www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2023;12(2):e120203
doi: 10.7363/120203
Received: 2023 Mar 15; revised: 2023 May 21; accepted: 2023 Jun 03; published online: 2023 Sept 04

Review

The clinical role of probiotic and prebiotic supplementations during and after maternal gestation

Giulio Perrotta

Istituto per lo Studio delle Psicoterapie – ISP, Rome, Italy

Abstract

Background: For over two decades we have been trying to study and demonstrate the role of the gut microbiota in the onset of cardiovascular, autoimmune, infectious and neurobiological diseases, and more generally the clinical efficacy.

Materials and methods: All clinical trials and randomized controlled trials were selected up to March 30, 2023, for a useful total of 45 studies.

Results: Significant evidence emerges in the literature that supports the therapeutic use for clinical purposes of prebiotics and probiotics even during gestation and within the first 2 years of life, of specific bacterial strains of *Lactobacillus* and *Bifidobacterium* (with almost no definite evidence for *S. boulardii*) to promote proper intestinal eubiosis, slow down inflammatory and infectious processes, including those of an allergic nature, and prevent or ameliorate disease states such as that of gestational diabetes mellitus, sepsis, necrosis, and preeclampsia. In addition, the use of high-fat polyunsaturated fatty acid (HF-PUFA) blends from fish oil, fermented milk supplemented with probiotic strains, and galactooligosaccharides/polydextrose (GOS/PDX) seems useful.

Conclusions: There emerges, therefore, the need, in such a varied and contradictory landscape, to design a research project that takes into account, first of all, a significant and representative population sample, but above all, one that does not underestimate the critical issues mentioned above,

to address with a scientific method the proper and functional use of prebiotics and probiotics in the neonatal and obstetrical fields in general; further studies that can confirm and expand scientific knowledge in this particular field are therefore needed.

Keywords

Premature infants, probiotics, prebiotics, maternal gestation, pregnancy.

Corresponding author

Giulio Perrotta, Istituto per lo Studio delle Psicoterapie – ISP, Via San Martino della Battaglia n. 31, 00185, Rome, Italy; e-mail: info@giulioperrotta.com.

How to cite

Perrotta G. The clinical role of probiotic and prebiotic supplementations during and after maternal gestation. J Pediatr Neonat Individual Med. 2023;12(2):e120203. doi: 10.7363/120203.

Background and aims

Introduction

For more than two decades, efforts have been made to study and demonstrate the role of the gut microbiota in the occurrence of cardiovascular, autoimmune, infectious, and neurobiological diseases, and more generally, the clinical efficacy of the integrative use of prebiotics and probiotics in human nutrition to reduce the risk of miscarriage and fetal malformations. Thus, there is a clinical need to answer with more certainty, to clarify the exact dynamics of the use of prebiotics and probiotics and their therapeutic interactions during and after the gestation of the pregnant woman, where the hypothesis of use for preventive and curative purposes seems to be not only a speculative suggestion [1].

In the literature, studies correlating the gut microbiota with the use of prebiotics and probiotics during and after gestation focus on specific topics of investigation, starting with compositions, and then extending the object of analysis to the purported claim of intervening on disease processes arising from opportunistic infections, overweight and obesity, hypertension and preeclampsia, dermatitis, diabetes, metabolic syndrome, and allergies [2].

Microbiotic composition

It has been determined through research that the development of the intestinal microbiota during the first few weeks of life is marked by the following phases: a) first phase: predominance of *Staphylococcus*; b) second phase: predominance of *Enterococcus* (but only in preterm infants and able to delay the later phases of microbiota development); c) third phase: predominance of *Enterobacter*; d) fourth phase: predominance of *Bifidobacterium* [3].

However, one study showed that the amount of *Bifidobacteria* differed between preterm and term births: differences in the presence of specific species were found at the age of 6 months, although alterations in the microbiota were more prominent after delivery. In addition to prematurity, mode of birth, intrapartum and neonatal exposure to antibiotics, and duration of breastfeeding had an additional impact on the development of the gut microbiota [4].

It has been shown that a vegetarian versus omnivorous diet does not change alpha diversity but only slightly beta, resulting in a reduction in *Collinsella* and *Holdemania*, and relative increases in *Roseburia* and *Lachnospiraceae*; a vegetarian versus omnivorous diet certainly exhibits a different gut microbiome, with features suggesting alterations in fermentation end products, particularly from a mixed acid fermentation toward one more oriented on the presence of acetate and butyrate [5].

Several studies have shown that the prolonged use of antibiotics during and after childbirth can alter the intestinal microbiota, correlating it with an increased risk of developing metabolic, inflammatory and immunological diseases, especially if the drug exposure is long-lasting, has multiple cycles or is drug recombined. At such a risk it is possible to administer a multispecies probiotic (consisting of different strains), even if the best therapy is breast milk, which can increase *Bifidobacteria* and reduce *Proteobacteria* and *Clostridia*. These results indicate that the unwanted changes in the composition and function of the intestinal microbiota caused by the pharmacological treatment of antibiotics, but also cortisone and neuroleptics or by the cesarean delivery itself can be corrected by supplementing the neonatal diet with a specific probiotic mixture together with breastfeeding (at least partial), whenever possible [6-8].

Breastfeeding remains the first choice both because of the greater beneficial interactions with the infant's microbiota and because of the nutritional and immune input given by the mother [9, 10].

However, although *Bifidobacteria* are an important component of the gut microbiota, their alteration has been directly related to some biological functions of the gut but not also to specific diseases [11]. Finally, other supplements, such as lipid supplements, have also been evaluated, demonstrating the provision of increased microbiota biodiversity without, however, altering microbiota maturation [12]; supplementation of short-chain galactooligosaccharides (scGOS), long-chain fructooligosaccharides (lcFOS), and *B. breve M-16V* [13] also resulted in a higher proportion of *Bifidobacteria* from day 3/5 through week 8, a reduction in *Enterobacteriaceae* from day 3/5 through week 12 compared with controls. The data showed lower fecal pH and higher acetate, demonstrating that early modulation of *Bifidobacterium* in infants with galactooligosaccharides (GOS) and lcFOS born by caesarean section is functional to eubiosis [14].

Equally interesting is the infant mycobiota. Fungi are now considered a significant part of the gut microbiota and have an important impact on human health. In a prospective study, about half of the pregnant mothers were randomized to drink probiotic milk during and after pregnancy. Probiotic bacteria included *L. rhamnosus GG* (*LGG*) and *B. animalis subsp. lactis Bb-12* and *L. acidophilus La-5*. Fungal alpha diversity in the intestines of infants increased from 10 days postpartum (first sampling point) onwards. The fungi showed a shift toward maternal mycobiota during growth: *D. hansenii* was the most abundant species during lactation and *S. cerevisiae* was the most abundant species after weaning. Probiotic consumption increased the abundance of intestinal mycobiota in pregnant mothers. This original study suggests that the fungal phenotype is transferred from mothers to infants [15]. The microbiota was investigated in 39 infants (19 preterm and 20 term), demonstrating among other things the presence of 8 bacterial species in the group of preterm infants and high levels of metabolites commonly found in milk, such as fucose and β-hydroxybutyrate, in term infants. Gestational age, birth weight and admission to the Neonatal Intensive Care Unit exert a lasting effect on the gut microbiota and metabolism in infants up to 1 year of age. The results suggest that early intervention may prevent alterations in gut microbial colonization in preterm infants [16].

Gut microbiota and preterm infants

The gut microbiota is a complex and diverse ecosystem, dominated by bacteria but also including viruses, archaea, fungi, and other eukaryotes. It has been called a "hidden" metabolic organ and encodes more than 3 million genes that produce thousands of metabolites. In short, 90% of the gastrointestinal microbiota is composed of bacteria belonging to two major *phyla*: *Bacteroidetes* and *Firmicutes*. Other *phyla* constantly present in the human gut are *Proteobacteria*, *Actinobacteria*, *Fusobacteria* and *Verrucomicrobia*. Each individual has its own distinctive microbial profile. Studies suggest that the early pattern of microbial colonization of the infant gut is critical. The neonatal intestinal microbiota plays an essential role in the proper development of the gastrointestinal tract, particularly in the acquisition of tolerance to postnatal intestinal endotoxins and specifically regulates the maturation of regulatory T-cells (CD4+, Foxp3+), natural killer cells, and gamma delta T-cells. Early dysbiosis during this vulnerable period of development is associated with various inflammatory, metabolic, neurological, cardiovascular, and gastrointestinal diseases. When compared with term infants, infants born prematurely are at increased risk for alterations in the gut microbiota [17].

Altered gastrointestinal colonization (and intestinal predominance of facultative anaerobes) is indeed associated with a higher risk of postnatal sepsis, necrotizing enterocolitis, and growth retardation in preterm infants. There is a link between the development of the gut microbiome and the lung microbiome (gut-lung axis), and the gut-brain cross-talk, under inflammatory conditions, can influence the immune system and impact neonatal outcomes. The microbiota participates in the creation of the intestinal barrier, and many data suggest its role as an immune-modulator. In addition, the development of gut-microbiota-lung axis appears to be associated with altered inflammatory responses determinant in the pathogenesis of bronchopulmonary dysplasia [18].

Aims

This paper investigates the effectiveness of using prebiotics and probiotics during and after maternal gestation, trying to demonstrate the advantages and disadvantages of their administration.

Materials and methods

The search was focused using the PubMed search engine, for all publications up to March 30, 2023, that were clinical trials, randomized controlled trials, meta-analyses and systematic reviews, using the combination of the keywords "gut microbiota", "maternal gestation", "preterm", "prebiotic" and "probiotic", selecting 1,638 useful results. To have a greater and complete overview of the topic, a total of 45 researches and studies were ultimately selected (**Fig. 1**). Simple reviews or opinion contributions were excluded because they were not relevant or redundant for this work. Moreover, 44 types of research were excluded from the final total because they did not present results or statistical samples but only protocol and research proposals, did not specifically address the relationship between the gut microbiota and pregnancy woman, the data were contradictory, unreliable, or otherwise, the research design had functional shortcomings, or the study sample was not directly pregnancy woman. To identify the papers considered in this one, we performed a literature search on PubMed. The search was not limited to English-language papers. No limit on the year of publication was set.

Selected manuscripts are presented in **Tab. 1**.

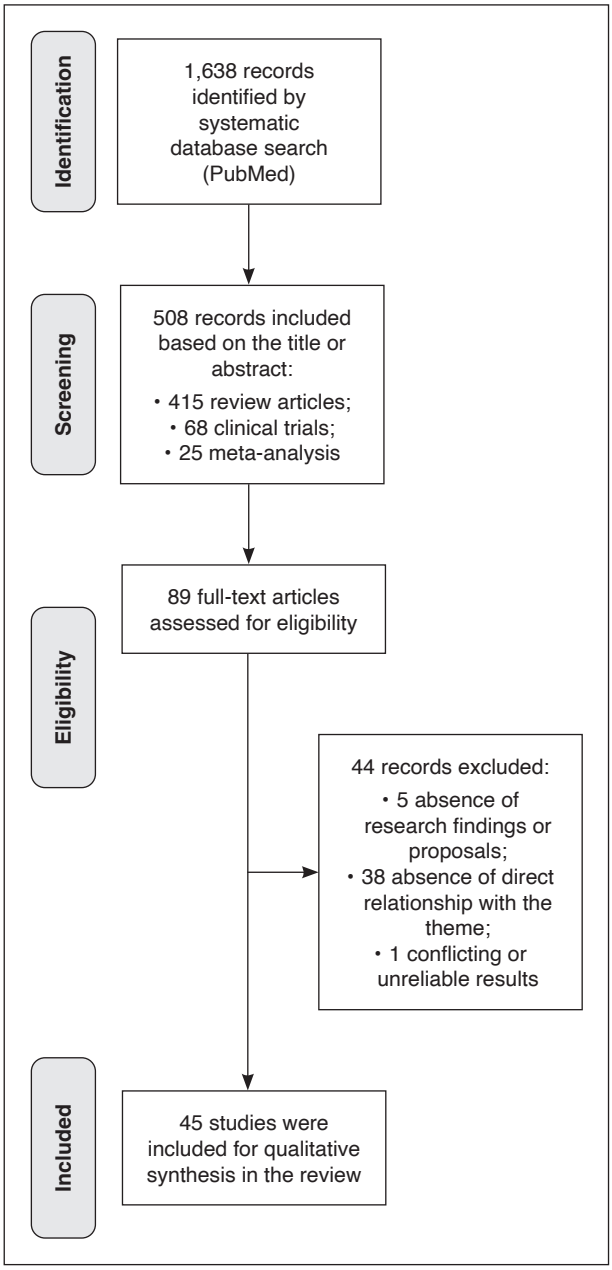

Figure 1. PRISMA flow diagram template for systematic reviews (adapted from: Page et al., 2021 [19]).

Results

Use of prebiotics and probiotics for maternal health

In a double-blind, randomized, placebo-controlled study, a probiotic mixture consisting of *B. bifidum W23*, *B. lactis W52*, and *L. lactis W58* (Ecologic® Panda) was administered to pregnant women in the last 6 weeks of pregnancy and to their children during the first year of life. During follow-up, fecal samples were collected from 99 children over 6 years at the following times: first week, second week, first month, 3 months, first year, 18 months, 2 years and 6 years. Probiotic strains predominated more in the probiotic group. Only minor and short-term differences in microbiota composition were found between the probiotic group and the placebo group and between children with and without atopy. *Bacteroidetes* diversity was significantly higher after 2 weeks in the placebo group, and at age 2 years, atopic children had significantly higher *Proteobacteria* diversity. An increasing evolution of the *phylum*-level composition of the microbiota toward an adult-like configuration was observed between 2 and 6 years of age [20].

"The Healthy Parents, Healthy Kids study is a prospectively registered randomized, controlled trial designed to evaluate the effectiveness of a dietary intervention to modify maternal and infant gut microbiota and improve perinatal diet quality. Compared with the control group, the intervention group improved diet quality before delivery. The intervention improved diet variety and increased intake of prebiotic and probiotic foods throughout the study period compared with the control group. Therefore, a dietary intervention focused

Table 1. Selected manuscripts on the clinical role of probiotic and prebiotic supplementations during and after maternal gestation (continues on the next page).

Author, year	Objectives	Type: n (women)	Key results and conclusions
Tang et al., 2022 [45]	Effectiveness of five interventions used for the prevention of gestational diabetes	M: 16,545	Physical activity and probiotic intervention are more effective than placebo in reducing the risk of developing GDM.
Tonon et al., 2021 [9]	Gut microbiota comparison of vaginally and cesarean-born infants exclusively breastfed by mothers secreting α1-2 fucosylated oligosaccharides in breast milk	RES: 78	Alpha and beta diversity were not significantly different in infants born by CS and fed with secretors (CSe+) compared with infants born vaginally and fed with secretors (VSe+). There were no significant differences in the relative fecal abundance of *Bifidobacterium* between CSe+ and VSe+ infants, but the prevalence of *B. longum* species was lower in CSe+. The relative fecal abundance of *Bacteroides* was also lower, while *Akkermansia* and *Kluyvera* were higher in CSe+ infants. Infants born by cesarean and vaginal delivery fed breast milk containing the α1-2 fucosylated fraction of HMOs had similar amounts of *Bifidobacterium* in the feces, but differences were observed in other members of the microbiota.
Yap et al., 2021 [16]	Neonatal Intensive Care Unit exposures exert a sustained influence on the progression of gut microbiota and metabolome in the first year of life	RES: 39	The results suggest that intervention in this early period could provide "metabolic rescue" to preterm infants from aberrations in gut microbial colonization.
Altemani et al., 2021 [37]	Pregnant women who develop preeclampsia have a lower abundance of the butyrate-producer *Coprococcus* in their gut microbiota	RES: 213	A reduction in the abundance of butyrate-producing bacteria, and *Coprococcus spp.* in particular, may contribute to an increased risk of developing preeclampsia in pregnant women.
Mokkala et al., 2021 [33]	Metagenomics analysis of gut microbiota in response to diet intervention and gestational diabetes in overweight and obese women	RES: 270	Specific species of the gut microbiota do not contribute to GDM in overweight/obese women; however, GDM status may disrupt the flexibility of the maternal gut microbiota and thus limit the ability of women with GDM to respond to diet, as evidenced by alterations in the gut microbiota observed only in women without GDM.
Dawson et al., 2021 [21]	Targeting the perinatal diet to modulate the gut microbiota increases the dietary variety and prebiotic and probiotic food intakes	RES: 45	A dietary intervention focused on "eating for the gut microbiota" may improve aspects of perinatal diet quality during and after pregnancy.
Grech et al., 2021 [42]	Maternal exposures and the infant gut microbiome	M: 17,509	Factors that influenced microbiome composition and diversity include the mother's use of antibiotics and probiotics, food intake, BMI before pregnancy, gestational weight gain, diabetes, mood, and other factors.
Sheyholislami et al., 2021 [43]	Probiotics and prebiotics used during pregnancy and lactation	M: 618	Probiotic and prebiotic products have shown potential health benefits, including the prevention of adverse pregnancy outcomes. Adverse effects associated with probiotic and prebiotic use do not pose any serious health concerns to the mother or infant. Our findings and knowledge translation visualisations provide healthcare professionals and consumers with information to make evidence-informed decisions about the use of pre- and probiotics.
Okesene-Gafa et al., 2020 [48]	Probiotic treatment for women with gestational diabetes	M: 650	Low-certainty evidence means we are not certain if there is any difference between probiotic and placebo groups in maternal hypertensive disorders of pregnancy, caesareans; and large-for-gestational-age babies. There were no adverse events reported by the trials. Due to the variability of probiotics used and the small sample sizes of trials, evidence from this review has limited ability to inform practice. Well-designed adequately-powered trials are needed to identify whether probiotics may improve maternal blood glucose levels and/or infant/child/adult outcomes; and whether they can be used to treat GDM.

Table 1. Selected manuscripts on the clinical role of probiotic and prebiotic supplementations during and after maternal gestation (continues from the previous page and on the next page).

Author, year	Objectives	Type: n (women)	Key results and conclusions
Wang et al., 2020 [49]	Effect of probiotic supplementation on newborn birth weight for mother with GDM or overweight/obesity	M: 1,093	High birth weight indicates the future risk of obesity and increased fat mass in childhood. GDM or maternal overweight are powerful predictors of high birth weight. The analysis revealed that probiotic intake by women with GDM reduced infant birth weight, while probiotic intake by obese pregnant women increased infant birth weight. Therefore, no evidence indicates that probiotic intake by pregnant women with GDM or overweight can control the birth weight of infants.
LeMay-Nedjelski et al., 2020 [27]	Examining the relationship between maternal body size, gestational glucose tolerance status, mode of delivery and ethnicity on human milk microbiota at 3 months post-partum	RES: 117	Human milk has diverse microbiota whose diversity and differential abundance appear to be associated with maternal BMI, glucose tolerance status, delivery mode, and ethnicity.
Hurkala et al., 2020 [22]	Effect of a short-time probiotic supplementation on the abundance of the main constituents of the gut microbiota of term newborns	RES: 150	Supplementation of term infants delivered by CS immediately after birth with a mixture of *L. rhamnosus* and *B. breve* enriched the composition of the intestinal microbiota with lactic acid bacteria.
Ismail et al., 2020 [23]	Prenatal administration of *LGG*	RES: 98	Prenatal *LGG* failed to modulate the diversity of the early infant gut microbiota while promoting a beneficial *Bifidobacteria* profile.
Avershina et al., 2020 [11]	Bifidobacterial succession and correlation networks in a large unselected cohort of mothers and their children	RES: 174	The highly age-structured development and correlation networks among *Bifidobacteria* species during the first 2 years of life reflect their different or competing nutritional requirements, which in turn may be associated with specific biological functions in the development of a healthy gut.
Zong-Jie and Zhen, 2020 [36]	Effects of metabolic syndrome on intestinal flora, inflammatory factors, and infants of pregnant patients	RES: 62	The levels of *Enterobacteria* and *Saccharomyces* were higher, while the levels of *Bifidobacteria*, *Lactobacilli* and *Bacteroidetes* were lower than those in the control group. Infant birth weight was higher in the case group than in the control group, and the incidence rates of fetal macrosomia, hyperbilirubinemia, fetal distress and meconium aspiration syndrome were higher in the case group than in the control group. Therefore, pregnant women with metabolic syndrome have a higher risk of gut flora imbalance, mild inflammatory response and disturbance of glucolipid metabolism.
Kamng'ona et al., 2020 [12]	Provision of lipid-based nutrient supplements to mothers	RES: 869	Prenatal and postnatal intake of lipid-based nutrient supplements promoted the diversity of the infant's gut microbiota at 18 months, after 12 months of infant supplementation, but did not alter the maturation of the microbiota.
Zhao et al., 2020 [34]	Integrated metabolome analysis reveals novel connections between the maternal fecal metabolome and the neonatal blood metabolome in women with GDM	RES: 40	GDM, which is related to changes in the gut microbiota, is a risk factor for neonatal congenital errors of metabolism (IEMs). Maternal hyperglycemia exerts epigenetic effects on genes encoding enzymes associated with IEMs, resulting in changes in the neonatal blood metabolome. However, the relationship between the maternal gut microbiota and the neonatal blood metabolome remains poorly understood. The results of this study suggested that maternal fecal metabolites contribute to the connections between the maternal fecal metabolome and the neonatal blood metabolome and may further influence the risk of IEMs.
Kamal et al., 2019 [8]	Impact of early exposure to cefuroxime on the composition of the gut microbiota in infants following cesarean delivery	RES: 42	The time at which cefuroxime is administered to mothers undergoing cesarean delivery does not have a significant effect on the intestinal microbiota and antibiotic resistance characteristics of the bacteria of infants.

Table 1. Selected manuscripts on the clinical role of probiotic and prebiotic supplementations during and after maternal gestation (continues from the previous page and on the next page).

Author, year	Objectives	Type: n (women)	Key results and conclusions
Pan et al., 2019 [47]	Efficacy of probiotic supplement for GDM	M: 830	Compared with control intervention in GDM, probiotic supplementation was found to significantly reduce insulin resistance (HOMA-IR) and fasting serum insulin, but had no substantial influence on fasting plasma glucose, gestational age and gestational weight.
Murphy et al., 2019 [38]	Eczema-protective probiotic alters infant gut microbiome functional capacity but not composition	RES: 650	The probiotic *L. rhamnosus HN001* administered in early life has been shown to reduce the risk of childhood eczema, but its effect on the development of the gut microbiota has not been examined quantitatively or functionally. Probiotic supplementation with *L. rhamnosus HN001* was associated with an increase in overall glycerol-3 phosphate transport capacity and enrichment of *L. rhamnosus*. There were no other significant changes in the composition or diversity of the child's gut microbiota. The increase in glycerol-3-phosphate transport capacity was positively correlated with the relative abundance of *L. rhamnosus*.
Blakstad et al., 2019 [30]	Enhanced nutrient supply and intestinal microbiota development in VLBW infants	RES: 50	A higher relative abundance of *Bifidobacterium* is associated with better weight gain, and nutrition, therefore, can influence the richness, diversity, and composition of the microbiota.
Callaway et al., 2019 [28]	Probiotics for the prevention of GDM in overweight and obese women	RES: 411	Administration of probiotics (specifically *L. rhamnosus* and *B. animalis subsp. lactis*) starting in the second trimester in overweight and obese women prevents GDM as assessed by an OGTT at 28 weeks of gestation; however, there has been an increase in cases of preeclampsia and weight gain in women taking probiotics.
Jarde et al., 2018 [25]	Pregnancy outcomes in women taking probiotics or prebiotics	M: 2,603	No evidence that taking probiotics or prebiotics during pregnancy either increases or decreases the risk of preterm birth or other infant and maternal adverse pregnancy outcomes.
Korpela et al., 2018 [6]	Intestinal microbiota development and gestational age in preterm neonates	RES: 45	Forty-five fecal samples from preterm infants with birth weight < 1,500 g, up to 60 days postnatal age were analyzed to characterize the development of the gut microbiota during the first weeks of life: a) first phase: predominance of *Staphylococcus*; b) second stage: predominance of *Enterococcus* (but only in preterm infants and able to delay later stages of microbiota development); c) third stage: predominance of *Enterobacter*; d) fourth stage: predominance of *Bifidobacterium*.
Nabhani et al., 2018 [35]	The effects of synbiotic supplementation on insulin resistance/sensitivity, lipid profile and total antioxidant capacity in women with GDM	RES: 90	The results showed that, in women with GDM, synbiotic supplementation had no effect on fasting plasma glucose and insulin resistance/sensitivity indices. Lipid profile and total antioxidant capacity status may be affected by synbiotic supplementation. Synbiotics are effective in reducing blood pressure in women with GDM.
Zheng et al., 2018 [46]	The effects of probiotics supplementation on metabolic health in pregnant women	M: 2,856	Probiotic supplementation during pregnancy has beneficial effects on glucose metabolism rather than lipid metabolism in pregnant women.
Grev et al., 2018 [50]	Maternal probiotic supplementation for prevention of morbidity and mortality in preterm infants	M: 1,450	There is insufficient evidence to conclude whether there is appreciable benefit or harm to neonates of either oral supplementation of probiotics administered to pregnant women at low risk for preterm birth or oral supplementation of probiotics to mothers of preterm infants after birth. Oral supplementation of probiotics to mothers of preterm infants after birth may decrease time to 50% enteral feeds; however, this estimate is extremely imprecise. More research is needed for the post-natal administration of probiotics to mothers of preterm infants, as well as to pregnant mothers at high risk for preterm birth.
Barrett et al., 2018 [5]	A vegetarian diet is a major determinant of gut microbiota composition in early pregnancy	RES: 15	A vegetarian versus omnivorous diet was associated with a different gut microbiome, with features suggesting alterations in fermentation end products from mixed acids toward greater amounts of acetate/butyrate.

Table 1. Selected manuscripts on the clinical role of probiotic and prebiotic supplementations during and after maternal gestation (continues from the previous page and on the next page).

Author, year	Objectives	Type: n (women)	Key results and conclusions
Korpela et al., 2018 [3]	Probiotic supplementation restores normal microbiota composition and function in antibiotic-treated and in caesarean-born infants	RES: 422	Results indicate that undesirable changes in microbiota composition and function caused by antibiotic treatment or cesarean delivery can be corrected by supplementing infants with a probiotic mixture along with at least partial breastfeeding.
Savage et al., 2018 [7]	Diet during pregnancy and infancy and the infant intestinal microbiome	RES: 323	Breastfeeding versus formula feeding is the dietary factor that is most consistently independently associated with the child's gut microbiome. The relationship between breastfeeding status and gut microbiome composition varies according to the child's race/ethnicity.
Chua et al., 2017 [13]	Effect of synbiotic on the gut microbiota of cesarean delivered infants	RES: 30	The effect of scGOS, lcFOS and *B. breve M-16V* on the intestinal microbiota of infants born by CS was determined.
Schei et al., 2017 [15]	Early gut mycobiota and mother-offspring transfer	RES: 594	Probiotic consumption increased the abundance of intestinal mycobiota in pregnant mothers. This study, therefore, provides the first insight into early fungal establishment and succession of fungal species in the intestinal mycobiota, supporting the idea that the fungal host phenotype is transferred from mother to offspring.
Forsgren et al., 2017 [4]	Late preterm birth has direct and indirect effects on infant gut microbiota development during the first 6 months of life	RES: 118	The prevalence of *Bifidobacteria* differed compared to term infants. Differences in the presence of specific species were detected at age 6 months, although alterations in the microbiota were more prominent after delivery. In addition to prematurity, mode of birth, intrapartum and neonatal exposure to antibiotics, and duration of breastfeeding had an additional impact on the development of the gut microbiota.
Sun et al., 2017 [44]	Effects of probiotics on NEC, sepsis, intraventricular hemorrhage, mortality, length of hospital stay, and weight gain in very preterm infants	M: 8,998	Probiotic consumption can significantly reduce the risk of developing medical complications associated with NEC and sepsis, reduce mortality and length of hospital stay, and promote weight gain in VLBW infants. Probiotics are more effective when taken in breast milk and formula form, consumed for < 6 weeks, administered with a dosage of $< 10^9$ CFU/d, and include multiple strains. Probiotics are not effective in reducing the incidence of intraventricular hemorrhage, in VLBW infants.
Zeber-Lubecka et al., 2016 [24]	Effect of *S. boulardii*	RES: 39	The role of *S. boulardii* in the gut microbiota of preterm infants cannot yet be estimated with certainty.
Gomez-Arango et al., 2016 [31]	Increased systolic and diastolic blood pressure is associated with altered gut microbiota composition and butyrate production in early pregnancy	RES: 205	In overweight and obese pregnant women at 16 weeks gestation, the abundance of butyrate-producing bacteria and butyrate production in the gut microbiota is significantly negatively associated with blood pressure and plasminogen activator inhibitor-1 levels. Increased butyrate production capacity may contribute to the maintenance of normal blood pressure in obese pregnant women.
Halkjaer et al., 2016 [29]	Effects of probiotics (Vivomixx®) in obese pregnant women and their newborns	RES: 50	Primary outcomes are maternal weight gain, glycated haemoglobin (HbA1c) level, and changes in glucose concentration measured during an OGTT. Secondary outcomes are microbiota and inflammatory markers in the mother and baby, pregnancy complications, pregnancy outcomes, physical activity, and body composition of the infant.
Rutten et al., 2015 [20]	Long-term development of gut microbiota composition in atopic children	RES: 99	Only minor and short-term differences in microbiota composition were found between the probiotic and placebo group and between children with and without atopy. The diversity of *Bacteroidetes* was significantly higher after 2 weeks in the placebo group, and at the age of 2 years, the atopic children had significantly higher *Proteobacteria* diversity.

Table 1. Selected manuscripts on the clinical role of probiotic and prebiotic supplementations during and after maternal gestation (continues from the previous page).

Author, year	Objectives	Type: n (women)	Key results and conclusions
Mastromarino et al., 2015 [26]	Administration of a multistrain probiotic product (VSL#3) to women in the perinatal period	RES: 66	Probiotic-dependent modulation of the breast milk microbiota in women delivering vaginally, possibly exerted through a systemic effect.
Dotterud et al., 2015 [40]	Probiotic supplementation	RES: 693	Different probiotic bacteria seem to have different transfer abilities from mother to child. No evidence was found that probiotics altered the microbial composition or alpha and beta diversity of infants.
Kim et al., 2015 [41]	Probiotic supplementation influences fecal SCFAs in infants at high risk for eczema	RES: 200	Multispecies probiotic supplementation appeared to induce higher levels of lactate and SCFA, and lower levels of lactose and succinate compared with the placebo group. This could explain the temporary preventive effect of probiotics on the development of eczema.
Grönlund et al., 2011 [10]	Influence of mother's intestinal microbiota on gut colonization in the infant	RES: 160	A clear mother-infant association in intestinal colonization by *Bifidobacteria* was found. Maternal *B. bifidum* colonization had the most consistent effects on the infant's bifidobacterial microbiota. Maternal probiotic treatment had a limited effect on this mother-infant association.
Luoto et al., 2010 [32]	The impact of the perinatal probiotic intervention on the development of overweight and obesity	RES: 159	Early modulation of the gut microbiota with probiotics may change the child's growth pattern by containing excessive weight gain during the first years of life.
Shadid et al., 2007 [14]	Effects of GOS and lcFOS supplementation during pregnancy on maternal and neonatal microbiota	RES: 48	GOS/lcFOS supplementation has a bifidogenic effect on the maternal gut microbiota that is not transferred to infants. The increase in maternal *Bifidobacteria* did not affect fetal immunity as measured by a comprehensive examination of cord blood immunity variables.
Kukkonen et al., 2007 [39]	Probiotics and prebiotic GOS in the prevention of allergic diseases	RES: 1,223	An inverse association between atopic diseases and gut colonization by probiotics.

BMI: body mass index; CS: cesarean section; GDM: gestational diabetes mellitus; GOS: galactooligosaccharides; HMOs: human milk oligosaccharides; lcFOS: long-chain fructooligosaccharides; *LGG*: *L. rhamnosus GG*; M: meta-analysis; NEC: necrotizing enterocolitis; OGTT: oral glucose tolerance test; RES: clinical trial or randomized controlled trial; SCFA: short-chain fatty acid; scGOS: short-chain galactooligosaccharides; VLBW: very low birth weight.

on 'eating for the gut microbiota' may improve aspects of perinatal diet quality during and after pregnancy" [21].

Recent research focuses on the use of probiotics in the prevention of intestinal dysbiosis in infants delivered by cesarean section (CS). In a recent prospective, randomized study, a total of 150 term infants delivered by CS were included in the study. They were randomized into the intervention group (oral administration with a probiotic containing *B. breve PB04* and *L. rhamnosus KL53A*) and the control group. Stool samples were collected for the study of major bacteria on days 5 and 6 of life and after 1 month of life. Application of two probiotic bacteria in the first days of life after CS resulted in rapid and abundant colonization by days 5 and 6, with high amounts of *L. rhamnosus* and *B. breve* present in most infants 1 month after birth [22].

It was then recently shown that maternal administration of *LGG* during late pregnancy can have beneficial effects on the early development of the infant's gut microbiota by promoting a *Bifidobacterium* profile similar to that of a healthy breastfed infant. "Day 7 fecal samples were collected from 98 infants at high risk for the allergic disease whose mothers participated in a study of prenatal eczema prevention with probiotics. A greater number of spikes represent a greater diversity of bacterial communities. Administration of *LGG* to mothers during late pregnancy did not affect the mean number of spikes in fecal samples from 1-week-old infants compared with the placebo. Prenatal *LGG* failed

to modulate the diversity of the early infant gut microbiota while promoting a beneficial *Bifidobacteria* profile" [23].

Probiotic supplementation to the mother during the perinatal period may have a positive impact on breast milk composition [24], but it appears to have no positive effect on the risk of preterm birth [25].

Another interesting study was published on the use of the supplementary probiotic VSL#3, during advanced pregnancy and lactation, to evaluate the levels of beneficial bacteria in breast milk and some functional components (such as oligosaccharides and lactoferrin). "The result demonstrated that the administered probiotic microorganisms did not pass from the maternal intestine to the mammary gland. In women who delivered vaginally, significantly higher amounts of *Lactobacilli* and *Bifidobacteria* were detected in the colostrum and mature milk of the probiotic-treated group than in the placebo group, while no significant difference was observed between groups in women who had a cut cesarean in colostrum or mature milk. The levels of oligosaccharides and lactoferrin in milk were similar in the placebo and probiotic supplemented groups at all time points and regardless of delivery mode" [26]. Thus, a probiotic-dependent modulation of the maternal milk microbiota in women who deliver vaginally, possibly exerted through a systemic effect, has been demonstrated, although the role of *S. boulardii* in the intestinal microbiota of preterm infants is still unknown.

Metabolic syndrome and pathological correlates

Although breast milk plays a key role and is associated with maternal body mass index, glucose tolerance status, delivery mode, and ethnicity [27], the administration of probiotics (specifically *L. rhamnosus* and *B. animalis subsp. lactis*) starting in the second trimester in overweight and obese women prevents gestational diabetes mellitus (GDM) as assessed by an oral glucose tolerance test (OGTT) at 28 weeks of gestation; however, there has been an increase in cases of preeclampsia and weight gain in women taking probiotics [28].

Another study confirmed that "overweight and obese women have an increased risk of pregnancy-induced hypertension, preeclampsia, and GDM and administration of specific probiotics gave as primary outcomes the maternal weight gain, glycated haemoglobin (HbA1c) level, and changes in glucose concentration measured during an OGTT, while as secondary outcomes the microbiota and inflammatory markers in the mother and baby, pregnancy complications, pregnancy outcomes, physical activity, and body composition of the infant" [29].

"Higher relative abundance of *Bifidobacterium* is associated with better weight gain, and nutrition, therefore, can influence the richness, diversity, and composition of the microbiota" [30].

The risk of developing hypertension in pregnancy and preeclampsia is higher in obese pregnant women. In obesity, the composition of the gut microbiota is altered. Obesity is also associated with low-grade inflammation, and gut microbiota metabolites may contribute to both hypertension and inflammation. One study investigated whether the composition of the gut microbiota in overweight and obese pregnant women is associated with blood pressure and plasminogen activator inhibitor-1 levels. Blood pressure was slightly but significantly higher in obese women than in overweight women. Abundance of the butyrate-producing genus *Odoribacter* was inversely correlated with systolic blood pressure. Plasminogen activator inhibitor-1 concentrations were increased in obese pregnant women. Plasminogen activator inhibitor-1 levels were inversely correlated with butyrate kinase expression and *Odoribacter* abundance. Increased butyrate production capacity may contribute to the maintenance of normal blood pressure in obese pregnant women [31].

However, the results in combating the growing trend of overweight and obesity have so far been inadequate. The recently discovered instrumental role of the gut microbiota in host metabolism may offer a new target in the prevention and management of obesity. On this basis, in a randomized, double-blinded study of gestating women 4 weeks before planned delivery and for 6 months postnatally, a perinatal probiotic intervention appears to moderate the early stage of excessive weight gain, especially among children who later became overweight, but not the second stage of excessive weight gain (major impact at age 4 years). In conclusion, from a practical point of view, early modulation of the gut microbiota with probiotics can modulate a child's growth by containing excessive weight gain in the early years of life [32].

Probiotic intake, however, is affected by many factors, including some disease processes, such as GDM; in fact, women without GDM exhibited changes in the relative abundance of bacterial species during pregnancy, particularly those who

received the fish oil and probiotic combination. Specific bacterial species or function did not predict the onset of GDM nor did it differ according to GDM status, except for the higher abundance of *R. obeum* at the end of pregnancy in the combination group in women with GDM compared with women without GDM. In the combination group, weak decreases throughout pregnancy were observed in basic bacterial housekeeping functions. Specific species of the gut microbiota do not contribute to GDM in overweight/obese women; however, GDM status may disrupt the flexibility of the maternal gut microbiota and thus limit the ability of women with GDM to respond to diet, as evidenced by alterations in the gut microbiota observed only in women without GDM [33].

Another study showed that supplementation of *L. acidophilus*, *L. plantarum*, *L. fermentum*, and *L. gasseri*, with fructooligosaccharides positively affects cholesterol values and hypertension but has no effect on blood sugar [34, 35].

On the other hand, it is known that pregnant women with metabolic syndrome have an increased risk of gut flora imbalance, mild inflammatory response, and disturbance of glucolipid metabolism [36]. "Alterations in the composition of the gut microbiota in fact can change the profile of short-chain fatty acids (SCFAs) released by bacteria and contribute to hypertension and metabolic syndrome. In one study, the abundance of the butyrate-producing genus *Coprococcus* was shown to be significantly decreased in late-onset (> 34 weeks gestation) preeclampsia. *Coprococcus* abundance significantly and positively correlated with the abundance of genes encoding the terminal phase in bacterial butyrate formation. Women with late-onset (> 34 weeks gestation) preeclampsia also had significantly reduced serum butyrate levels before symptom development compared with controls. This study suggests that a reduction in the abundance of butyrate-producing bacteria, and *Coprococcus spp.* in particular, may contribute to an increased risk of developing preeclampsia in pregnant women" [37].

Allergies and dermatitis

"The probiotic *L. rhamnosus HN001* administered in early life has been shown to reduce the risk of childhood eczema, but its effect on the development of the gut microbiota has not been examined quantitatively or functionally. Probiotic supplementation with *L. rhamnosus HN001* was associated with an increase in overall glycerol-3-phosphate transport capacity and enrichment of *L. rhamnosus*. There were no other significant changes in the composition or diversity of the child's gut microbiota. The increase in glycerol-3-phosphate transport capacity was positively correlated with the relative abundance of *L. rhamnosus*" [38].

Another study confirmed that probiotic treatment reduces eczema and atopic eczema [39].

Again, maternal probiotic supplementation appears to prevent the development of atopic dermatitis in offspring. In a randomized, double-blind study, women received probiotic milk or placebo from 36 week gestation until 3 months postpartum while breastfeeding. The probiotic milk contained *LGG*, *L. acidophilus La-5* and *B. animalis subsp. lactis Bb-12*. Stool samples were collected from mothers at 30-36 weeks' gestation and 3 months after birth, and from the child at ages 10 days, 3 months, 1 year and 2 years. Three months after birth, the presence of probiotic bacteria administered to the mothers was significantly increased among mothers in the probiotic group compared with those in the placebo group. Only *LGG* bacteria colonized the infants at 10 days and 3 months of age. There were no significant differences in the abundance of probiotic bacteria administered between the groups at 1 and 2 years of age. Regarding bacterial classes and genera and alpha and beta diversity, no significant differences were found between the groups [40].

The composition of the gut microbiota plays a role in the development of allergies. In one study, it was shown that significantly fewer children developed eczema after supplementation with probiotics (*B. bifidum W23*, *B. animalis subsp. lactis W52* and *L. lactis W58*, Ecologic® Panda) at 3 months of age compared with controls. Regarding the metabolites present in fecal samples at 3 months of age, lower amounts of SCFAs, succinate, phenylalanine, and alanine were found in children who later developed eczema, while the amounts of glucose, galactose, lactate, and lactose were higher than in children who did not develop eczema. It should be noted that although these differences were already present at the age of 3 months, eczema did not develop in most children until the age of 1 year. Probiotic supplementation appears to induce higher levels of lactate and SCFAs and lower levels of lactose and succinate compared with the placebo

group with possible temporary preventive effect on the development of eczema [41].

Discussion and limitations

The early years of life, including the establishment of the gut microbiome, represent a critical window of growth and development. Postnatal factors influencing the microbiome, including the manner of delivery, type of feeding, and exposure to antibiotics, have been extensively studied, but questions remain about the influence of *in-utero* exposures on the assembly of the child's gut microbiome. This haziness is mainly determined by the intrinsic and extrinsic limitations of the published studies, which have obvious structural shortcomings in their designs, especially with regard to anthropomorphic and clinical variables, the representativeness of the selected population sample, the lack of longitudinal follow-up, and in the analytical methods of biological samples and methodology; it seems clear, therefore, that standardization of working procedures is necessary to improve the understanding of this complex and rapidly evolving field [42] (**Tab. 2**).

Probiotic and prebiotic products have demonstrated potential health benefits, including for the prevention of adverse pregnancy outcomes and on the health of preterm infants; however, the incidence of adverse effects in pregnant women and their infants associated with probiotic/prebiotic/synbiotic intake remains unclear. To date, however, adverse effects associated with the use of probiotics and prebiotics do not pose a serious health problem for the mother or baby, except to the extent of an alteration in natural eubiosis [43, 44].

And while several studies [45-47] would seem to favor the conscious use of probiotics, especially coupled with consistent sports activity and a balanced diet, to positively impact prenatal metabolic conditions such as diabetes (precisely because of their efficacy on glucose metabolism rather than on lipid metabolism), other studies [48-50] point to the structural shortcomings of the studies, relative to their designs, to demonstrate their ineffectiveness, by low-certainty evidence,

Table 2. Summary of typical development of the intestinal microbiome from birth to early childhood (adapted from: Grech et al., 2021 [42]).

Stage of development	General microbiome characteristics
Neonate (0-4 weeks)	• Rapid colonization by anaerobic bacteria. • Meconium is likely to be more reflective of maternal microbiome composition than in response to the delivery mode or environmental conditions. • Altered pattern of colonization associated with prematurity; preterm infants have higher counts of *Enterobacteriaceae* and lower counts of *Bacteroidaceae* and *Bifidobacteria* compared to those born at term. Lower species diversity was also observed in preterm compared to term neonates. • Differences in microbiota composition due to birth mode are present. Infants born vaginally are characterized by a higher relative abundance of *Bacteroides* whereas those born via CS delivery have a lower relative abundance of *Bifidobacterium* and higher levels of *Klebsiella*, *Haemophilus*, and *Veillonella*.
Milk-fed infant (0-6 months)	• Overall low species diversity continues. • Differences in individual species abundance differ by feeding type (breastmilk or formula). • Highly individual composition (i.e., high beta diversity). • *Bifidobacterium* is the dominant bacterial genus, particularly in breastfed infants.
Mixed-fed infant (6-12 months)	• The introduction of solid food spearheads changes in composition, including an increase in the relative abundance of *Bacteroides* and newly dominant genera such as *Ruminococcus* and *Akkermansia*. • Cessation of breastfeeding may or may not occur, and has a major impact on composition independent of the introduction of solid foods. • Increasing alpha diversity (Shannon Index) is driven largely by increasing species richness. • Highly individual composition (beta diversity) persists.
Toddler (12-36 months)	• Increasing phylogenetic diversity and reducing beta diversity. • Cessation of breastfeeding has a major impact on microbiota composition and alpha diversity alongside increasing dietary diversity. • Approaching microbiome "stability" with ongoing adaptation to the environment.
'Adult-like' microbiota (> 36 months)	• The microbiome is more resilient to environmental challenges. Stable microbiota "signature" is established. • Alpha diversity (Shannon Index) in early childhood continues to be lower than that of adults.

CS: cesarean section.

although certain shortcomings capable of affecting the outcome of the aforementioned studies are undeniable.

Thus, the need to design studies capable of robustly supporting conclusive outcomes, ensuring good variability in anthropometric and clinical analyses, a population sample as respectful as possible of representativeness criteria, comprehensive statistical analysis, and prospective double-blind studies emerges in an imposing manner, as to date, published studies have structural shortcomings that may be able to negate the credibility of the conclusive outcome of the studies themselves.

Conclusion

Significant evidence emerges in the literature that supports the therapeutic use for clinical purposes of prebiotics and probiotics even during gestation and within the first 2 years of life, of specific bacterial strains of *Lactobacillus* and *Bifidobacterium* (with almost no definite evidence for *S. boulardii*) to promote proper intestinal eubiosis, slow down inflammatory and infectious processes, including those of an allergic nature, and prevent or ameliorate disease states such as that of GDM, sepsis, necrosis, and preeclampsia. In addition, the use of high-fat polyunsaturated fatty acid (HF-PUFA) blends from fish oil, fermented milk supplemented with probiotic strains, and galactooligosaccharides/polydextrose (GOS/PDX) seems useful. There emerges, therefore, the need, in such a varied and contradictory landscape, to design a research project that takes into account, first of all, a significant and representative population sample, but above all, one that does not underestimate the critical issues mentioned above, to address with a scientific method the proper and functional use of prebiotics and probiotics in the neonatal and obstetrical fields in general. Further studies that can confirm and expand scientific knowledge in this particular field are therefore needed.

Declaration of interest

The Author declares that there is no conflict of interest.

References

1. Perrotta G. The intestinal microbiota: towards a multifactorial integrative model. Eubiosis and dysbiosis in morbid physical and psychological conditions. Arch Clin Gastroenterol. 2021;7(2):24-35.
2. Perrotta G. Il microbiota intestinale nella pratica clinica. Guida completa all'uso «consapevole» e mirato dei prebiotici, probiotici e postbiotici. Milan: LK ed., 2022.
3. Korpela K, Blakstad EW, Moltu SJ, Strømmen K, Nakstad B, Rønnestad AE, Brække K, Iversen PO, Drevon CA, de Vos W. Intestinal microbiota development and gestational age in preterm neonates. Sci Rep. 2018;8(1):2453.
4. Forsgren M, Isolauri E, Salminen S, Rautava S. Late preterm birth has direct and indirect effects on infant gut microbiota development during the first six months of life. Acta Paediatr. 2017;106(7):1103-9.
5. Barrett HL, Gomez-Arango LF, Wilkinson SA, Mcintyre HD, Callaway LK, Morrison M, Nitert MD. A Vegetarian Diet Is a Major Determinant of Gut Microbiota Composition in Early Pregnancy. Nutrients. 2018;10(7):890.
6. Korpela K, Salonen A, Vepsäläinen O, Suomalainen M, Kolmeder C, Varjosalo M, Miettinen S, Kukkonen K, Savilahti E, Kuitunen M, de Vos WM. Probiotic supplementation restores normal microbiota composition and function in antibiotic-treated and caesarean-born infants. Microbiome. 2018;6(1):182.
7. Savage JH, Lee-Sarwar KA, Sordillo JE, Lange NE, Zhou Y, O'Connor GT, Sandel M, Bacharier LB, Zeiger R, Sodergren E, Weinstock GM, Gold DR, Weiss ST, Litonjua AA. Diet during Pregnancy and Infancy and the Infant Intestinal Microbiome. J Pediatr. 2018;203:47-54.e4.
8. Kamal SS, Hyldig N, Krych L, Greisen G, Krogfelt KA, Zachariassen G, Nielsen DS. Impact of Early Exposure to Cefuroxime on the Composition of the Gut Microbiota in Infants Following Cesarean Delivery. J Pediatr. 2019;210:99-105.e2.
9. Tonon KM, Morais TB, Taddei CR, Araujo-Filho HB, Abrao ACFV, Miranda A, de Morais MB. Gut microbiota comparison of vaginally and cesarean born infants exclusively breastfed by mothers secreting α1-2 fucosylated oligosaccharides in breast milk. PLoS One. 2021;16(2):e0246839.
10. Grönlund MM, Grzeskowiak L, Isolauri E, Salminen S. Influence of mother's intestinal microbiota on gut colonization in the infant. Gut Microbes. 2011;2(4):227-33.
11. Avershina E, Storro O, Oien T, Johsen R, Wilson R, Egeland T, Rudi K. Bifidobacterial succession and correlation networks in a large unselected cohort of mothers and their children. Appl Environ Microbiol. 2020;79(2):497-507.
12. Kamng'ona AW, Young R, Arnold CD, Patson N, Jorgensen JM, Kortekangas E, Chaima D, Malamba C, Ashorn U, Cheung YB, Ashorn P, Maleta K, Dewey KG. Provision of Lipid-Based Nutrient Supplements to Mothers During Pregnancy and 6 Months Postpartum and to Their Infants from 6 to 18 Months Promotes Infant Gut Microbiota Diversity at 18 Months of Age but Not Microbiota Maturation in a Rural Malawian Setting: Secondary Outcomes of a Randomized Trial. J Nutr. 2020;150(4):918-28.
13. Chua MC, Ben-Amor K, Lay C, Neo AGE, Chiang WC, Rao R, Chew C, Chaithongwongwatthana S, Khemapech N, Knol J, Chongsrisawat V. Effect of Synbiotic on the Gut Microbiota of Cesarean Delivered Infants: A Randomized, Double-blind, Multicenter Study. J Pediatr Gastroenterol Nutr. 2017;65(1):102-6.

14. Shadid R, Haarman M, Knol J, Theis W, Beermann C, Rjosk-Dendorfer D, Schendel DJ, Koletzko BV, 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(5):1426-37.
15. Schei K, Avershina E, Øien T, Rudi K, Follestad T, Salamati S, Ødegård RA. Early gut mycobiota and mother-offspring transfer. Microbiome. 2017;5(1):107.
16. Yap PSX, Chong CW, Kamar AA, Yap IKS, Choo YM, Lai NM, Teh CSJ. Neonatal intensive care unit (NICU) exposures exert a sustained influence on the progression of gut microbiota and metabolome in the first year of life. Sci Rep. 2021;11(1):1353.
17. Cuna A, Morowitz MJ, Ahmed I, Umar S, Sampath V. Dynamics of the preterm gut microbiome in health and disease. Am J Physiol Gastrointest Liver Physiol. 2021;320(4):G411-9.
18. Tirone C, Pezza L, Paladini A, Tana M, Aurilia C, Lio A, D'Ippolito S, Tersigni C, Posteraro B, Sanguinetti M, Di Simone N, Vento G. Gut and Lung Microbiota in Preterm Infants: Immunological Modulation and Implication in Neonatal Outcomes. Front Immunol. 2019;10:2910.
19. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
20. Rutten NB, Gorissen DM, Eck A, Niers LE, Vlieger AM, Besseling-van der Vaart I, Budding AE, Savelkoul PH, van der Ent CK, Rijkers GT. Long Term Development of Gut Microbiota Composition in Atopic Children: Impact of Probiotics. PLoS One. 2015;10(9):e0137681.
21. Dawson SL, Mohebbi M, Craig JM, Dawson P, Clarke G, Tang ML, Jacka FN. Targeting the perinatal diet to modulate the gut microbiota increases dietary variety and prebiotic and probiotic food intakes: results from a randomised controlled trial. Public Health Nutr. 2021;24(5):1129-41.
22. Hurkala, J, Lauterback, R, Radziszewska, R, Strus, M, Heczko, P. Effect of a Short-Time Probiotic Supplementation on the Abundance of the Main Constituents of the Gut Microbiota of Term Newborns Delivered by Cesarean Section – A Randomized, Prospective, Controlled Clinical Trial. Nutrients. 2020;12(10):3128.
23. Ismail IH, Oppedisano F, Joseph SJ, Boyle RJ, Robins-Browne RM, Tang ML. Prenatal administration of Lactobacillus rhamnosus has no effect on the diversity of the early infant gut microbiota. Pediatr Allergy Immunol. 2020;23(3):255-8.
24. Zeber-Lubecka N, Kulecka M, Ambrozkiewicz F, Paziewska A, Lechowicz M, Konopka E, Majewska U, Borszewska-Kornacka M, Mikula M, Cukrowska B, Ostrowski J. Effect of Saccharomyces boulardii and Mode of Delivery on the Early Development of the Gut Microbial Community in Preterm Infants. PLoS One. 2016;11(2):e0150306.
25. Jarde A, Lewis-Mikhael AM, Moayyedi P, Stearns JC, Collins SM, Beyene J, McDonald SD. Pregnancy outcomes in women taking probiotics or prebiotics: a systematic review and meta-analysis. BMC Pregnancy Childbirth. 2018;18(1):14.
26. Mastromarino P, Capobianco D, Miccheli A, Praticò G, Campagna G, Laforgia N, Capursi T, Baldassarre ME. Administration of a multistrain probiotic product (VSL#3) to women in the perinatal period differentially affects breast milk beneficial microbiota in relation to mode of delivery. Pharmacol Res. 2015;95-96:63-70.
27. LeMay-Nedjelski L, Butcher J, Ley SH, Asbury MR, Hanley AJ, Kiss A, Unger S, Copeland JK, Wang PW, Zinman B, Stintzi A, O'Connor DL. Examining the relationship between maternal body size, gestational glucose tolerance status, mode of delivery and ethnicity on human milk microbiota at three months post-partum. BMC Microbiol. 2020;20(1):219.
28. Callaway LK, McIntyre HD, Barrett HL, Foxcroft K, Tremellen A, Lingwood BE, Tobin JM, Wilkinson S, Kothari A, Morrison M, O'Rourke P, Pelecanos A, Dekker Nitert M. Probiotics for the Prevention of Gestational Diabetes Mellitus in Overweight and Obese Women: Findings From the SPRING Double-Blind Randomized Controlled Trial. Diabetes Care. 2019;42(3):364-71.
29. Halkjaer SI, Nilas L, Carlsen EM, Cortes D, Halldórsson TI, Olsen SF, Pedersen AE, Krogfelt KA, Petersen AM. Effects of probiotics (Vivomixx®) in obese pregnant women and their newborn: study protocol for a randomized controlled trial. Trials. 2016;17(1):491.
30. Blakstad EW, Korpela K, Lee S, Nakstad B, Moltu SJ, Strømmen K, Rønnestad AE, Brække K, Iversen PO, de Vos WM, Drevon CA. Enhanced nutrient supply and intestinal microbiota development in very low birth weight infants. Pediatr Res. 2019;86(3):323-32.
31. Gomez-Arango LF, Barrett HL, McIntyre HD, Callaway LK, Morrison M, Dekker Nitert M; SPRING Trial Group. Barrett Increased Systolic and Diastolic Blood Pressure Is Associated With Altered Gut Microbiota Composition and Butyrate Production in Early Pregnancy. Hypertension. 2016;68(4):974-81.
32. Luoto R, Kalliomaki 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(10):1531-7.
33. Mokkala K, Paulin N, Houttu N, Koivuniemi E, Pellonperä O, Khan S, Pietilä S, Tertti K, Elo LL, Laitinen K. Metagenomics analysis of gut microbiota in response to diet intervention and gestational diabetes in overweight and obese women: a randomised, double-blind, placebo-controlled clinical trial. Gut. 2021;70(2):309-18.
34. Zhao C, Ge J, Li X, Jiao R, Li Y, Jiao R, Li Y, Quan H, Li J, Guo Q, Wang W. Integrated metabolome analysis reveals novel connections between maternal fecal metabolome and the neonatal blood metabolome in women with gestational diabetes mellitus. Sci Rep. 2020;10(1):3660.
35. Nabhani Z, Hezaveh SJG, Razmpoosh E, Asghari-Jafarabadi M, Gargari BP. The effects of synbiotic supplementation on insulin resistance/sensitivity, lipid profile and total antioxidant capacity in women with gestational diabetes mellitus: A randomized double

blind placebo controlled clinical trial. Diabetes Res Clin Pract. 2018;138:149-57.

36. Zong-Jie LV, Zhen C. Effects of Metabolic Syndrome on Intestinal Flora, Inflammatory Factors, and Infants of Pregnant Patients. Clin Lab. 2020;66(10):200226.
37. Altemani F, Barrett HL, Gomez-Arango L, Josh P, McIntyre HD, Callaway LK, Morrison M, Tyson GW, Dekker Nitert M. Pregnant women who develop preeclampsia have lower abundance of the butyrate-producer Coprococcus in their gut microbiota. Pregnancy Hypertens. 2021;23:211-9.
38. Murphy R, Morgan XC, Wang XY, Wickens K, Purdie G, Fitzharris P, Otal A, Lawley B, Stanley T, Barthow C, Crane J, Mitchell EA, Tannock GW. Eczema-protective probiotic alters infant gut microbiome functional capacity but not composition: sub-sample analysis from a RCT. Benef Microbes. 2019;10(1):5-17.
39. Kukkonen K, Savilahti E, Haahtela T, Juntunen-Backman K, Korpela R, Poussa T, Tuure T, Kuitunen M. Probiotics and prebiotic galacto-oligosaccharides in the prevention of allergic diseases: a randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunol. 2007;119(1):192-8.
40. Dotterud CK, Avershina E, Sekelja M, Simpson MR, Rudi K, Storrø O, Johnsen R, Øien T. Does Maternal Perinatal Probiotic Supplementation Alter the Intestinal Microbiota of Mother and Child? J Pediatr Gastroenterol Nutr. 2015;61(2):200-7.
41. Kim HK, Rutten NB, Besseling-van der Vaart I, Niers LE, Choi YH, Rijkers GT, van Hemert S. Probiotic supplementation influences faecal short chain fatty acids in infants at high risk for eczema. Benef Microbes. 2015;6(6):783-90.
42. Grech A, Collins CE, Holmes A, Lal R, Duncanson K, Taylor R, Gordon A. Maternal exposures and the infant gut microbiome: a systematic review with meta-analysis. Gut Microbes. 2021;13(1): 1-30.
43. Sheyholislami H, Connor KL. Are Probiotics and Prebiotics Safe for Use during Pregnancy and Lactation? A Systematic Review and Meta-Analysis. Nutrients. 2021;13(7):2382.
44. Sun J, Marwah G, Westgarth M, Buys N, Ellwood D, Gray PH. Effects of Probiotics on Necrotizing Enterocolitis, Sepsis, Intraventricular Hemorrhage, Mortality, Length of Hospital Stay, and Weight Gain in Very Preterm Infants: A Meta-Analysis. Adv Nutr. 2017;8(5):749-63.
45. Tang Q, Zhong Y, Xu C, Li W, Wang H, Hou Y. Effectiveness of five interventions used for prevention of gestational diabetes: A network meta-analysis. Medicine (Baltimore). 2022;101(15):e29126.
46. Zheng J, Feng Q, Zheng S, Xiao X. The effects of probiotics supplementation on metabolic health in pregnant women: An evidence based meta-analysis. PLoS One. 2018;13(5):e0197771.
47. Pan J, Pan Q, Chen Y, Zhang H, Zheng X. Efficacy of probiotic supplement for gestational diabetes mellitus: a systematic review and meta-analysis. J Matern Fetal Neonatal Med. 2019;32(2):317-23.
48. Okesene-Gafa KA, Moore AE, Jordan V, McCowan L, Crowther CA. Probiotic treatment for women with gestational diabetes to improve maternal and infant health and well-being. Cochrane Database Syst Rev. 2020;6(6):CD012970.
49. Wang CC, Tung YT, Chang HC, Lin CH. Effect of Probiotic Supplementation on Newborn Birth Weight for Mother with Gestational Diabetes Mellitus or Overweight/Obesity: A Systematic Review and Meta-Analysis. Nutrients. 2020;12(11):3477.
50. Grev J, Soll R, Berg M. Maternal probiotic supplementation for prevention of morbidity and mortality in preterm infants. Cochrane Database Syst Rev. 2018;12(12):CD012519.