinal mucosal integrity and consecutively gut microbiota composition [158–160]. It was shown to be associated with decreased intestinal microbiota members such as *Roseburia*, *Faecalibacterium*, *Blautia*, *Bacteroides*, and *Lachnospiraceae*, low levels of butyrate-producing *Clostridiales*, *Bifidobacterium*, and *Lactobacillus*, increased gut permeability, and inflammation [161–164]. This different microbiota pattern results in



enhanced alcohol metabolism and local inflammation [161]. In a study with pregnant mice, reduced *Bacillus* bacteria were observed after ethanol exposure [165]. Little is known about the impact of gestational alcohol consumption on pre- and neonatal microbiota. In one human study, in newborns with mothers admitting alcohol use during pregnancy, an increased ratio in the *Megamonas* genus was observed in the gut microbiota [166]. Interestingly, *Megamonas* was shown to be associated with major depressive disorders, and it is well known that maternal alcohol use affects newborns' cognitive and behavioral development such as depression and autism [167–169].

**Table 1.** Effects of maternal dietary factors on offspring's microbiota composition.

Author, Year	Study Population	Investigated Fetal Side Microbiota	Method	Main Findings
Maternal High-Fat diet, Obesity				
Collado et al., 2010 [30]	Infants of obese mothers ( $n = 16$ ) vs. infants of normal-weight mothers ( $n = 26$ )	Infant fecal samples at 1 and 6 months of age	FISH qPCR	Higher weights of mothers were correlated with higher concentrations of <i>Bacteroides</i> , <i>Clostridium</i> , and <i>Staphylococcus</i> , and lower concentrations of the <i>Bifidobacterium</i> group prevalence of <i>Akkermansia muciniphila</i> , <i>Staphylococcus</i> , and <i>Clostridium difficile</i> groups were lower in infants of normal-weight mothers
Galley et al. 2014 [126]	Children of obese ( $n = 26$ ) vs. nonobese mothers	Fecal samples from children 18–27 months of age	16S ribosomal RNA (rRNA) sequencing	Effects of maternal obesity on offspring's gut microbiota were stronger among children of mothers of higher socioeconomic status Higher alpha and beta diversity in children of obese vs. nonobese mothers Children born to obese vs. nonobese mothers had greater abundances of <i>Parabacteroides</i> spp. and <i>Oscillibacter</i> spp., as well as lower <i>Blautia</i> spp. and <i>Eubacterium</i> spp.
Mueller et al, 2016 [128]	Neonates ( $n = 18$ ) born vaginally (5 to overweight mothers), neonates ( $n = 56$ ) by elective C-section (26 to overweight mothers)	Second-day fecal samples from neonates	16S ribosomal RNA (rRNA) sequencing	Compared to neonates delivered vaginally to normal-weight mothers, microbiota of neonates born to overweight or obese mothers were enriched in <i>Bacteroides</i> and depleted in <i>Enterococcus</i> , <i>Acinetobacter</i> , <i>Pseudomonas</i> , and <i>Hydrogenophilus</i>
Gestational Diabetes Mellitus				
Hu et al., 2013 [140]	Newborns ( $n = 23$ ): 5 from mothers with DM, 5 from mothers with GDM, 13 from mothers with no diabetes	Meconium samples	16S ribosomal RNA (rRNA) sequencing	The phylum <i>Bacteroidota</i> and the genus <i>Parabacteriodes</i> were enriched in the meconium in the DM group compared to the nondiabetes group

Table 1. Cont.

Author, Year	Study Population	Investigated Fetal Side Microbiota	Method	Main Findings
Bassols et al., 2016 [44,155]	Placentas from women with GDM ( $n = 11$ ) and from control women ( $n = 11$ )	Placenta	16S ribosomal RNA (rRNA) sequencing	<i>Pseudomonadales</i> and <i>Acinetobacter</i> showed lower relative abundance in women with GDM compared to control. Increase in placental <i>Acinetobacter</i> ratio was associated with a more adverse metabolic and inflammatory phenotype.
Wang et al., 2018 [139]	Pregnant women and their neonates with and without GDM	Oral, pharyngeal, meconium, and amniotic fluid samples	16S ribosomal RNA (rRNA) sequencing	In the amniotic fluid of the GDM group, a lower relative abundance of <i>Anoxybacillus</i> and a higher relative abundance of <i>Corynebacterium</i> were detected. In the meconium of the GDM group, a lower relative abundance of <i>Corynebacterium</i> and a higher relative abundance of <i>Enterobacter</i> were detected. Microbes varied by the same trend between the maternal and neonatal microbiota.
Vegetarian Diet				
None				
Artificial Sweeteners				
Laforest-Lapointe et al., 2021 [155]	Infants ( $n = 100$ ) selected based on maternal sweetener consumption during pregnancy (50 nonconsumers and 50 daily consumers)	Infant fecal samples at 3 and 12 months of age	16S ribosomal RNA (rRNA) sequencing	Maternal sweetener consumption did not differ between clusters reflecting the maturation of gut microbiota but was associated with community-level shifts in infant's gut bacterial taxonomy structure and depletion of several <i>Bacteroides</i> sp. in a certain cluster. Nine bacterial taxa from <i>Bacteroides</i> sp. were enriched or depleted at high levels of maternal sweetener consumption at 12 months of age. Daily maternal sweetener consumption is associated with higher infant weight and altered microbiota composition.
Alcohol Consumption				
Wang et al., 2021 [166]	Pregnant women and their neonates with ( $n = 10$ ) and without ( $n = 19$ ) alcohol consumption	Fecal samples of newborns within 48 h	16S ribosomal RNA (rRNA) sequencing	A positive relationship showed between <i>Megamonas</i> and newborns with maternal alcohol consumption.

## 5. Modulation of Maternal Gut Microbiota for Offspring's Benefits

Given the proven impact of maternal microbiota on fetal health and development perinatally and postnatally, modulation of gestational dysbiosis could have prophylactic potential regarding noncommunicable diseases such as obesity, immunoinflammatory disorders, and neurocognitive complications. Since modification of the microbiota can be carried out easily, prenatal maternal oral pro- and/or prebiotic treatment could represent a safe, effective, and cheap interventional tool for disease prevention of the offspring.

### 5.1. Probiotics

Probiotics are live, beneficial microorganisms found in certain foods and supplements. They are thought to help to restore the physiological balance of the intestinal microbiota community. Most probiotic intervention studies are restricted to the use of *Lactobacilli* and *Bifidobacteria* strains. The beneficial effects of these strains are complex. They promote colonization resistance, limit mucosal adherence of pathogens, strengthen mucosal integrity, and enhance local immune defense, thereby reducing inflammation [170].

Most studies in the field of probiotics in pregnancy have focused on either the clinical outcome in pregnant women or in their offspring. Controversy exists regarding the preventive and useful effects of probiotics on the development of immune-mediated allergic disorders. While several clinical trials revealed the beneficial effect of maternal probiotics on lowering the risk of allergic conditions [171–182], others failed to confirm an advantage of probiotic treatment [183–186]. Regarding obesity, perinatal probiotic treatment could modify the growth pattern of the child by restricting excessive weight gain during the first years of life. Probiotic effects on GDM occurrence and symptoms have been intensively studied, with promising results [183–190].

Limited data are available on the mechanism of action and on the effect of probiotics on the maternal–fetal gut microbiota axis. There is good evidence that maternally derived probiotic bacteria can colonize the gastrointestinal tract of infants and persist there for 1–2 years [176,181,191–196]. However, another study revealed that the probiotic strain *Lactobacillus rhamnosus* GG increased the infant gut colonization by *Bifidobacterium* spp, but not by itself when administered to mothers in late pregnancy. This suggests that probiotics may promote fetal seeding with other bacteria, probably through the action of bacterial metabolites [197]. There is also the possibility that different probiotic bacteria could have different abilities to be transferred from the mother to the infant [173]. Furthermore, maternal dietary probiotic intake led to the modulated expression of TLR-related genes in the placenta and fetal intestinal tract, interfering thereby with fetal immune system development [175]. Since there is no consensus about the real impact of maternal probiotic intake on fetal gut microbiota composition and health issues, further investigations are needed [169].

### 5.2. Prebiotics

Prebiotics are food compounds that promote the growth and/or activity of beneficial microorganisms. The most common example is oligosaccharides resistant to digestion in the small intestine. Modulating maternal gut microbiota through the administration of prebiotics during pregnancy could be a safer alternative than probiotic consumption, as suggested by animal experiments [198]. In a mouse model of atopic dermatitis, prenatal maternal supplementation with a fructo-oligosaccharide modulated the intestinal microbiome of the offspring and suppressed the increase in clinical skin severity score and scratching behavior in offspring [199]. Prebiotic oligofructose treatment of diet-induced obese pregnant rats was found to reduce maternal energy uptake, reduce gestational weight gain, and prevent increased adiposity in dams and their offspring [122]. A high-fiber diet of mice led to marked suppression of allergic airways disease in the offspring's, which could be mediated in utero via modulation of maternal gut microbiota [82]. Only few studies exist reporting offspring's modulated gut microbiota and health benefits from maternal prebiotic intake in mice [198–202].

## 6. Conclusions

Studies of germ-free animals revealed that the absence of a healthy microbiota is associated with deficits in immune and neuronal development, impaired stress adaptation, and metabolic dysfunction later in life [83,86,203,204]. This observation was supported by plenty of human studies describing altered microbiota composition and dysbiosis as possible etiologic factors of several noncommunicable diseases in humans. Thus, the establishment and maintenance of a healthy microbiota are crucial for human health. Among the human microbiota at different body sites, the intestinal microbiota is thought to be the most important concerning health effects.

The main source of a newborn's intestinal microbiota is the maternal gut. During the last decade, it has become obvious that maternal commensal microbes or their products are transferred to the fetus through the placenta in utero and/or postnatally. There they affect the composition of the fetal/neonatal intestinal microbial community. The establishment of a healthy early gut microbiota in life has long-lasting effects on the offspring's metabolism and immune system and lowers the risk of developing a range of diseases later in life. Therefore, it is conceivable that any factors that affect the establishment of a healthy gut microbiota in the newborn/infant can potentially have a long-term impact on the offspring's health. Maternal dietary factors could have a significant impact on the maternal–fetal microbiota axis, and modulation of dysbiotic gut microbiota may be beneficial both for the mother and also for her baby.

## 7. Future Directions

Despite convincing results discussed in this review, knowledge on some critical points and major events is still missing in this field. The possibility of an in utero translocation of maternal gut microbiota to the fetus should be further investigated, and phases of the process should be determined. Further investigations are needed to explore the complex association between early gut microbiota composition and its long-term effects on adult health issues. Determination of key bacteria or bacterial shifts in the background of certain noncommunicable diseases would be a major step forward.

Beneficial effects of prenatal pro- and prebiotic treatment on offspring's health were also shown, although it requires detailed studies regarding the type, the dosage, and the timing of pro-/prebiotic intake during pregnancy. Furthermore, there are some investigational microbiome therapeutics, which may have preventive potential on the maternal transfer of dysbiotic microbiota to the fetus/newborn.

Healthy maternal diet has a significant impact on healthy maternal gut microbiota, which, in turn, affects the formation of the fetal/newborn intestinal microbiota. However, this is only the beginning. Maintenance of eubiosis is critical for long-lasting beneficial effects in terms of preventing noncommunicable diseases. As postnatal development of the child proceeds, the role of the mother's bacteria becomes less important, and environmental factors occur. However, a good start in life ensured by the maternal gut microbiota remains always a major health determining factor.

**Author Contributions:** Conceptualization and writing, E.M.; review, A.C.; conceptualization, J.B.; figure and table, review, K.K. All authors have read and agreed to the published version of the manuscript.

**Funding:** This work was supported by the National Laboratory on Human Reproduction as part of the “Establishment of National Laboratories 2020” program, the University of Pecs Medical School Research Grant (PTE-ÁOK KA-2018-07).

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

1. Dominguez-Bello, M.G.; Godoy-Vitorino, F.; Knight, R.; Blaser, M.J. Role of the Microbiome in Human Development. *Gut* **2019**, *68*, 1108–1114. [[CrossRef](#)] [[PubMed](#)]
2. Derrien, M.; van Hylckama Vlieg, J.E.T. Fate, Activity, and Impact of Ingested Bacteria within the Human Gut Microbiota. *Trends Microbiol.* **2015**, *23*, 354–366. [[CrossRef](#)] [[PubMed](#)]
3. O'Hara, A.M.; Shanahan, F. The Gut Flora as a Forgotten Organ. *EMBO Rep.* **2006**, *7*, 688–693. [[CrossRef](#)] [[PubMed](#)]
4. Dethlefsen, L.; Relman, D.A. Incomplete Recovery and Individualized Responses of the Human Distal Gut Microbiota to Repeated Antibiotic Perturbation. *Proc. Natl. Acad. Sci. USA* **2011**, *108* (Suppl. 1), 4554–4561. [[CrossRef](#)]
5. Eckburg, P.B.; Bik, E.M.; Bernstein, C.N.; Purdom, E.; Dethlefsen, L.; Sargent, M.; Gill, S.R.; Nelson, K.E.; Relman, D.A. Diversity of the Human Intestinal Microbial Flora. *Science* **2005**, *308*, 1635–1638. [[CrossRef](#)]
6. Qin, J.; Li, R.; Raes, J.; Arumugam, M.; Burgdorf, K.S.; Manichanh, C.; Nielsen, T.; Pons, N.; Levenez, F.; Yamada, T.; et al. A Human Gut Microbial Gene Catalogue Established by Metagenomic Sequencing. *Nature* **2010**, *464*, 59–65. [[CrossRef](#)]
7. Adak, A.; Khan, M.R. An Insight into Gut Microbiota and Its Functionalities. *Cell. Mol. Life Sci.* **2018**, *76*, 473–493. [[CrossRef](#)]
8. Gomaa, E.Z. Human Gut Microbiota/Microbiome in Health and Diseases: A Review. *Antonie Leeuwenhoek* **2020**, *113*, 2019–2040. [[CrossRef](#)]
9. Kobylak, N.; Virchenko, O.; Falalyeyeva, T. Pathophysiological Role of Host Microbiota in the Development of Obesity. *Nutr. J.* **2016**, *15*, 43. [[CrossRef](#)]
10. Laukens, D.; Brinkman, B.M.; Raes, J.; de Vos, M.; Vandenaabeele, P. Heterogeneity of the Gut Microbiome in Mice: Guidelines for Optimizing Experimental Design. *FEMS Microbiol. Rev.* **2016**, *40*, 117. [[CrossRef](#)]
11. Coscia, A.; Bardanzellu, F.; Caboni, E.; Fanos, V.; Peroni, D.G. When a Neonate Is Born, So Is a Microbiota. *Life* **2021**, *11*, 148. [[CrossRef](#)] [[PubMed](#)]
12. Brown, J.; de Vos, W.M.; Distefano, P.S.; Doré, J.; Huttenhower, C.; Knight, R.; Lawley, T.D.; Raes, J.; Turnbaugh, P. Translating the Human Microbiome. *Nat. Biotechnol.* **2013**, *31*, 304–308. [[CrossRef](#)] [[PubMed](#)]
13. Stinson, L.F.; Boyce, M.C.; Payne, M.S.; Keelan, J.A. The Not-so-Sterile Womb: Evidence That the Human Fetus Is Exposed to Bacteria Prior to Birth. *Front. Microbiol.* **2019**, *10*, 1124. [[CrossRef](#)] [[PubMed](#)]
14. Daniel, H. Diet and Gut Microbiome and the “Chicken or Egg” Problem. *Front. Nutr.* **2021**, *8*, 828630. [[CrossRef](#)] [[PubMed](#)]
15. Shanahan, F.; Ghosh, T.S.; O'Toole, P.W. The Healthy Microbiome—What Is the Definition of a Healthy Gut Microbiome? *Gastroenterology* **2021**, *160*, 483–494. [[CrossRef](#)] [[PubMed](#)]
16. Freemark, M. Regulation of Maternal Metabolism by Pituitary and Placental Hormones: Roles in Fetal Development and Metabolic Programming. *Horm. Res.* **2006**, *65*, 41–49. [[CrossRef](#)]
17. Arck, P.C.; Hecher, K. Fetomaternal Immune Cross-Talk and Its Consequences for Maternal and Offspring's Health. *Nat. Med.* **2013**, *19*, 548–556. [[CrossRef](#)]
18. Erlebacher, A. Why Isn't the Fetus Rejected? *Curr. Opin. Immunol.* **2001**, *13*, 590–593. [[CrossRef](#)]
19. Belo, L.; Santos-Silva, A.; Rocha, S.; Caslake, M.; Cooney, J.; Pereira-Leite, L.; Quintanilha, A.; Rebelo, I. Fluctuations in C-Reactive Protein Concentration and Neutrophil Activation during Normal Human Pregnancy. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **2005**, *123*, 46–51. [[CrossRef](#)]
20. Fink, N.R.; Chawes, B.; Bønnelykke, K.; Thorsen, J.; Stokholm, J.; Rasmussen, M.A.; Brix, S.; Bisgaard, H. Levels of Systemic Low-Grade Inflammation in Pregnant Mothers and Their Offspring Are Correlated. *Sci. Rep.* **2019**, *9*, 3043. [[CrossRef](#)]
21. Nuriel-Ohayon, M.; Neuman, H.; Koren, O. Microbial Changes during Pregnancy, Birth, and Infancy. *Front. Microbiol.* **2016**, *7*, 1031. [[CrossRef](#)] [[PubMed](#)]
22. Koren, O.; Goodrich, J.K.; Cullender, T.C.; Spor, A.; Laitinen, K.; Bäckhed, H.K.; Gonzalez, A.; Werner, J.J.; Angenent, L.T.; Knight, R.; et al. Host Remodeling of the Gut Microbiome and Metabolic Changes during Pregnancy. *Cell* **2012**, *150*, 470–480. [[CrossRef](#)] [[PubMed](#)]
23. Mesa, M.D.; Loureiro, B.; Iglesia, I.; Gonzalez, S.F.; Olivé, E.L.; Algar, O.G.; Solana, M.J.; Perez, M.J.C.; Sainz, T.; Martinez, L.; et al. The Evolving Microbiome from Pregnancy to Early Infancy: A Comprehensive Review. *Nutrients* **2020**, *12*, 133. [[CrossRef](#)]
24. Wallace, J.G.; Bellissimo, C.J.; Yeo, E.; Fei Xia, Y.; Petrik, J.J.; Surette, M.G.; Bowdish, D.M.E.; Sloboda, D.M. Obesity during Pregnancy Results in Maternal Intestinal Inflammation, Placental Hypoxia, and Alters Fetal Glucose Metabolism at Mid-Gestation. *Sci. Rep.* **2019**, *9*, 1–16. [[CrossRef](#)] [[PubMed](#)]
25. Neuman, H.; Koren, O. The Pregnancy Microbiome. *Nestle Nutr. Inst. Workshop Ser.* **2017**, *88*, 1–9. [[CrossRef](#)]
26. Peelen, M.J.; Luef, B.M.; Lamont, R.F.; de Milliano, I.; Jensen, J.S.; Limpens, J.; Hajenius, P.J.; Jørgensen, J.S.; Menon, R. The Influence of the Vaginal Microbiota on Preterm Birth: A Systematic Review and Recommendations for a Minimum Dataset for Future Research. *Placenta* **2019**, *79*, 30–39. [[CrossRef](#)]
27. DiGiulio, D.B.; Callahan, B.J.; McMurdie, P.J.; Costello, E.K.; Lyell, D.J.; Robaczewska, A.; Sun, C.L.; Goltsman, D.S.A.; Wong, R.J.; Shawa, G.; et al. Temporal and Spatial Variation of the Human Microbiota during Pregnancy. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 11060–11065. [[CrossRef](#)]
28. Santacruz, A.; Collado, M.C.; García-Valdés, L.; Segura, M.T.; Maritn-Lagos, J.A.; Anjos, T.; Martí-Romero, M.; Lopez, R.M.; Florido, J.; Campoy, C.; et al. Gut Microbiota Composition Is Associated with Body Weight, Weight Gain and Biochemical Parameters in Pregnant Women. *Br. J. Nutr.* **2010**, *104*, 83–92. [[CrossRef](#)]

29. Collado, M.C.; Isolauri, E.; Laitinen, K.; Salminen, S. Distinct Composition of Gut Microbiota during Pregnancy in Overweight and Normal-Weight Women. *Am. J. Clin. Nutr.* **2008**, *88*, 894–899. [[CrossRef](#)]
30. Collado, M.C.; Isolauri, E.; Laitinen, K.; Salminen, S. Effect of Mother's Weight on Infant's Microbiota Acquisition, Composition, and Activity during Early Infancy: A Prospective Follow-up Study Initiated in Early Pregnancy. *Am. J. Clin. Nutr.* **2010**, *92*, 1023–1030. [[CrossRef](#)]
31. García-Mantrana, I.; Alcántara, C.; Selma-Royo, M.; Boix-Amorós, A.; Dzidic, M.; Gimeno-Alcañiz, J.; Úbeda-Sansano, I.; Sorribes-Monrabal, I.; Escuriet, R.; Gil-Raga, F.; et al. MAMI: A Birth Cohort Focused on Maternal-Infant Microbiota during Early Life. *BMC Pediatrics* **2019**, *19*, 140. [[CrossRef](#)] [[PubMed](#)]
32. Garcia-Mantrana, I.; Selma-Royo, M.; Alcantara, C.; Collado, M.C. Shifts on Gut Microbiota Associated to Mediterranean Diet Adherence and Specific Dietary Intakes on General Adult Population. *Front. Microbiol.* **2018**, *9*, 890. [[CrossRef](#)] [[PubMed](#)]
33. Olivier-Van Stichelen, S.; Rother, K.I.; Hanover, J.A. Maternal Exposure to Non-Nutritive Sweeteners Impacts Progeny's Metabolism and Microbiome. *Front. Microbiol.* **2019**, *10*, 1–13. [[CrossRef](#)] [[PubMed](#)]
34. Wankhade, U.D.; Zhong, Y.; Kang, P.; Alfaro, M.; Chintapalli, S.V.; Piccolo, B.D.; Mercer, K.E.; Andres, A.; Thakali, K.M.; Shankar, K. Maternal High-Fat Diet Programs Offspring Liver Steatosis in a Sexually Dimorphic Manner in Association with Changes in Gut Microbial Ecology in Mice. *Sci. Rep.* **2018**, *8*, 1–15. [[CrossRef](#)] [[PubMed](#)]
35. Gomez-Arango, L.F.; Barrett, H.L.; McIntyre, H.D.; Callaway, L.K.; Morrison, M.; Nitert, M.D.; Tremellen, A.; Tobin, J.; Wilkinson, S.; McSweeney, C.; et al. Connections Between the Gut Microbiome and Metabolic Hormones in Early Pregnancy in Overweight and Obese Women. *Diabetes* **2016**, *65*, 2214–2223. [[CrossRef](#)]
36. Kelly, J.R.; Kennedy, P.J.; Cryan, J.F.; Dinan, T.G.; Clarke, G.; Hyland, N.P. Breaking down the Barriers: The Gut Microbiome, Intestinal Permeability and Stress-Related Psychiatric Disorders. *Front. Cell. Neurosci.* **2015**, *9*, 392. [[CrossRef](#)] [[PubMed](#)]
37. Alhmoud, T.; Kumar, A.; Lo, C.C.; Al-Sadi, R.; Clegg, S.; Alomari, I.; Zmeili, T.; Gleasne, C.D.; Mcmurry, K.; Dichosa, A.E.K.; et al. Investigating Intestinal Permeability and Gut Microbiota Roles in Acute Coronary Syndrome Patients. *Hum. Microbiome, J.* **2019**, *13*, 100059. [[CrossRef](#)]
38. Escherich, T.H. The Intestinal Bacteria of the Neonate and Breast-Fed Infant 1885. *Rev. Infect. Dis.* **1989**, *11*, 352–356. [[CrossRef](#)]
39. Perez-Muñoz, M.E.; Arrieta, M.-C.; Ramer-Tait, A.E.; Walter, J. A Critical Assessment of the “Sterile Womb” and “Utero Colonization” Hypotheses: Implications for Research on the Pioneer Infant Microbiome. *Microbiome* **2017**, *5*, 48. [[CrossRef](#)]
40. Stout, M.J.; Conlon, B.; Landeau, M.; Lee, I.; Bower, C.; Zhao, Q.; Roehl, K.A.; Nelson, D.M.; MacOnes, G.A.; Mysorekar, I.U. Identification of Intracellular Bacteria in the Basal Plate of the Human Placenta in Term and Preterm Gestations. *Am. J. Obstet. Gynecol.* **2013**, *208*, 226.e1–226.e7. [[CrossRef](#)]
41. Zheng, J.; Xiao, X.; Zhang, Q.; Mao, L.; Yu, M.; Xu, J. The Placental Microbiome Varies in Association with Low Birth Weight in Full-Term Neonates. *Nutrients* **2015**, *7*, 6924–6937. [[CrossRef](#)] [[PubMed](#)]
42. Parnell, L.A.; Briggs, C.M.; Cao, B.; Delannoy-Bruno, O.; Schieffer, A.E.; Mysorekar, I.U. Microbial Communities in Placentas from Term Normal Pregnancy Exhibit Spatially Variable Profiles. *Sci. Rep.* **2017**, *7*, 11200. [[CrossRef](#)] [[PubMed](#)]
43. Collado, M.C.; Rautava, S.; Aakko, J.; Isolauri, E.; Salminen, S. Human Gut Colonisation May Be Initiated in Utero by Distinct Microbial Communities in the Placenta and Amniotic Fluid. *Sci. Rep.* **2016**, *6*, 23129. [[CrossRef](#)] [[PubMed](#)]
44. Bassols, J.; Serino, M.; Carreras-Badosa, G.; Burcelin, R.; Blasco-Baque, V.; Lopez-Bermejo, A.; Fernandez-Real, J.M. Gestational Diabetes Is Associated with Changes in Placental Microbiota and Microbiome. *Pediatr. Res.* **2016**, *80*, 777–784. [[CrossRef](#)]
45. Cao, B.; Mysorekar, I.U. Intracellular Bacteria in Placental Basal Plate Localize to Extravillous Trophoblasts. *Placenta* **2014**, *35*, 139–142. [[CrossRef](#)]
46. Aagaard, K.; Ma, J.; Antony, K.M.; Ganu, R.; Petrosino, J.; Versalovic, J. The Placenta Harbors a Unique Microbiome. *Sci. Transl. Med.* **2014**, *6*, 237ra65. [[CrossRef](#)]
47. Younge, N.; McCann, J.R.; Ballard, J.; Plunkett, C.; Akhtar, S.; Araújo-Pérez, F.; Murtha, A.; Brandon, D.; Seed, P.C. Fetal Exposure to the Maternal Microbiota in Humans and Mice. *JCI Insight* **2019**, *4*, e127806. [[CrossRef](#)]
48. Gomez-Arango, L.F.; Barrett, H.L.; McIntyre, H.D.; Callaway, L.K.; Morrison, M.; Nitert, M.D. Contributions of the Maternal Oral and Gut Microbiome to Placental Microbial Colonization in Overweight and Obese Pregnant Women. *Sci. Rep.* **2017**, *7*, 2860. [[CrossRef](#)]
49. Perez, P.F.; Doré, J.; Leclerc, M.; Levenez, F.; Benyacoub, J.; Serrant, P.; Segura-Roggero, I.; Schiffrin, E.J.; Donnet-Hughes, A. Bacterial Imprinting of the Neonatal Immune System: Lessons from Maternal Cells? *Pediatrics* **2007**, *119*, e724–e732. [[CrossRef](#)]
50. Hohlweg, U.; Doerfler, W. On the Fate of Plant or Other Foreign Genes upon the Uptake in Food or after Intramuscular Injection in Mice. *Mol. Genet. Genom.* **2001**, *265*, 225–233. [[CrossRef](#)]
51. Schubbert, R.; Hohlweg, U.; Renz, D.; Doerfler, W. On the Fate of Orally Ingested Foreign DNA in Mice: Chromosomal Association and Placental Transmission to the Fetus. *Mol. Genet. Genom.* **1998**, *259*, 569–576. [[CrossRef](#)] [[PubMed](#)]
52. Jiménez, E.; Marín, M.L.; Martín, R.; Odriozola, J.M.; Olivares, M.; Xaus, J.; Fernández, L.; Rodríguez, J.M. Is Meconium from Healthy Newborns Actually Sterile? *Res. Microbiol.* **2008**, *159*, 187–193. [[CrossRef](#)] [[PubMed](#)]
53. Jiménez, E.; Fernández, L.; Marín, M.L.; Martín, R.; Odriozola, J.M.; Nueno-Palop, C.; Narbad, A.; Olivares, M.; Xaus, J.; Rodríguez, J.M. Isolation of Commensal Bacteria from Umbilical Cord Blood of Healthy Neonates Born by Cesarean Section. *Curr. Microbiol.* **2005**, *51*, 270–274. [[CrossRef](#)] [[PubMed](#)]

54. Borgo, P.V.; Rodrigues, V.A.A.; Feitosa, A.C.R.; Xavier, K.C.B.; Avila-Campos, M.J. Association between Periodontal Condition and Subgingival Microbiota in Women during Pregnancy: A Longitudinal Study. *J. Appl. Oral Sci.* **2014**, *22*, 528. [[CrossRef](#)] [[PubMed](#)]
55. Fujiwara, N.; Tsuruda, K.; Iwamoto, Y.; Kato, F.; Odaki, T.; Yamane, N.; Hori, Y.; Harashima, Y.; Sakoda, A.; Tagaya, A.; et al. Significant Increase of Oral Bacteria in the Early Pregnancy Period in Japanese Women. *J. Investig. Clin. Dent.* **2017**, *8*, e12189. [[CrossRef](#)]
56. Arce, R.M.; Barros, S.P.; Wacker, B.; Peters, B.; Moss, K.; Offenbacher, S. Increased TLR4 Expression in Murine Placentas after Oral Infection with Periodontal Pathogens. *Placenta* **2009**, *30*, 156. [[CrossRef](#)]
57. Lin, D.; Smith, M.A.; Elter, J.; Champagne, C.; Downey, C.L.; Beck, J.; Offenbacher, S. Porphyromonas Gingivalis Infection in Pregnant Mice Is Associated with Placental Dissemination, an Increase in the Placental Th1/Th2 Cytokine Ratio, and Fetal Growth Restriction. *Infect. Immun.* **2003**, *71*, 5163–5168. [[CrossRef](#)]
58. Han, Y.W.; Redline, R.W.; Li, M.; Yin, L.; Hill, G.B.; McCormick, T.S. Fusobacterium Nucleatum Induces Premature and Term Stillbirths in Pregnant Mice: Implication of Oral Bacteria in Preterm Birth. *Infect. Immun.* **2004**, *72*, 2272. [[CrossRef](#)]
59. Prince, A.L.; Antony, K.M.; Chu, D.M.; Aagaard, K.M. The Microbiome, Parturition, and Timing of Birth: More Questions than Answers. *J. Reprod. Immunol.* **2014**, *104–105*, 12–19. [[CrossRef](#)]
60. Mysorekar, I.U.; Cao, B. Microbiome in Parturition and Preterm Birth. *Semin. Reprod. Med.* **2014**, *32*, 50–55. [[CrossRef](#)]
61. Jefferson, K.K. The Bacterial Etiology of Preterm Birth. *Adv. Appl. Microbiol.* **2012**, *80*, 1–22. [[CrossRef](#)] [[PubMed](#)]
62. Gibbs, R.S.; Romero, R.; Hillier, S.L.; Eschenbach, D.A.; Sweet, R.L. A Review of Premature Birth and Subclinical Infection. *Am. J. Obstet. Gynecol.* **1992**, *166*, 1515–1528. [[CrossRef](#)]
63. Neu, J. The Microbiome during Pregnancy and Early Postnatal Life. *Semin. Fetal. Neonatal. Med.* **2016**, *21*, 373–379. [[CrossRef](#)] [[PubMed](#)]
64. DiGiulio, D.B. Diversity of Microbes in Amniotic Fluid. *Semin. Fetal. Neonatal. Med.* **2012**, *17*, 2–11. [[CrossRef](#)]
65. Mishra, A.; Lai, G.C.; Yao, L.J.; Aung, T.T.; Shental, N.; Rotter-Maskowitz, A.; Shepherdson, E.; Singh, G.S.N.; Pai, R.; Shanti, A.; et al. Microbial Exposure during Early Human Development Primes Fetal Immune Cells. *Cell* **2021**, *184*, 3394–3409.e20. [[CrossRef](#)]
66. Kennedy, K.M.; Bellissimo, C.J.; Breznik, J.A.; Barrett, J.; Braun, T.; Bushman, F.D.; de Goffau, M.; Elovitz, M.A.; Heimesaat, M.M.; Konnikova, L.; et al. Over-Celling Fetal Microbial Exposure. *Cell* **2021**, *184*, 5839–5841. [[CrossRef](#)]
67. Salter, S.J.; Cox, M.J.; Turek, E.M.; Calus, S.T.; Cookson, W.O.; Moffatt, M.F.; Turner, P.; Parkhill, J.; Loman, N.J.; Walker, A.W. Reagent and Laboratory Contamination Can Critically Impact Sequence-Based Microbiome Analyses. *BMC Biol.* **2014**, *12*, 87. [[CrossRef](#)]
68. Gschwind, R.; Fournier, T.; Kennedy, S.; Tsatsaris, V.; Cordier, A.G.; Barbut, F.; Butel, M.J.; WydauDematteis, S. Evidence for Contamination as the Origin for Bacteria Found in Human Placenta Rather than a Microbiota. *PLoS ONE* **2020**, *15*, e0237232. [[CrossRef](#)]
69. Lauder, A.P.; Roche, A.M.; Sherrill-Mix, S.; Bailey, A.; Laughlin, A.L.; Bittinger, K.; Leite, R.; Elovitz, M.A.; Parry, S.; Bushman, F.D. Comparison of Placenta Samples with Contamination Controls Does Not Provide Evidence for a Distinct Placenta Microbiota. *Microbiome* **2016**, *4*, 29. [[CrossRef](#)]
70. Edgar, R.C. Accuracy of Microbial Community Diversity Estimated by Closed- and Open-Reference OTUs. *PeerJ* **2017**, *2017*, e3889. [[CrossRef](#)]
71. Rescigno, M.; Urbano, M.; Valzasina, B.; Francolini, M.; Rotta, G.; Bonasio, R.; Granucci, F.; Kraehenbuhl, J.P.; Ricciardi-Castagnoli, P. Dendritic Cells Express Tight Junction Proteins and Penetrate Gut Epithelial Monolayers to Sample Bacteria. *Nat. Immunol.* **2001**, *2*, 361–367. [[CrossRef](#)] [[PubMed](#)]
72. Macpherson, A.J.; Uhr, T. Induction of Protective IgA by Intestinal Dendritic Cells Carrying Commensal Bacteria. *Science* **2004**, *303*, 1662–1665. [[CrossRef](#)] [[PubMed](#)]
73. Kelsall, B. Recent Progress in Understanding the Phenotype and Function of Intestinal Dendritic Cells and Macrophages. *Mucosal Immunol.* **2008**, *1*, 460–469. [[CrossRef](#)] [[PubMed](#)]
74. Akira, S.; Uematsu, S.; Takeuchi, O. Pathogen Recognition and Innate Immunity. *Cell* **2006**, *124*, 783–801. [[CrossRef](#)] [[PubMed](#)]
75. Smolen, K.K.; Ruck, C.E.; Fortuno, E.S.; Ho, K.; Dimitriu, P.; Mohn, W.W.; Speert, D.P.; Cooper, P.J.; Esser, M.; Goetghebuer, T.; et al. Pattern Recognition Receptor-Mediated Cytokine Response in Infants across 4 Continents. *J. Allergy Clin. Immunol.* **2014**, *133*, 818–826. [[CrossRef](#)]
76. Kawai, T.; Akira, S. Toll-like Receptor and RIG-I-like Receptor Signaling. *Ann. N. Y. Acad. Sci.* **2008**, *1143*, 1–20. [[CrossRef](#)]
77. Strunk, T.; Currie, A.; Richmond, P.; Simmer, K.; Burgner, D. Innate Immunity in Human Newborn Infants: Prematurity Means More than Immaturity. *J. Matern. Fetal Neonatal. Med.* **2011**, *24*, 25–31. [[CrossRef](#)]
78. Sadeghi, K.; Berger, A.; Langgartner, M.; Prusa, A.R.; Hayde, M.; Herkner, K.; Pollak, A.; Spittler, A.; Förster-Waldl, E. Immaturity of Infection Control in Preterm and Term Newborns Is Associated with Impaired Toll-like Receptor Signaling. *J. Infect. Dis.* **2007**, *195*, 296–302. [[CrossRef](#)]
79. Leeansyah, E.; Loh, L.; Nixon, D.F.; Sandberg, J.K. Acquisition of Innate-like Microbial Reactivity in Mucosal Tissues during Human Fetal MAIT-Cell Development. *Nat. Commun.* **2014**, *5*, 3143. [[CrossRef](#)]
80. Schreurs, R.R.C.E.; Baumdick, M.E.; Sagebiel, A.F.; Kaufmann, M.; Mokry, M.; Klarenbeek, P.L.; Schaltenberg, N.; Steinert, F.L.; van Rijn, J.M.; Drewniak, A.; et al. Human Fetal TNF- $\alpha$ -Cytokine-Producing CD4 + Effector Memory T Cells Promote Intestinal Development and Mediate Inflammation Early in Life. *Immunity* **2019**, *50*, 462–476. [[CrossRef](#)]

81. Blümer, N.; Pfefferle, P.I.; Renz, H. Development of Mucosal Immune Function in the Intrauterine and Early Postnatal Environment. *Curr. Opin. Gastroenterol.* **2007**, *23*, 655–660. [[CrossRef](#)] [[PubMed](#)]
82. Thorburn, A.N.; McKenzie, C.I.; Shen, S.; Stanley, D.; MacIa, L.; Mason, L.J.; Roberts, L.K.; Wong, C.H.Y.; Shim, R.; Robert, R.; et al. Evidence That Asthma Is a Developmental Origin Disease Influenced by Maternal Diet and Bacterial Metabolites. *Nat. Commun.* **2015**, *6*, 7320. [[CrossRef](#)] [[PubMed](#)]
83. Jašarević, E.; Bale, T.L. Prenatal and Postnatal Contributions of the Maternal Microbiome on Offspring Programming. *Front. Neuroendocrinol.* **2019**, *55*. [[CrossRef](#)] [[PubMed](#)]
84. Stinson, L.F.; Payne, M.S.; Keelan, J.A. Planting the Seed: Origins, Composition, and Postnatal Health Significance of the Fetal Gastrointestinal Microbiota. *Crit. Rev. Microbiol.* **2017**, *43*, 352–369. [[CrossRef](#)]
85. Hapfelmeier, S.; Lawson, M.A.E.; Slack, E.; Kirundi, J.K.; Stoel, M.; Heikenwalder, M.; Cahenzli, J.; Velykoredko, Y.; Balmer, M.L.; Endt, K.; et al. Reversible Microbial Colonization of Germ-Free Mice Reveals the Dynamics of IgA Immune Responses. *Science* **2010**, *328*, 1705–1709. [[CrossRef](#)]
86. Gomez de Agüero, M.; Ganal-Vonarburg, S.C.; Fuhrer, T.; Rupp, S.; Uchimura, Y.; Li, H.; Steinert, A.; Heikenwalder, M.; Hapfelmeier, S.; Sauer, U.; et al. The Maternal Microbiota Drives Early Postnatal Innate Immune Development. *Science* **2016**, *351*, 1296–1302. [[CrossRef](#)]
87. Stockinger, B.; Meglio, P.D.; Gialitakis, M.; Duarte, J.H. The Aryl Hydrocarbon Receptor: Multitasking in the Immune System. *Annu. Rev. Immunol.* **2014**, *32*, 403–432. [[CrossRef](#)]
88. Ziętek, M.; Celewicz, Z.; Szczuko, M. Short-Chain Fatty Acids, Maternal Microbiota and Metabolism in Pregnancy. *Nutrients* **2021**, *13*, 1244. [[CrossRef](#)]
89. Hayward, L.; Watkins, J.; Bautista, B.; Lin, C.; Malphurs, W.; Zubcevic, J. Nicotine Exposure during Pregnancy Alters the Maternal Gut Microbiome and Both Cecal and Plasma Short Chain Fatty Acids in Sprague Dawley Rats. *FASEB J.* **2020**, *34*, 1-1. [[CrossRef](#)]
90. Nilsen, M.; Saunders, C.M.; Angell, I.L.; Arntzen, M.; Lødrup Carlsen, K.C.; Carlsen, K.H.; Haugen, G.; Hagen, L.H.; Carlsen, M.H.; Hedlin, G.; et al. Butyrate Levels in the Transition from an Infant- to an Adult-Like Gut Microbiota Correlate with Bacterial Networks Associated with Eubacterium Rectale and Ruminococcus Gnavus. *Genes* **2020**, *11*, 1245. [[CrossRef](#)]
91. Soderborg, T.K.; Carpenter, C.M.; Janssen, R.C.; Weir, T.L.; Robertson, C.E.; Ir, D.; Young, B.E.; Krebs, N.F.; Hernandez, T.L.; Barbour, L.A.; et al. Gestational Diabetes Is Uniquely Associated With Altered Early Seeding of the Infant Gut Microbiota. *Front. Endocrinol.* **2020**, *11*, 603021. [[CrossRef](#)] [[PubMed](#)]
92. Gray, L.E.K.; O’Hely, M.; Ranganathan, S.; Sly, P.D.; Vuillermin, P. The Maternal Diet, Gut Bacteria, and Bacterial Metabolites during Pregnancy Influence Offspring Asthma. *Front. Immunol.* **2017**, *8*, 365. [[CrossRef](#)] [[PubMed](#)]
93. Kimura, I.; Miyamoto, J.; Ohue-Kitano, R.; Watanabe, K.; Yamada, T.; Onuki, M.; Aoki, R.; Isobe, Y.; Kashihara, D.; Inoue, D.; et al. Maternal Gut Microbiota in Pregnancy Influences Offspring Metabolic Phenotype in Mice. *Science* **2020**, *367*, eaaw8429. [[CrossRef](#)] [[PubMed](#)]
94. Yang, S.; Fujikado, N.; Kolodin, D.; Benoist, C.; Mathis, D. Immune Tolerance. Regulatory T Cells Generated Early in Life Play a Distinct Role in Maintaining Self-Tolerance. *Science* **2015**, *348*, 589–594. [[CrossRef](#)] [[PubMed](#)]
95. Gao, Z.; Yin, J.; Zhang, J.; Ward, R.E.; Martin, R.J.; Lefevre, M.; Cefalu, W.T.; Ye, J. Butyrate Improves Insulin Sensitivity and Increases Energy Expenditure in Mice. *Diabetes* **2009**, *58*, 1509–1517. [[CrossRef](#)]
96. Park, J.; Kim, M.; Kang, S.G.; Jannasch, A.H.; Cooper, B.; Patterson, J.; Kim, C.H. Short-Chain Fatty Acids Induce Both Effector and Regulatory T Cells by Suppression of Histone Deacetylases and Regulation of the MTOR-S6K Pathway. *Mucosal Immunol.* **2015**, *8*, 80–93. [[CrossRef](#)]
97. Georgieff, M.K. Nutrition and the Developing Brain: Nutrient Priorities and Measurement. *Am. J. Clin. Nutr.* **2007**, *85*, 614S–620S. [[CrossRef](#)]
98. Burbridge, S.; Stewart, I.; Placzek, M. Development of the Neuroendocrine Hypothalamus. *Compr. Physiol.* **2016**, *6*, 623–643. [[CrossRef](#)]
99. Jašarević, E.; Howard, C.D.; Morrison, K.; Misisic, A.; Weinkopff, T.; Scott, P.; Hunter, C.; Beiting, D.; Bale, T.L. The Maternal Vaginal Microbiome Partially Mediates the Effects of Prenatal Stress on Offspring Gut and Hypothalamus. *Nat. Neurosci.* **2018**, *21*, 1061–1071. [[CrossRef](#)]
100. Wang, H.B.; Wang, P.Y.; Wang, X.; Wan, Y.L.; Liu, Y.C. Butyrate Enhances Intestinal Epithelial Barrier Function via Up-Regulation of Tight Junction Protein Claudin-1 Transcription. *Dig. Dis. Sci.* **2012**, *57*, 3126–3135. [[CrossRef](#)]
101. Oh, J.Z.; Ravindran, R.; Chassaing, B.; Carvalho, F.A.; Maddur, M.S.; Bower, M.; Hakimpour, P.; Gill, K.P.; Nakaya, H.I.; Yarovinsky, F.; et al. TLR5-Mediated Sensing of Gut Microbiota Is Necessary for Antibody Responses to Seasonal Influenza Vaccination. *Immunity* **2014**, *41*, 478–492. [[CrossRef](#)] [[PubMed](#)]
102. Iwamura, C.; Bouladoux, N.; Belkaid, Y.; Sher, A.; Jankovic, D. Sensing of the Microbiota by NOD1 in Mesenchymal Stromal Cells Regulates Murine Hematopoiesis. *Blood* **2017**, *129*, 171–176. [[CrossRef](#)] [[PubMed](#)]
103. Uchimura, Y.; Fuhrer, T.; Li, H.; Lawson, M.A.; Zimmermann, M.; Yilmaz, B.; Zindel, J.; Ronchi, F.; Sorribas, M.; Hapfelmeier, S.; et al. Antibodies Set Boundaries Limiting Microbial Metabolite Penetration and the Resultant Mammalian Host Response. *Immunity* **2018**, *49*, 545–559.e5. [[CrossRef](#)] [[PubMed](#)]
104. Ganal-Vonarburg, S.C.; Hornef, M.W.; Macpherson, A.J. Microbial-Host Molecular Exchange and Its Functional Consequences in Early Mammalian Life. *Science* **2020**, *368*, 604–607. [[CrossRef](#)]



105. Williams, P.J.; Searle, R.F.; Robson, S.C.; Innes, B.A.; Bulmer, J.N. Decidual Leucocyte Populations in Early to Late Gestation Normal Human Pregnancy. *J. Reprod. Immunol.* **2009**, *82*, 24–31. [[CrossRef](#)]
106. Brugman, S.; Perdijk, O.; van Neerven, R.J.J.; Savelkoul, H.F.J. Mucosal Immune Development in Early Life: Setting the Stage. *Arch. Immunol. Ther. Exp. (Warsz.)* **2015**, *63*, 251–268. [[CrossRef](#)]
107. Romano-Keeler, J.; Weitkamp, J.H. Maternal Influences on Fetal Microbial Colonization and Immune Development. *Pediatr. Res.* **2015**, *77*, 189–195. [[CrossRef](#)]
108. Hsu, P.; Nanan, R. Foetal Immune Programming: Hormones, Cytokines, Microbes and Regulatory T Cells. *J. Reprod. Immunol.* **2014**, *104–105*, 2–7. [[CrossRef](#)]
109. D’Argenio, V. The Prenatal Microbiome: A New Player for Human Health. *High-Throughput* **2018**, *7*, 38. [[CrossRef](#)]
110. Fleming, T.P.; Watkins, A.J.; Velazquez, M.A.; Mathers, J.C.; Prentice, A.M.; Stephenson, J.; Barker, M.; Saffery, R.; Yajnik, C.S.; Eckert, J.J.; et al. Origins of Lifetime Health around the Time of Conception: Causes and Consequences. *Lancet* **2018**, *391*, 1842–1852. [[CrossRef](#)]
111. Bolte, E.E.; Moorshead, D.; Aagaard, K.M. Maternal and Early Life Exposures and Their Potential to Influence Development of the Microbiome. *Genome Med.* **2022**, *14*, 4. [[CrossRef](#)] [[PubMed](#)]
112. Baker, J.L.; Michaelsen, K.F.; Rasmussen, K.M.; Sørensen, T.I.A. Maternal Prepregnant Body Mass Index, Duration of Breastfeeding, and Timing of Complementary Food Introduction Are Associated with Infant Weight Gain. *Am. J. Clin. Nutr.* **2004**, *80*, 1579–1588. [[CrossRef](#)] [[PubMed](#)]
113. Morrison, J.L.; Regnault, T.R.H. Nutrition in Pregnancy: Optimising Maternal Diet and Fetal Adaptations to Altered Nutrient Supply. *Nutrients* **2016**, *8*, 342. [[CrossRef](#)] [[PubMed](#)]
114. Dunlop, A.L.; Mulle, J.G.; Ferranti, E.P.; Edwards, S.; Dunn, A.B.; Corwin, E.J. Maternal Microbiome and Pregnancy Outcomes That Impact Infant Health: A Review. *Adv. Neonatal. Care* **2015**, *15*, 377–385. [[CrossRef](#)]
115. Luoto, R.; Collado, M.C.; Salminen, S.; Isolauri, E. Reshaping the Gut Microbiota at an Early Age: Functional Impact on Obesity Risk? *Ann. Nutr. Metab.* **2013**, *63*, 17–26. [[CrossRef](#)]
116. Gaudet, L.; Ferraro, Z.M.; Wen, S.W.; Walker, M. Maternal Obesity and Occurrence of Fetal Macrosomia: A Systematic Review and Meta-Analysis. *Biomed Res. Int.* **2014**, *2014*, 640291. [[CrossRef](#)]
117. Papachatzzi, E.; Dimitriou, G.; Dimitropoulos, K.; Vantarakis, A. Pre-Pregnancy Obesity: Maternal, Neonatal and Childhood Outcomes. *J. Neonatal-Perinat. Med.* **2013**, *6*, 203–216. [[CrossRef](#)]
118. Flenady, V.; Koopmans, L.; Middleton, P.; Frøen, J.F.; Smith, G.C.; Gibbons, K.; Coory, M.; Gordon, A.; Ellwood, D.; McIntyre, H.D.; et al. Major Risk Factors for Stillbirth in High-Income Countries: A Systematic Review and Meta-Analysis. *Lancet* **2011**, *377*, 1331–1340. [[CrossRef](#)]
119. Rasmussen, S.A.; Chu, S.Y.; Kim, S.Y.; Schmid, C.H.; Lau, J. Maternal Obesity and Risk of Neural Tube Defects: A Metaanalysis. *Am. J. Obstet. Gynecol.* **2008**, *198*, 611–619. [[CrossRef](#)]
120. Garcia-Mantrana, I.; Collado, M.C. Obesity and Overweight: Impact on Maternal and Milk Microbiome and Their Role for Infant Health and Nutrition. *Mol. Nutr. Food Res.* **2016**, *60*, 1865–1875. [[CrossRef](#)]
121. Rosenbaum, M.; Knight, R.; Leibel, R.L. The Gut Microbiota in Human Energy Homeostasis and Obesity. *Trends Endocrinol. Metab.* **2015**, *26*, 493–501. [[CrossRef](#)] [[PubMed](#)]
122. Walters, W.A.; Xu, Z.; Knight, R. Meta-Analyses of Human Gut Microbes Associated with Obesity and IBD. *FEBS Lett.* **2014**, *588*, 4223–4233. [[CrossRef](#)] [[PubMed](#)]
123. Paul, H.A.; Bomhof, M.R.; Vogel, H.J.; Reimer, R.A. Diet-Induced Changes in Maternal Gut Microbiota and Metabolomic Profiles Influence Programming of Offspring Obesity Risk in Rats. *Sci. Rep.* **2016**, *6*, 20683. [[CrossRef](#)] [[PubMed](#)]
124. le Chatelier, E.; Nielsen, T.; Qin, J.; Prifti, E.; Hildebrand, F.; Falony, G.; Almeida, M.; Arumugam, M.; Batto, J.M.; Kennedy, S.; et al. Richness of Human Gut Microbiome Correlates with Metabolic Markers. *Nature* **2013**, *500*, 541–546. [[CrossRef](#)]
125. Rojttö, H.; Morkkala, K.; Vahlberg, T.; Laitinen, K. Dietary Intake of Fat and Fibre According to Reference Values Relates to Higher Gut Microbiota Richness in Overweight Pregnant Women. *Br. J. Nutr.* **2017**, *118*, 343–352. [[CrossRef](#)]
126. Galley, J.D.; Bailey, M.; Dush, C.K.; Schoppe-Sullivan, S.; Christian, L.M. Maternal Obesity Is Associated with Alterations in the Gut Microbiome in Toddlers. *PLoS ONE* **2014**, *9*, e113026. [[CrossRef](#)]
127. Ma, J.; Prince, A.L.; Bader, D.; Hu, M.; Ganu, R.; Baquero, K.; Blundell, P.; Alan Harris, R.; Frias, A.E.; Grove, K.L.; et al. High-Fat Maternal Diet during Pregnancy Persistently Alters the Offspring Microbiome in a Primate Model. *Nat. Commun.* **2014**, *5*, 3889. [[CrossRef](#)]
128. Mueller, N.T.; Shin, H.; Pizoni, A.; Werlang, I.C.; Matte, U.; Goldani, M.Z.; Goldani, H.A.S.; Dominguez-Bello, M.G. Birth Mode-Dependent Association between Pre-Pregnancy Maternal Weight Status and the Neonatal Intestinal Microbiome. *Sci. Rep.* **2016**, *6*, 23133. [[CrossRef](#)]
129. Selma-Royo, M.; García-Mantrana, I.; Calatayud, M.; Parra-Llorca, A.; Martínez-Costa, C.; Collado, M.C. Maternal Diet during Pregnancy and Intestinal Markers Are Associated with Early Gut Microbiota. *Eur. J. Nutr.* **2021**, *60*, 1429–1442. [[CrossRef](#)]
130. Chu, D.M.; Meyer, K.M.; Prince, A.L.; Aagaard, K.M. Impact of Maternal Nutrition in Pregnancy and Lactation on Offspring Gut Microbial Composition and Function. *Gut Microbes* **2016**, *7*, 459–470. [[CrossRef](#)]
131. Kozyrskyj, A.L.; Kalu, R.; Koleva, P.T.; Bridgman, S.L. Fetal Programming of Overweight through the Microbiome: Boys Are Disproportionately Affected. *J. Dev. Orig. Health Dis.* **2016**, *7*, 25–34. [[CrossRef](#)] [[PubMed](#)]
132. Olabi, B.; Bhopal, R. Diagnosis of Diabetes Using the Oral Glucose Tolerance Test. *BMJ* **2009**, *339*, 1268. [[CrossRef](#)] [[PubMed](#)]

133. Marchi, J.; Berg, M.; Dencker, A.; Olander, E.K.; Begley, C. Risks Associated with Obesity in Pregnancy, for the Mother and Baby: A Systematic Review of Reviews. *Obes. Rev.* **2015**, *16*, 621–638. [[CrossRef](#)] [[PubMed](#)]
134. Saad, M.J.A.; Santos, A.; Prada, P.O. Linking Gut Microbiota and Inflammation to Obesity and Insulin Resistance. *Physiology* **2016**, *31*, 283–293. [[CrossRef](#)]
135. Hasain, Z.; Mokhtar, N.M.; Kamaruddin, N.A.; Mohamed Ismail, N.A.; Razalli, N.H.; Gnanou, J.V.; Raja Ali, R.A. Gut Microbiota and Gestational Diabetes Mellitus: A Review of Host-Gut Microbiota Interactions and Their Therapeutic Potential. *Front. Cell. Infect. Microbiol.* **2020**, *10*, 188. [[CrossRef](#)]
136. Medici Dualib, P.; Ogassavara, J.; Mattar, R.; Mariko Koga da Silva, E.; Atala Dib, S.; de Almeida Pititto, B. Gut Microbiota and Gestational Diabetes Mellitus: A Systematic Review. *Diabetes Res. Clin. Pract.* **2021**, *180*, 109078. [[CrossRef](#)]
137. Mokkalá, K.; Houttu, N.; Vahlberg, T.; Munukka, E.; Rönnemaa, T.; Laitinen, K. Gut Microbiota Aberrations Precede Diagnosis of Gestational Diabetes Mellitus. *Acta Diabetol.* **2017**, *54*, 1147–1149. [[CrossRef](#)]
138. Wang, J.; Qin, J.; Li, Y.; Cai, Z.; Li, S.; Zhu, J.; Zhang, F.; Liang, S.; Zhang, W.; Guan, Y.; et al. A Metagenome-Wide Association Study of Gut Microbiota in Type 2 Diabetes. *Nature* **2012**, *490*, 55–60. [[CrossRef](#)]
139. Wang, J.; Zheng, J.; Shi, W.; Du, N.; Xu, X.; Zhang, Y.; Ji, P.; Zhang, F.; Jia, Z.; Wang, Y.; et al. Original Article: Dysbiosis of Maternal and Neonatal Microbiota Associated with Gestational Diabetes Mellitus. *Gut* **2018**, *67*, 1614. [[CrossRef](#)]
140. Hu, J.; Nomura, Y.; Bashir, A.; Fernandez-Hernandez, H.; Itzkowitz, S.; Pei, Z.; Stone, J.; Loudon, H.; Peter, I. Diversified Microbiota of Meconium Is Affected by Maternal Diabetes Status. *PLoS ONE* **2013**, *8*, e78257. [[CrossRef](#)]
141. Rocha, J.P.; Laster, J.; Parag, B.; Shah, N.U. Multiple Health Benefits and Minimal Risks Associated with Vegetarian Diets. *Curr. Nutr. Rep.* **2019**, *8*, 374–381. [[CrossRef](#)] [[PubMed](#)]
142. Sakkas, H.; Bozidis, P.; Touzios, C.; Kolios, D.; Athanasiou, G.; Athanasopoulou, E.; Gerou, I.; Gartzonika, C. Nutritional Status and the Influence of the Vegan Diet on the Gut Microbiota and Human Health. *Medicina* **2020**, *56*, 88. [[CrossRef](#)] [[PubMed](#)]
143. Kashtanova, D.A.; Popenko, A.S.; Tkacheva, O.N.; Tyakht, A.B.; Alexeev, D.G.; Boytsov, S.A. Association between the Gut Microbiota and Diet: Fetal Life, Early Childhood, and Further Life. *Nutrition* **2016**, *32*, 620–627. [[CrossRef](#)] [[PubMed](#)]
144. Barrett, H.L.; Gomez-Arango, L.F.; Wilkinson, S.A.; McIntyre, H.D.; Callaway, L.K.; Morrison, M.; Nitert, M.D. A Vegetarian Diet Is a Major Determinant of Gut Microbiota Composition in Early Pregnancy. *Nutrients* **2018**, *10*, 890. [[CrossRef](#)] [[PubMed](#)]
145. Sylvetsky, A.C.; Rother, K.I. Trends in the Consumption of Low-Calorie Sweeteners. *Physiol. Behav.* **2016**, *164*, 446–450. [[CrossRef](#)]
146. Nettleton, J.E.; Cho, N.A.; Klancic, T.; Nicolucci, A.C.; Shearer, J.; Borgland, S.L.; Johnston, L.A.; Ramay, H.R.; Noye Tuplin, E.; Chleilat, F.; et al. Maternal Low-Dose Aspartame and Stevia Consumption with an Obesogenic Diet Alters Metabolism, Gut Microbiota and Mesolimbic Reward System in Rat Dams and Their Offspring. *Gut* **2020**, *69*, 1807–1817. [[CrossRef](#)] [[PubMed](#)]
147. Bian, X.; Chi, L.; Gao, B.; Tu, P.; Ru, H.; Lu, K. Gut Microbiome Response to Sucralose and Its Potential Role in Inducing Liver Inflammation in Mice. *Front. Physiol.* **2017**, *8*, 487. [[CrossRef](#)]
148. Bian, X.; Chi, L.; Gao, B.; Tu, P.; Ru, H.; Lu, K. The Artificial Sweetener Acesulfame Potassium Affects the Gut Microbiome and Body Weight Gain in CD-1 Mice. *PLoS ONE* **2017**, *12*, e0178426. [[CrossRef](#)]
149. Abou-Donia, M.B.; El-Masry, E.M.; Abdel-Rahman, A.A.; McLendon, R.E.; Schiffman, S.S. Splenda Alters Gut Microflora and Increases Intestinal P-Glycoprotein and Cytochrome p-450 in Male Rats. *Journal of toxicology and environmental health. J. Toxicol. Environ. Health Part A* **2008**, *71*, 1415–1429. [[CrossRef](#)]
150. Palmnäs, M.S.A.; Cowan, T.E.; Bomhof, M.R.; Su, J.; Reimer, R.A.; Vogel, H.J.; Hittel, D.S.; Shearer, J. Low-Dose Aspartame Consumption Differentially Affects Gut Microbiota-Host Metabolic Interactions in the Diet-Induced Obese Rat. *PLoS ONE* **2014**, *9*, e109841. [[CrossRef](#)]
151. Suez, J.; Korem, T.; Zeevi, D.; Zilberman-Schapira, G.; Thaiss, C.A.; Maza, O.; Israeli, D.; Zmora, N.; Gilad, S.; Weinberger, A.; et al. Artificial Sweeteners Induce Glucose Intolerance by Altering the Gut Microbiota. *Nature* **2014**, *514*, 181–186. [[CrossRef](#)] [[PubMed](#)]
152. Schneeberger, M.; Everard, A.; Gómez-Valadés, A.G.; Matamoros, S.; Ramírez, S.; Delzenne, N.M.; Gomis, R.; Claret, M.; Cani, P.D. Akkermansia Muciniphila Inversely Correlates with the Onset of Inflammation, Altered Adipose Tissue Metabolism and Metabolic Disorders during Obesity in Mice. *Sci. Rep.* **2015**, *5*, 16643. [[CrossRef](#)] [[PubMed](#)]
153. Hansen, C.H.F.; Krych, L.; Nielsen, D.S.; Vogensen, F.K.; Hansen, L.H.; Sørensen, S.J.; Buschard, K.; Hansen, A.K. Early Life Treatment with Vancomycin Propagates Akkermansia Muciniphila and Reduces Diabetes Incidence in the NOD Mouse. *Diabetologia* **2012**, *55*, 2285–2294. [[CrossRef](#)] [[PubMed](#)]
154. Ley, R.E.; Bäckhed, F.; Turnbaugh, P.; Lozupone, C.A.; Knight, R.D.; Gordon, J.I. Obesity Alters Gut Microbial Ecology. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 11070–11075. [[CrossRef](#)]
155. Laforest-Lapointe, I.; Becker, A.B.; Mandhane, P.J.; Turvey, S.E.; Moraes, T.J.; Sears, M.R.; Subbarao, P.; Sycuro, L.K.; Azad, M.B.; Arrieta, M.C. Maternal Consumption of Artificially Sweetened Beverages during Pregnancy Is Associated with Infant Gut Microbiota and Metabolic Modifications and Increased Infant Body Mass Index. *Gut Microbes* **2021**, *13*, 1–15. [[CrossRef](#)]
156. Ouellette, E.M.; Rosett, H.L.; Rosman, N.P.; Weiner, L. Adverse Effects on Offspring of Maternal Alcohol Abuse during Pregnancy. *N. Engl. J. Med.* **1977**, *297*, 528–530. [[CrossRef](#)]
157. Miyake, Y.; Tanaka, K.; Okubo, H.; Sasaki, S.; Arakawa, M. Alcohol Consumption during Pregnancy and Birth Outcomes: The Kyushu Okinawa Maternal and Child Health Study. *BMC Pregnancy Childbirth* **2014**, *14*, 79. [[CrossRef](#)]
158. Bode, J.C.; Bode, C.; Heidebach, R.; Dürr, H.K.; Martini, G.A. Jejunal Microflora in Patients with Chronic Alcohol Abuse. *Hepatology* **1984**, *31*, 30–34.
159. Lucey, M.R. Management of Alcoholic Liver Disease. *Clin. Liver Dis.* **2009**, *13*, 267–275. [[CrossRef](#)]

160. Bode, C.; Bode, J.C. Effect of Alcohol Consumption on the Gut. Best practice & research. *J. Clin. Gastroenterol.* **2003**, *17*, 575–592. [[CrossRef](#)]
161. Dubinkina, V.B.; Tyakht, A.V.; Odintsova, V.Y.; Yarygin, K.S.; Kovarsky, B.A.; Pavlenko, A.V.; Ischenko, D.S.; Popenko, A.S.; Alexeev, D.G.; Taraskina, A.Y.; et al. Links of Gut Microbiota Composition with Alcohol Dependence Syndrome and Alcoholic Liver Disease. *Microbiome* **2017**, *5*, 141. [[CrossRef](#)] [[PubMed](#)]
162. Bull-Otterson, L.; Feng, W.; Kirpich, I.; Wang, Y.; Qin, X.; Liu, Y.; Gobejishvili, L.; Joshi-Barve, S.; Ayvaz, T.; Petrosino, J.; et al. Metagenomic Analyses of Alcohol Induced Pathogenic Alterations in the Intestinal Microbiome and the Effect of Lactobacillus Rhamnosus GG Treatment. *PLoS ONE* **2013**, *8*, e53028. [[CrossRef](#)] [[PubMed](#)]
163. Bajaj, J.S.; Heuman, D.M.; Hylemon, P.B.; Sanyal, A.J.; White, M.B.; Monteith, P.; Noble, N.A.; Unser, A.B.; Daita, K.; Fisher, A.R.; et al. Altered Profile of Human Gut Microbiome Is Associated with Cirrhosis and Its Complications. *J. Hepatol.* **2014**, *60*, 940–947. [[CrossRef](#)]
164. Mutlu, E.A.; Gillevet, P.M.; Rangwala, H.; Sikaroodi, M.; Naqvi, A.; Engen, P.A.; Kwasny, M.; Lau, C.K.; Keshavarzian, A. Colonic Microbiome Is Altered in Alcoholism. *American journal of physiology. Am. J. Physiol. Gastrointest.* **2012**, *302*, G966–G978. [[CrossRef](#)] [[PubMed](#)]
165. Labrecque, M.T.; Malone, D.; Caldwell, K.E.; Allan, A.M. Impact of Ethanol and Saccharin on Fecal Microbiome in Pregnant and Non-Pregnant Mice. *J. Pregnancy Child Health* **2015**, *2*, 1000193. [[CrossRef](#)] [[PubMed](#)]
166. Wang, Y.; Xie, T.; Wu, Y.; Liu, Y.; Zou, Z.; Bai, J. Impacts of Maternal Diet and Alcohol Consumption during Pregnancy on Maternal and Infant Gut Microbiota. *Biomolecules* **2021**, *11*, 369. [[CrossRef](#)]
167. Jiang, H.; Ling, Z.; Zhang, Y.; Mao, H.; Ma, Z.; Yin, Y.; Wang, W.; Tang, W.; Tan, Z.; Shi, J.; et al. Altered Fecal Microbiota Composition in Patients with Major Depressive Disorder. *Brain Behav. Immun.* **2015**, *48*, 186–194. [[CrossRef](#)]
168. Ciafrè, S.; Ferraguti, G.; Greco, A.; Polimeni, A.; Ralli, M.; Ceci, F.M.; Ceccanti, M.; Fiore, M. Alcohol as an Early Life Stressor: Epigenetics, Metabolic, Neuroendocrine and Neurobehavioral Implications. *Neurosci. Biobehav. Rev.* **2020**, *118*, 654–668. [[CrossRef](#)]
169. Lees, B.; Mewton, L.; Jacobus, J.; Valadez, E.A.; Stapinski, L.A.; Teesson, M.; Tapert, S.F.; Squeglia, L.M. Association of Prenatal Alcohol Exposure With Psychological, Behavioral, and Neurodevelopmental Outcomes in Children From the Adolescent Brain Cognitive Development Study. *Am. J. Psychiatry* **2020**, *177*, 1060–1072. [[CrossRef](#)]
170. Gareau, M.G.; Sherman, P.M.; Walker, W.A. Probiotics and the Gut Microbiota in Intestinal Health and Disease. *Nat. Rev. Gastroenterol. Hepatol.* **2010**, *7*, 503–514. [[CrossRef](#)]
171. Dotterud, C.K.; Storrø, O.; Johnsen, R.; Øien, T. Probiotics in Pregnant Women to Prevent Allergic Disease: A Randomized, Double-Blind Trial. *Br. J. Dermatol. Suppl.* **2010**, *163*, 616–623. [[CrossRef](#)] [[PubMed](#)]
172. Dotterud, C.K.; Avershina, E.; Sekelja, M.; Simpson, M.R.; Rudi, K.; Storrø, O.; Johnsen, R.; Eien, T. Does Maternal Perinatal Probiotic Supplementation Alter the Intestinal Microbiota of Mother and Child? *J. Pediatr. Gastroenterol. Nutr.* **2015**, *61*, 200–207. [[CrossRef](#)] [[PubMed](#)]
173. Kallio, S.; Kukkonen, A.K.; Savilahti, E.; Kuitunen, M. Perinatal Probiotic Intervention Prevented Allergic Disease in a Caesarean-Delivered Subgroup at 13-Year Follow-Up. *Clin. Exp. Allergy* **2019**, *49*, 506–515. [[CrossRef](#)] [[PubMed](#)]
174. Enomoto, T.; Sowa, M.; Nishimori, K.; Shimazu, S.; Yoshida, A.; Yamada, K.; Furukawa, F.; Nakagawa, T.; Yanagisawa, N.; Iwabuchi, N.; et al. Effects of Bifidobacterial Supplementation to Pregnant Women and Infants in the Prevention of Allergy Development in Infants and on Fecal Microbiota. *Allergol. Int.* **2014**, *63*, 575–585. [[CrossRef](#)]
175. Rautava, S.; Collado, M.C.; Salminen, S.; Isolauri, E. Probiotics Modulate Host-Microbe Interaction in the Placenta and Fetal Gut: A Randomized, Double-Blind, Placebo-Controlled Trial. *Neonatology* **2012**, *102*, 178–184. [[CrossRef](#)]
176. Kim, J.Y.; Kwon, J.H.; Ahn, S.H.; Lee, S.I.; Han, Y.S.; Choi, Y.O.; Lee, S.Y.; Ahn, K.M.; Ji, G.E. Effect of Probiotic Mix (Bifidobacterium Bifidum, Bifidobacterium Lactis, Lactobacillus Acidophilus) in the Primary Prevention of Eczema: A Double-Blind, Randomized, Placebo-Controlled Trial. *Pediatr. Allergy Immunol.* **2010**, *21*, e386–e393. [[CrossRef](#)]
177. Niers, L.; Martín, R.; Rijkers, G.; Sengers, F.; Timmerman, H.; van Uden, N.; Smidt, H.; Kimpen, J.; Hoekstra, M. The Effects of Selected Probiotic Strains on the Development of Eczema (the PandA Study). *Allergy* **2009**, *64*, 1349–1358. [[CrossRef](#)]
178. Simpson, M.R.; Dotterud, C.K.; Storrø, O.; Johnsen, R.; Øien, T. Perinatal Probiotic Supplementation in the Prevention of Allergy Related Disease: 6 Year Follow up of a Randomised Controlled Trial. *BMC Dermatol.* **2015**, *15*, 13. [[CrossRef](#)]
179. Tannock, G.W.; Fuller, R.; Smith, S.L.; Hall, M.A. Plasmid Profiling of Members of the Family Enterobacteriaceae, Lactobacilli, and Bifidobacteria to Study the Transmission of Bacteria from Mother to Infant. *J. Clin. Microbiol.* **1990**, *28*, 1225–1228. [[CrossRef](#)]
180. Krebs, N.F.; Westcott, J.E.; Butler, N.; Robinson, C.; Bell, M.; Hambidge, K.M. Meat as a First Complementary Food for Breastfed Infants: Feasibility and Impact on Zinc Intake and Status. *J. Pediatr. Gastroenterol. Nutr.* **2006**, *42*, 207–214. [[CrossRef](#)]
181. Schultz, M.; Göttl, C.; Young, R.J.; Iwen, P.; Vanderhoof, J.A. Administration of Oral Probiotic Bacteria to Pregnant Women Causes Temporary Infantile Colonization. *J. Pediatr. Gastroenterol. Nutr.* **2004**, *38*, 293–297. [[CrossRef](#)] [[PubMed](#)]
182. Barthow, C.; Wickens, K.; Stanley, T.; Mitchell, E.A.; Maude, R.; Abels, P.; Purdie, G.; Murphy, R.; Stone, P.; Kang, J.; et al. The Probiotics in Pregnancy Study (PiP Study): Rationale and Design of a Double-Blind Randomised Controlled Trial to Improve Maternal Health during Pregnancy and Prevent Infant Eczema and Allergy. *BMC Pregnancy Childbirth* **2016**, *16*, 133. [[CrossRef](#)] [[PubMed](#)]
183. Abrahamsson, T.R.; Jakobsson, T.; Böttcher, M.F.; Fredrikson, M.; Jenmalm, M.C.; Björkstén, B.; Oldaeus, G. Probiotics in Prevention of IgE-Associated Eczema: A Double-Blind, Randomized, Placebo-Controlled Trial. *J. Allergy Clin. Immunol.* **2007**, *119*, 1174–1180. [[CrossRef](#)] [[PubMed](#)]

184. Bertelsen, R.J.; Brantsæter, A.L.; Magnus, M.C.; Haugen, M.; Myhre, R.; Jacobsson, B.; Longnecker, M.P.; Meltzer, H.M.; London, S.J. Probiotic Milk Consumption in Pregnancy and Infancy and Subsequent Childhood Allergic Diseases. *J. Allergy Clin. Immunol.* **2014**, *133*, 165–171.e1-8. [[CrossRef](#)]
185. Wickens, K.; Stanley, T.V.; Mitchell, E.A.; Barthow, C.; Fitzharris, P.; Purdie, G.; Siebers, R.; Black, P.N.; Crane, J. Early Supplementation with *Lactobacillus Rhamnosus* HN001 Reduces Eczema Prevalence to 6 Years: Does It Also Reduce Atopic Sensitization? *Clin. Exp. Allergy* **2013**, *43*, 1048–1057. [[CrossRef](#)]
186. Ou, C.Y.; Kuo, H.C.; Wang, L.; Hsu, T.Y.; Chuang, H.; Liu, C.A.; Chang, J.C.; Yu, H.R.; Yang, K.D. Prenatal and Postnatal Probiotics Reduces Maternal but Not Childhood Allergic Diseases: A Randomized, Double-Blind, Placebo-Controlled Trial. *Clin. Exp. Allergy* **2012**, *42*, 1386–1396. [[CrossRef](#)]
187. Luoto, R.; Kalliomäki, M.; Laitinen, K.; Isolauri, E. The Impact of Perinatal Probiotic Intervention on the Development of Overweight and Obesity: Follow-up Study from Birth to 10 Years. *Int. J. Obes. (Lond)* **2010**, *34*, 1531–1537. [[CrossRef](#)]
188. Wickens, K.L.; Barthow, C.A.; Murphy, R.; Abels, P.R.; Maude, R.M.; Stone, P.R.; Mitchell, E.A.; Stanley, T.V.; Purdie, G.L.; Kang, J.M.; et al. Early Pregnancy Probiotic Supplementation with *Lactobacillus Rhamnosus* HN001 May Reduce the Prevalence of Gestational Diabetes Mellitus: A Randomised Controlled. *Br. J. Nutr.* **2017**, *117*, 804–813. [[CrossRef](#)]
189. Jafarnejad, S.; Saremi, S.; Jafarnejad, F.; Arab, A. Effects of a Multispecies Probiotic Mixture on Glycemic Control and Inflammatory Status in Women with Gestational Diabetes: A Randomized Controlled Clinical Trial. *J. Nutr. Metab.* **2016**, *2*, 5190846. [[CrossRef](#)]
190. Hajifaraji, M.; Jahanjou, F.; Abbasalizadeh, F. Effect of Probiotic Supplementation on Blood Pressure of Females with Gestational Diabetes Mellitus: A Randomized Double Blind Controlled Clinical Trial. *Iran. Red Crescent Med. J.* **2017**, *9*, 6. [[CrossRef](#)]
191. Dolatkah, N.; Hajifaraji, M.; Abbasalizadeh, F.; Aghamohammadzadeh, N.; Mehrabi, Y.; Abbasi, M.M. Is There a Value for Probiotic Supplements in Gestational Diabetes Mellitus? A Randomized Clinical Trial. *J. Health Popul. Nutr.* **2015**, *33*, 25. [[CrossRef](#)] [[PubMed](#)]
192. Badehnoosh, B.; Karamali, M.; Zarrati, M.; Jamilian, M.; Bahmani, F.; Tajabadi-Ebrahimi, M.; Jafari, P.; Rahmani, E.; Asemi, Z. The Effects of Probiotic Supplementation on Biomarkers of Inflammation, Oxidative Stress and Pregnancy Outcomes in Gestational Diabetes. *J. Matern.-Fetal Neonatal Med.* **2018**, *31*, 1128–1136. [[CrossRef](#)] [[PubMed](#)]
193. Jamilian, M.; Bahmani, F.; Vahedpoor, Z.; Salmani, A.; Tajabadi-Ebrahimi, M.; Jafari, P.; Dizaji, S.H.; Asemi, Z. Effects of Probiotic Supplementation on Metabolic Status in Pregnant Women: A Randomized, Double-Blind, Placebo-Controlled Trial. *Arch. Iran. Med.* **2016**, *19*, 687–692. [[PubMed](#)]
194. Buddington, R.K.; Williams, C.H.; Kostek, B.M.; Buddington, K.K.; Kullen, M.J. Maternal-to-Infant Transmission of Probiotics: Concept Validation in Mice, Rats, and Pigs. *Neonatology* **2009**, *97*, 250–256. [[CrossRef](#)]
195. Gueimonde, M.; Sakata, S.; Kalliomäki, M.; Isolauri, E.; Benno, Y.; Salminen, S. Effect of Maternal Consumption of *Lactobacillus GG* on Transfer and Establishment of Fecal Bifidobacterial Microbiota in Neonates. *J. Pediatr. Gastroenterol. Nutr.* **2006**, *42*, 166–170.
196. Lahtinen, S.J.; Boyle, R.J.; Kivivuori, S.; Oppedisano, F.; Smith, K.R.; Robins-Browne, R.; Salminen, S.J.; Tang, M.L.K. Prenatal Probiotic Administration Can Influence Bifidobacterium Microbiota Development in Infants at High Risk of Allergy. *J. Allergy Clin. Immunol.* **2009**, *123*, 499–501. [[CrossRef](#)]
197. Kijmanawat, A.; Panburana, P.; Reutrakul, S.; Tangshewinsirikul, C. Effects of Probiotic Supplements on Insulin Resistance in Gestational Diabetes Mellitus: A Double-blind Randomized Controlled Trial. *J. Diabetes Investig.* **2019**, *10*, 163–170. [[CrossRef](#)]
198. Shadid, R.; Haarman, M.; Knol, J.; Theis, W.; Beermann, C.; Rjosk-Dendorfer, D.; Schendel, D.J.; Schendel, D.V.; Krauss-Etschmann, S. Effects of Galactooligosaccharide and Long-Chain Fructooligosaccharide Supplementation during Pregnancy on Maternal and Neonatal Microbiota and Immunity—a Randomized, Double-Blind, Placebo-Controlled Study. *Am. J. Clin. Nutr.* **2007**, *86*, 1426–1437. [[CrossRef](#)]
199. Fujiwara, R.; Takemura, N.; Watanabe, J.; Sonoyama, K. Maternal Consumption of Fructo-Oligosaccharide Diminishes the Severity of Skin Inflammation in Offspring of NC/Nga Mice. *Br. J. Nutr.* **2009**, *103*, 530–538. [[CrossRef](#)]
200. Thum, C.; Cookson, A.L.; Otter, D.E.; McNabb, W.C.; Hodgkinson, A.J.; Dyer, J.; Roy, N.C. Can Nutritional Modulation of Maternal Intestinal Microbiota Influence the Development of the Infant Gastrointestinal Tract? *J. Nutr.* **2012**, *142*, 1921–1928. [[CrossRef](#)]
201. Fujiwara, R.; Watanabe, J.; Sonoyama, K. Assessing Changes in Composition of Intestinal Microbiota in Neonatal BALB/c Mice through Cluster Analysis of Molecular Markers. *Br. J. Nutr.* **2008**, *99*, 1174–1177. [[CrossRef](#)] [[PubMed](#)]
202. Desbuards, N.; Gourbeyre, P.; Haure-Mirande, V.; Darmaun, D.; Champ, M.; Bodinier, M. Impact of Perinatal Prebiotic Consumption on Gestating Mice and Their Offspring: A Preliminary Report. *Br. J. Nutr.* **2012**, *107*, 1245–1248. [[CrossRef](#)] [[PubMed](#)]
203. Cryan, J.F.; Dinan, T.G. Mind-Altering Microorganisms: The Impact of the Gut Microbiota on Brain and Behaviour. *Nat. Rev. Neurosci.* **2012**, *13*, 701–712. [[CrossRef](#)] [[PubMed](#)]
204. Sudo, N.; Chida, Y.; Aiba, Y.; Sonoda, J.; Oyama, N.; Yu, X.-N.; Kubo, C.; Koga, Y. Postnatal Microbial Colonization Programs the Hypothalamic–Pituitary–Adrenal System for Stress Response in Mice. *J. Physiol.* **2004**, *558*, 263–275. [[CrossRef](#)] [[PubMed](#)]