REVIEW ARTICLE

Intestinal microbiota composition in pregnant women and its influence on the incidence of adverse perinatal outcomes

Composição da microbiota intestinal de gestantes e sua influência na ocorrência de desfechos perinatais adversos

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ABSTRACT

Objective: Investigating the association between intestinal microbiota composition in pregnant women and incidence of adverse perinatal outcomes based on a systematic review. Methods: The search was carried out in PubMed, Embase, Lilacs, Scopus and Web of Science databases. A formal protocol was registered in PROSPERO database (registration number CRD42023470580). The quality of the selected studies was assessed based on the Joanna Briggs Institute Reviewer Manual. Results: In total, 7.393 articles were identified after the search and twelve studies were selected for the present review. Sample size ranged from 16 to 1.479 women, and participants' chronological age ranged from 20 to 40 years old. For the analysis of intestinal microbiota, all articles used fecal samples, with genetic extraction of nucleic acids such as deoxyribonucleic acid and ribonucleic acid, and sequencing of specific genes from fecal. Eight different outcomes were identified, including fetal demise, fetal abdominal circumference, intrauterine growth, femoral length, weight, head circumference, premature birth and gestational weight gain. These outcomes were associated with more than thirty (30) intestinal strains, such as those from the families *Eubacteriaceae, Lachnospiraceae, Ruminococcaceae, Parabacteroides,* and the genus *Streptococcus.* Conclusion: This review highlighted the existence of an association between intestinal microbiota and adverse perinatal outcomes, such as fetal demise, fetal abdominal circumference, intrauterine growth, femoral length, weight, head circumference, and premature birth, with over thirty strains of intestinal bacteria.

Keywords: Microbiome, Pregnancy, Perinatal care

RESUMO

Objetivo: Investigar a associação entre a composição da microbiota intestinal em mulheres grávidas e a incidência de desfechos perinatais adversos com base em uma revisão sistemática. Métodos: A busca foi realizada nas bases de dados PubMed, Embase, Lilacs, Scopus e Web of Science. Um protocolo formal foi registrado no banco de dados PROSPERO (número de registro CRD42023470580). A qualidade dos estudos selecionados foi avaliada com base no Manual do Revisor do Instituto Joanna Briggs. Resultados: No total, foram identificados 7.393 artigos após a busca, e onze estudos foram selecionados para a presente revisão. O tamanho da amostra variou de 16 a 1.479 mulheres, e a idade cronológica dos participantes variou de 20 a 40 anos. Para a análise da microbiota intestinal, todos os artigos utilizaram amostras fecais, onde ocorreu a extração

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genética de ácidos nucleicos, como o ácido desoxirribonucleico (DNA) e ácido ribonucleico (RNA), e o sequenciamento de genes específicos a partir das fezes. Oito desfechos diferentes foram identificados, incluindo óbito fetal, circunferência abdominal fetal, crescimento intrauterino, comprimento femoral, peso, circunferência cefálica, nascimento prematuro e ganho de peso gestacional. Esses desfechos foram associados a mais de trinta cepas intestinais, tais como aquelas das famílias *Eubacteriaceae, Lachnospiraceae, Ruminococcaceae e Parabacteroides,* e do gênero *Streptococcus*. Conclusão: Esta revisão destacou a existência de uma associação entre a microbiota intestinal e desfechos perinatais adversos, tais como óbito fetal, circunferência abdominal fetal, crescimento intrauterino, comprimento femoral, peso, circunferência cefálica e nascimento prematuro, com mais de trinta cepas de bactérias intestinais.

Palavras-chave: Microbioma, Gravidez, Assistência perinatal.

INTRODUCTION

Pregnancy is a biological event comprising several changes in a woman's bodies, such as physiological and hormonal changes, whose main purpose lies in ensuring adequate fetal growth[1]. Maternal lifestyle can have significant short-, medium- and long-term impacts on fetal life during this period[2].

Throughout the perinatal period, which begins in the 22nd week of pregnancy and lasts until the seventh day after the birth of the conceptus, the mother and child binomial are vulnerable to the development of several adverse outcomes, the most prevalent being low birth weight, prematurity, and fetal malformations, with these problems listed as important causes of high fetal mortality.

During pregnancy, changes in mothers' immune systems have a direct impact on their intestinal function and bacterial composition as pregnancy progresses. Healthy pregnancies present increased amounts of bacteria and changes in intestinal microbiota composition[4-6]. This stage is characterized by decreased diversity of individual bacteria and by increased populations of Firmicutes (including *Lactobacillus* and *Faecalibacterium*), Actinobacteria, Proteobacteria, and Bacteroidetes (including *Bacteroides*)[4-6].

Studies in the literature have suggested that the health of pregnant women's intestinal microbiota plays a significant role in healthy fetal development, since it is intrinsically linked to nutrient absorption, brain/intestine communication, as well as to immunological processes. These influence types can have adverse effects on the mother-child binomial, even during pregnancy[7-8].

The association between maternal intestinal microbiota and fetal exposure to it is a complex process that is yet to be fully explained, although some studies in the literature have shown that bacteria found in the maternal microbiota can translocate to the placenta. Consequently, they can increase pregnancy's inflammatory condition and harm the fetus[9]. According to recent studies, these findings likely result from contamination during clinical procedures, such as fetal sample collections, or during nucleic acid extraction and sequencing processes. These studies ruled out the role played by bacterial translocation in these outcomes[10-11].

Despite divergent results, it is known that maternal microbiota can induce changes in the expression of the main nutrient transporters and, consequently, regulate fetal growth[12]. In addition, a study has shown that maternal intestinal microbiota can either suppress or promote intestinal inflammation, which is associated with enteric dysfunction biomarkers that, in turn, have been associated with premature and the birth of babies with fetal growth restriction[13].

Despite updates observed in research, the literature in this field still lacks results associated with this topic, although its importance has been highlighted. It is important to emphasize that no systematic review on this topic was identified, so far. Accordingly, this investigation type plays a relevant role to help improve maternal and child's health, if one takes into consideration the impacts caused by intestinal microbiota composition on this population's health. In addition, results in these investigations can be used to help preventing or treating associated comorbidities, guiding clinical and nutritional practice by health professionals involved in prenatal care, reducing the likelihood of developing different diseases during pregnancy, as well as mitigating undesirable outcomes for the mother-child binomial due to changes in intestinal microbiota.

Therefore, the objective of this study was investigating the association between intestinal microbiota composition in pregnant women and incidence of adverse perinatal outcomes based on a systematic review.

METHODS

Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)[14] checklists were applied, and all study-development stages, such as searches, data extraction and methodological quality assessment, were conducted by two evaluators, separately. Disagreements were solved by consensus. A formal protocol was published in PROSPERO Database for systematic reviews (registration number CRD42023470580).

Search and selection strategy

The search for articles was carried out until late February 2024, in the following databases: MEDLINE (via PubMed), Lilacs, Scielo, Web of Science, Embase and Scopus. Following the PRISMA guidelines, relevant studies were considered to the extent that they met the inclusion criteria established according to population, intervention, comparison, outcomes and study design (PICOS) (Table 1)[15].

Table 1: PICOS eligibility criteria for the inclusion of studies in the systematic review.

Parameters	Inclusion criteria
Population	Intestinal microbiota of pregnant women, with or without pregnancy complications
Intervention	No intervention
Comparators	Intestinal microbiota of control groups, been health women, pregnant or non-pregnant
Outcomes	Adverse perinatal outcomes, like fetal macrossomia, small for gestational age, preterm birth, low birth weight low apgar score, neonatal mortality, cesarean delivery
Study design	Observational studies

The following keywords were used by taking into consideration MeSH terms linked to pregnancy, as well as to the investigated condition (intestinal microbiota) and outcome (adverse perinatal outcome): pregnant, pregnancy, pregnant women, gestation, preeclampsia, pre-eclampsia, gestational hypertension, diabetes mellitus, gestational diabetes mellitus, gut microbiota, microbiome, intestinal microbiota, maternal microbiota, perinatal outcome, birth outcome, pregnancy complications, newborn, newborn infant, neonate, infant, fetus, fetal macrosomia, small for gestational age, preterm birth, preterm delivery, premature birth, birth weight, low birth weight, high birth weight, instant, very low birth weight, infant, apgar score, neonatal mortality, cesarean section, cesarean delivery, obstetric labor, premature and developmental outcome . The search strategy was set up to answer the following guiding question: Does the composition of the intestinal microbiota of pregnant women influence the incidence of adverse perinatal outcomes?

After insertion into the Rayyan software, duplicate search results were removed. Subsequently, two reviewers independently analyzed titles and abstracts, following pre-specified criteria. The defined eligibility criteria were as follows: articles that assessed the intestinal microbiota of pregnant women and its influence on potential adverse perinatal outcomes. Pregnant women were evaluated regardless of whether they had related diseases or not, and articles in English, Portuguese, or Spanish were included, regardless of the year of publication.

On the other hand, studies that performed any type of intervention, randomized clinical trials, reviews or experimental articles using animals or in vitro, conferences, abstracts, case reports, editorial letters, and full-text works in other languages were excluded. Abstracts were then read, and finally, full texts were considered for evaluation, and those meeting the predefined eligibility criteria were included.

Data extraction

Extracted data comprised author and publication year, study type, sample size, pregnant women' age, microorganisms' strain, microbiota analysis method, as well as maternal and fetal outcomes.

Methodological quality assessment

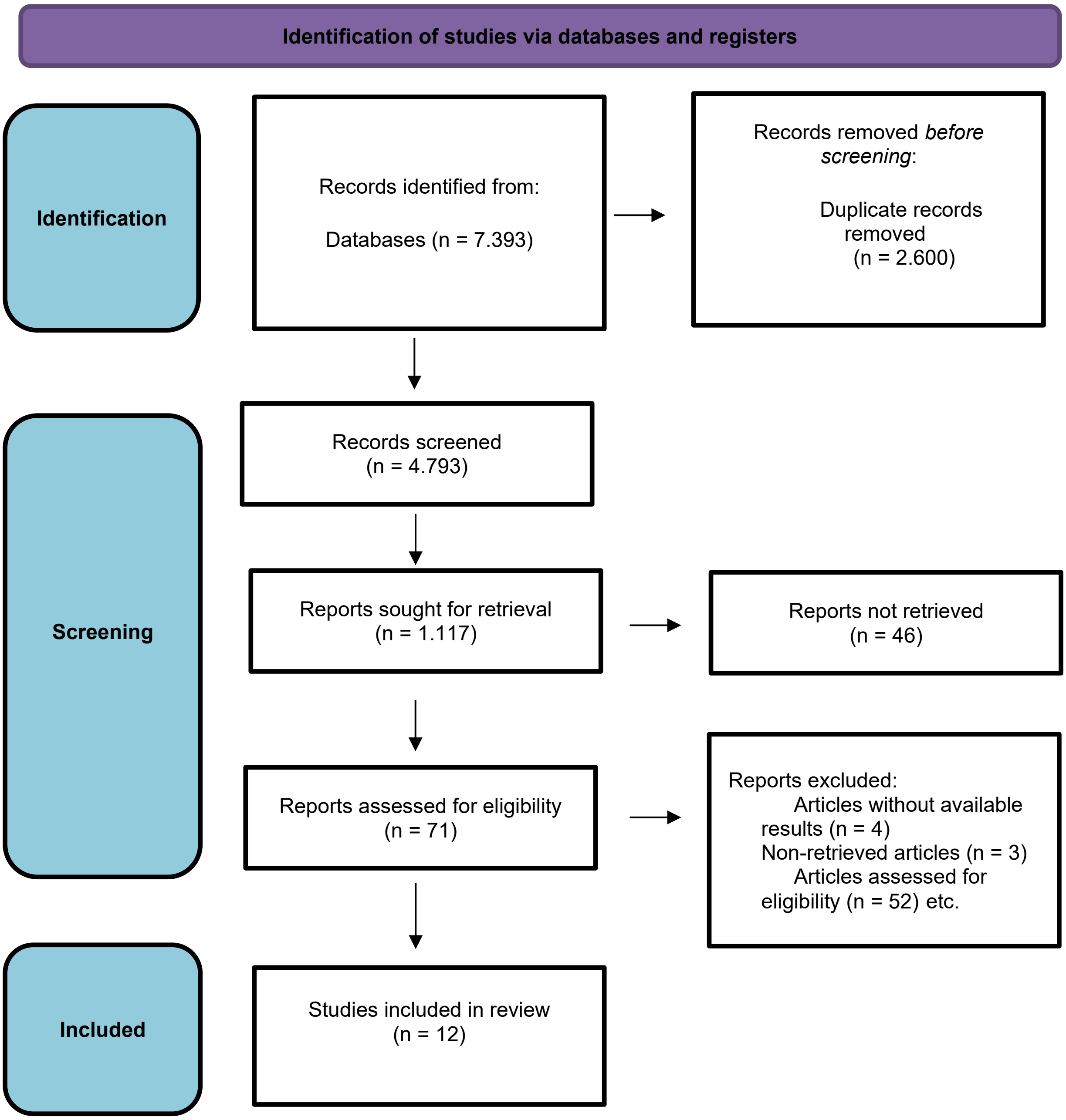
Eligible studies were critically assessed by two independent study-level reviewers based on using standardized critical appraisal instruments from the Joanna Briggs Institute (JBI)[16] Center of Excellence for Observational Studies.

RESULTS

Initially, 7.393 articles were found in the investigated databases. After the reviewers' first analysis was over, 2.600 duplicate articles were excluded from the study and the remaining 4.793 articles had their titles read.

After this first reading stage was over, 121 articles were subjected to the abstract-reading stage, which resulted in 71 articles eligible for full-text reading. After this stage was over, only 11 articles that had fully met the eligibility criteria defined in the systematic review remained in the study. The study selection flowchart is shown in Figure 1.

Figure 1. Systematic review flowchart.



Features of the analyzed studies

The main features of studies included in the present review, which focused on analyzing the intestinal microbiota of pregnant women and its influence on perinatal outcomes, are shown in Table 2. The sample size of the selected studies ranged from 16 to 1.479 women, whose chronological age ranged from 20 to 40 years old. Some studies did not provide information about gestational age, whereas others included pregnant women in all gestational trimesters.

More than 50% (n= 7) of the analyzed studies were carried out in China[18,20,22,23,24,25,26]. The other studies were carried out in Japan[26], Africa[6,13] and only one was carried out in the American continent[19]. For the analysis of intestinal microbiota, all articles used fecal samples, with genetic extraction of nucleic acids such as deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), and sequencing of specific genes from fecal. In total, 55,5% (n= 7) of the analyzed studies assessed pregnant women with human immunodeficiency virus[6,13], pre-eclampsia[26], hyperthyroidism[22] and gestational diabetes mellitus[23].

Despite the identification of eight adverse perinatal outcomes, only four were identified in the analyzed studies that evaluated low-risk pregnant women. These included miscarriage[20], intrauterine growth restriction[18], birth weight[17,18,24], and head circumference[26] (Table 3). When high-risk pregnancies were analyzed, six outcomes were identified in the studies, including fetal abdominal circumference[21], femoral length[21], birth weight[6,13,23,25], head circumference[21], premature birth[19], and gestational weight gain[22] (Table 4). Some of these outcomes were associated with complications in the analyzed studies, such as low birth weight[6,25] and intrauterine growth restriction[18], whereas others have only evidenced microbiota contribution to the assessed markers.

More than thirty intestinal microorganism strains were associated with perinatal outcomes in the current research. Some studies have directly associated microbial profile with outcome (birth weight), without describing the related strains[17,24,25]. Of the three studies identified that investigated the microbial profile, none specified the strains. One of these studies analyzed the top 30 microbial taxa and their association with the outcome[17]. Another correlated less abundant genera during pregnancy with the outcome without specifying them[25]. The last study highlighted the properties of bacteria associated with the outcome without detailing which properties were studied[24].

Most of these studies have managed to identify some strains linked to the aforementioned outcomes, such as those from the families Eubacteriaceae[21], Lachnospiraceae[23], Ruminococcaceae[23], *Parabacteroides*[26], and the genus *Streptococcus*[26].

Assessing the quality of the selected studies

The analysis of the methodological quality of the articles included in this review revealed a variety of ratings. These assessments were detailed in Table 5, where the studies were evaluated according to their design. Most studies satisfactorily met the quality requirements, reflecting a robust foundation for the analysis and interpretation of the presented results. The study results indicate consistency in quality, ranging from 70% to 100%. A high methodological quality was highlighted in several studies, with a rate of 91.6%. This suggests that the designs and execution of the included studies were robust, increasing confidence in the conclusions of this review.

DISCUSSION

In order to ensure the well-being of both mother and fetus, it is essential to apply thorough analysis to elements capable of increasing the likelihood of adverse perinatal outcomes that, in their turn, can lead to negative consequences, both in the short- and long-run. The current review covers twelve studies focused on investigating associations between gut microbiota and a wide variety of outcomes affecting both maternal and fetal health.

These findings have emphasized the importance of understanding gut microbiota impacts on both maternal and child's health. Comprehensive analysis helped identify eight significant results in the analyzed studies, namely: fetal demise, fetal abdominal circumference, intrauterine growth, femoral length, weight, head circumference, premature birth and. gestational weight gain. These results were associated with more than 30 different microorganism types.

However, some of these studies have associated the microbiota of women with gestational disorders such as gestational diabetes, preeclampsia, and human immunodeficiency virus with adverse perinatal outcomes. It is known that such diseases can significantly affect the composition and diversity of the microbiota during pregnancy. Nevertheless, these findings can help understand the complex interaction between gestational disorders, maternal microbiota, and perinatal outcomes, thereby improving prevention, diagnosis, and treatment strategies for these conditions.

In addition, it is important to emphasize that some microbial strains do not have their physiological effects fully understood, yet, because this research field remains relatively new in the literature. Furthermore, understanding the complexity of microbial diversity often results in some bacteria lacking precise taxonomic classification. This may occur due to a lack of detailed studies on their phylogeny or the recent discovery of these microorganisms. Recognizing this reality is crucial for us to understand that bacterial taxonomy is constantly evolving.

Initially analyzing the adverse outcomes associated with low-risk pregnant women, Liu et al.[20] observed positive association between bacterial strains of the phyla *Firmicutes, Spirochaetae, Fibrobacteres,* and *Tenericutes*, the family Prevotellaceae, the order Bacteroidales, and the genus *Eubacterium,* and spontaneous abortion (or miscarriage) cases. This term refers to involuntary fetal loss before the 20th gestational week, which poses risks to mothers' physical and emotional health[27]. Physical risks comprise complications, such as excessive bleeding, uterine infection and retention of fetal tissue remains[27]. With respect to emotional risks, miscarriage can trigger a wide range of significant emotions like sadness, grief, guilt, anxiety and depression[27].

It is worth emphasizing that *Eubacterium*, which is often detected in the first gestational trimester, is one of the bacterial groups associated with miscarriage. This group is closely linked to induced production of anti-inflammatory butyrate, which is a short-chain fatty acid that plays a crucial role in the intestine by providing anti-inflammatory effects due to its ability to modulate the immune response and to regulate inflammation in the intestinal tract.

The herein conducted analysis has

evidenced association between eight bacteria and intrauterine growth restriction, with emphasis on its association with *Streptococcus*. These bacteria play vital roles in digestion, nutrient metabolism and immune system modulation processes. However, certain Streptococcus species can also lead to infections or health issues in the gastrointestinal tract[25]. This study established direct links between intrauterine growth restriction and Streptococcus, which can lead to low-birth-weight newborns, increase the risk of respiratory and feeding complications, of hypoglycemia, as well as of heart issues and neurological complications[25]. In addition, this association can also contribute to developing different diseases in adulthood and, in the most severe cases, it can increase perinatal mortality rates[25].

Studies carried out by Yang et al.[24] and Lv et al.[25] associated full microbial profile during pregnancy with birth weight development. On the other hand, Chandiwana et al.[6], He et al.[18], Gough et al.[13] and Xu et al.[23] have emphasized that increased number of bacteria, such as *Spirochaetes* (including: *Seillonellaceae* and *Treponema*), *Candidatus Arthromitus, Thermohydrogenium* and *Roseomonas*, among others, may be directly linked to adequate fetal weight during pregnancy. Bacteria belonging to the phylum *Firmicutes* (*Ruminococcaceae, Lachnospiraceae* and Eubacteriaceae) play a relevant role in the recorded resistant starch-degradation rate[13]. However, excessive or unbalanced fermentation released by this degradation process can potentially increase local inflammation and, consequently, contribute to the aforementioned outcome[13]. According to these findings, maternal gut microbiota composition can play a crucial role in influencing fetuses' birth weight and healthy development; it is worth noting that such association was found in both high-risk and low-risk pregnant women.

Regardless of the gestational period's severity, the studies analyzed here also demonstrated a significant association between the newborn's head circumference and the incidence of bacteria, such as *Lachnospiraceae*, *Veillonellaceae*, *Parabacteroides* and *Eggerthella*. Head circumference is an important measurement capable of indicating newborns' brain development and general health, besides being relevant to assess fetal growth and neurological development[28-29]. Assumingly, changes in intestinal microbiota described in these studies can lead to a systemic inflammatory condition capable of triggering head circumference restriction[30].

As indicated by Sato et al.[26], genus Parabacteroides is highly prevalent in patients predisposed to vaginal colonization, and it triggers the release of inflammatory cytokines in placental tissues or in the amniotic fluid. Accordingly, one can infer that systemic inflammatory conditions deriving from maternal intestinal microbiota can affect fetal development[30]. The literature has shown that inflammation processes occurring during pregnancy are associated with limitations in fetal head circumference, as well as interference with neurological development, due to the action of pro-inflammatory cytokines and chemokines[30].

Despite being associated with high-risk pregnancies, the outcomes found can provide insights, as they may pose risks to both the mother and the fetus, such as premature birth being one of the outcomes associated with gut microbiota. Although it is defined as childbirth before completing 37 gestational weeks, it is seen as the main cause of death in children under the age of five years[26]. Children who survive premature birth often face challenges linked to neurodevelopment, cognitive deficiencies, as well as to behavioral and emotional impairments[30-31].

Gershuni et al.[19] identified a likely association between decreased number of *Betaproteobacteria* bacteria in a group of 48 pregnant women and premature birth. These bacteria have short-chain fatty acids as metabolites. In addition, although they are often found in the human intestinal microbiota, reduced amounts of them can contribute to systemic and local inflammatory processes, as well as can have negative influence on labor and potentially increase the risk of premature birth[33].

According to the World Health Organization (WHO), 60%-80% of newborns who do not survive are classified as premature and/or small for gestational age, and it highlights the importance of taking these measurements[34]. It is essential to emphasize that premature and low birth weight children face risk of death 2 to 10 times higher than that observed for those born at term, with adequate weight[34]. This vulnerability highlights the importance of investigating factors capable of affecting child development, such as intestinal microorganism strains, which the herein conducted analysis has shown to be linked to birth weight, and indicated its likely significant impact on children's development and health.

Fetal femur length is a bone assessment carried out during the second gestational trimester, in compliance with international guidelines. This anthropometric measurement was defined as perinatal outcome associated with intestinal microbiota in some of the herein assessed studies. This indicator is used to detect aneuploidies and skeletal dysplasia, among other genetic anomalies[35]. Femoral length shorter than the expected may also be associated with intrauterine growth restriction or with the birth of neonates classified as small for gestational age[36]. The herein conducted analysis highlighted the association between bacteria belonging to families *Enterobacteriaceae* and *Lachnospiraceae* and this anthropometric parameter. It is worth emphasizing that the literature highlights close associations between these bacteria and several metabolites involved in hosts' carbohydrate metabolism. Yet, there is the potential for these bacteria to exacerbate gestational issues capable of affecting fetal development.

Measuring fetal abdominal circumference during pregnancy is extremely important to help preserve the gestational period and avoid the risk of adverse outcomes, since it provides crucial information about fetal growth and contributes to maternal health assessment[37-38]. This procedure enables monitoring fetal growth to check whether it is happening properly or whether there are issues, such as excess fetal growth or restriction. Furthermore, fetal abdominal circumference is a relevant indicator at the time to define the delivery type to be adopted. Excessively large abdominal circumference indicates the need of performing cesarean section, whereas smaller circumference measurements can enable uncomplicated vaginal birth[37-38].

The current review identified studies that have associated fetal abdominal circumference with intestinal microbiota, mainly with bacteria like *Lachnospiraceae, Ruminococcaceae* and *Enterobacteriaceae*. *Enterobacteriaceae* is often found during the third gestational trimester and it prevails in pregnant women with pre-eclampsia. Therefore, it increases gestational risk because it induces pro-inflammatory pathways and changes in molecules associated with the intestinal barrier in the small intestinal tissue during translocation to internal organs[7,39-40].

The current review has also evidenced association between intestinal microbiota and weight gain during pregnancy, based on findings by Liu et al.[20]. It may have implications for both the mother and the fetus. Insufficient weight gain during pregnancy can increase the risk of premature birth, as well as of low-birth-weight newborns and nutritional deficiencies[41]. On the other hand, excessive gestational weight gain can lead to complications, such as gestational diabetes, hypertension and complications during childbirth[39]. Association between bacterial family Porphyromonadaceae and gestational weight gain was herein identified. The literature suggests that, despite limited knowledge about these bacteria, they may play a peculiar role in susceptibility to obesity in pregnant women with hypothyroidism during pregnancy[19].

It is worth emphasizing that all studies included in this review focused on assessing participants' intestinal microbiota through fecal analysis. This analysis type was mainly selected due to its less invasive approach, since it does not require endoscopic procedures or aspirations, unlike duodenal aspirates[42].

The current review was conducted by taking into consideration limitations inherent to the analyzed studies and the current availability of evidence. Although it followed a research protocol registered at PROSPERO and performed meticulous data extraction for comprehensive analysis purposes, it is important pointing out the limited number of studies on this topic available in the literature and the remarkable heterogeneity in the analyzed data, such as gestational age, sample size, location, and age.

Furthermore, some of the reviewed studies focused on investigating women with pregnancy issues, leading to reflections on the uncertainty regarding the substantial role played by the intestinal microbiota in the development of different diseases and symptoms, as well as the likelihood of certain health conditions influencing microbiota composition.

Finally, although gaps in the literature are yet to be filled, the presented evidence has emphasized the urgency of carrying out further in-depth research in this field to help better understand these complex interactions.

It is noticeable that several factors, such as diet, age, medication use, physical activity and nutritional status, can influence the intestinal microbiota, although they were not addressed in the current review. These elements play a significant role in the composition of the microbiota and should be taken into consideration in future investigations. Therefore, observational studies focused on investigating mothers' intestinal microbiota during pregnancy should be conducted, with emphasis on the assessment and adequate control of associated risk factors.

CONCLUSION

This review highlighted the existence of an association between intestinal microbiota and adverse perinatal outcomes, such as fetal demise, fetal abdominal circumference, intrauterine growth, femoral length, weight, head circumference, and premature birth, with over thirty strains of intestinal bacteria.

Although the associations are linked to pregnancies of both low and high risk, it is expected that these findings will serve as a basis for the development of protocols for monitoring the microbiota of pregnant women, as well as for the development of therapies that support the development of an adequate microbiota.

Table 2. Features of studies aimed at assessing maternal fecal microbiota

First author, year	Country	Study type	Gestation	Sample size (control)	Sample size (case)	Pregnant women's age (control)	Pregnant women's age (case)	Gestational age (control)	Gestational age (case)	Sample	Sequencing Method
Chandiwana, 2023[6]	Africa	Cross-sectional	HIV+	59	35	24.0 (21.0–29.0)	32.0 (28.0–34.5)	35.5 (32.5–37.3)	34.3 (32.7–36.7)	Stool	16S rRNA (V5-V6)
Dreisbach, 2023[17]	Not included	Longitudinal cohort	Habitual risk	102	NA	28.9 (±5.0)	NA	NI	NI	Stool	Unspecified
He, 2023[18]	China	Case - control	Habitual risk	8	8	32.25 (±4.46)	31.88 (±2.3)	39.3 (±0.83)	38.38 (±0.74)	Stool	Unspecified
Gershuni, 2021[19]	United States of America	Case - control	PE	32	16	28.38 (± 5.77)	28.88 (± 4.92)	20-26	20-26	Stool	16S

Gough, 2021[13]	Africa	Case - control	HIV+	110	97	27.2 (± 6.7)	31.2 (± 5.9)	1st:21, 2nd: 56 and 3rd: 15.	1st: 13, 2nd: 65 and 3rd: 8.	Stool	Shotgun metagenomics
Liu, 2021[20]	China	Case - control	Habitual risk	19	41	32.4 (± 4.7)	31.3 (± 5.0)	NI	NI	Stool	16S rRNA (V3-V4)
Wang, 2020[21]	China	Case - control	GDM	48	59	29.19 (± 3.04)	30.56 (± 4.24)	NI	NI	Stool	16S rRNA (V3-V4)
Wang, 2020[22]	China	Case-control	HTO	31	30	32.26 (± 4.04)	30.04 (± 4.93)	37-40	37-40	Stool	16S rRNA (V3-V4)
Xu, 2020[23]	China	Case - control	GDM	30	30	32.3 (± 4.3)	33.7 (± 4.7)	38.5 (±0.8)	38.3 (±0.7)	Stool	16S rRNA (V3-V4)
Yang, 2020[24]	China	Cohort	Habitual risk	1479	NA	30.6 (± 4.3)	NA	9-37	9-37	Stool	16S rRNA (V4)
Lv, 2019[25]	China	Cohort	PE	72	78	29.7 (± 4)	32.2 (±5.5)	39.8 (± 1.3)	31.2 (± 4.2)	Stool	16S rRNA (V4)
Sato, 2019[26]	Japan	Cohort	Habitual risk	51	NA	34 (± 5.0)	NA	NI	NI	Stool	16S rRNA (V1–V2)

Subtitles: HIV (human immunodeficiency virus); GDM (gestational diabetes mellitus); PE (preeclampsia); HTO (hyperthyroidism); NA (not appliable); NI (not included)

Table 3. Strain association with risks of perinatal outcomes in low-risk pregnant women.

First author, year	Perinatal outcomes			
	Miscarriage	Intrauterine growth	Birth weight	Head circumference
Dreisbach, 2023[17]			Microbial profile	
He, 2023[18]		↑*Dysgonomonas* ↑*Candidatus arthromitus* ↑*Thermohydrogenium* ↑*Roseomonas* ↑Propionibacteriaceae ↑*Marinisporobacter* ↑Fusobacteria ↑*Plesiomonas* ↑*Sphingomonas*	↑*Dysgonomonas* ↑Candidatus arthromitus ↑*Thermohydrogenium* ↑*Roseomonas* ↑Propionibacteriaceae	
Liu, 2021[20]	↑Firmicutes ↑Spirochaetae ↑Fibrobacteres ↑Tenericutes ↓*Prevotella* ↓Provotellaceae ↓*Roseburia* ↓*Selenomas* ↑*Eubacterium*			
Yang, 2020[24]			Microbial profile	
Sato, 2019[26]		↑*Streptococcus*		↓*Parabacteroides* ↓*Eggerthella*

Table 4. Strain association with risks of perinatal outcomes in high-risk pregnant women.

First author, year	Perinatal outcomes					
	Fetal abdominal circumference	Femoral length	Birth weight	Head circumference	Premature birth	Gestational weight gain
Chandiwana, 2023[6]			↑Spirochaetes ↑Seillonellaceae ↑ *Treponema*			
Gershuni, 2021[19]					↓Betaproteobacteria	
Gough, 2021[13]			↑Ruminococcaceae ↑Lachnospiraceae ↑Eubacteriaceae			
Wang, 2020[21]	↓Enterobacteriaceae ↑Lachnospiraceae ↑Veillonellaceae ↓Ruminococcaceae	↑Lachnospiracea*e* ↓*Prevotellaceae* ↑Enterobacteriocea		↑Lachnospiraceae ↑Ruminococcaceae		
Wang., 2020[22]						↑*Porphyromonaceae*
Xu, 2020[23]			↑*Gemmiger*			
Lv, 2019[25]			Microbial profile			

Table 5: Critical Assessment of selected studies

Quote	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11
Chandiwana, 2023[6]	Y	Y	Y	Y	N	N	Y	Y	-	-	-
Dreisbach, 2023[17]	Y	Y	Y	Y	Y	Y	Y	Y	-	-	-
He, 2023[18]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	-
Gershuni, 2021[19]	N	Y	Y	Y	Y	Y	Y	Y	Y	AT	N
Gough, 2021[13]	Y	Y	Y	N	N	Y	U	Y	N	U	Y
Liu, 2021[20]	Y	Y	N	Y	Y	Y	Y	Y	AT	Y	-
Wang, 2020[21]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Wang, 2020[22]	Y	Y	Y	Y	Y	N	N	Y	Y	Y	-
Xu, 2020[23]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	-
Yang, 2020[24]	U	U	Y	Y	Y	Y	Y	Y	Y	AT	Y
Lv, 2019[25]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Sato, 2019[26]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	-
%	83.3%	91.6%	91.6%	91.6%	83.3%	83.3%	83.3%	100%	80.0%	70.0%	80.0%

Subtitles:Y (yes); N (no); AT (appraisal too); U (uncle

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