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Research Article

The Effect of Maternal Microbiota on Gestational Diabetes Mellitus

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Abstract

Aim: Gestational Diabetes Mellitus (GDM) is a condition identified with high blood sugar levels in pregnancy. It can increase risks for both the mother and the child, although it usually resolves after childbirth. Pregnancy outcomes are greatly influenced by the maternal microbiome, which includes the gut, vaginal, oral, and placental microbiome. GDM is associated with gut microbiome dysbiosis, which affects both the mother and child.

Methods: The purpose of this systematic review is to determine the gut microbiota composition of women with GDM. We also determine the microbial communities, which contribute a significant part to the pathophysiology of GDM. Following PRISMA guidelines, we conducted a comprehensive review of relevant studies focusing on the gut microbiota in women with GDM. Studies unrelated to GDM, non-human studies, and those lacking sufficient data were excluded to ensure relevance and quality.

Results: Our investigation demonstrated that the gut microbiota composition of GDM-affected women differed significantly from that of healthy controls. Specifically, we observed potential increases in genera such as Blautia and Collinsella among women with GDM. This review emphasizes the importance of addressing maternal microbiomes in understanding pregnancy outcomes.

Conclusion: The dysbiosis found in GDM patients' gut microbiomes suggests a potential approach to reduce potential risks to both mother and fetal health.

Keywords: Maternal Microbiome; Gut Microbiota; Gestational diabetes mellitus (GDM); Systematic Review

Introduction

The microbiome of the human stomach is a dynamic ecology that is mutually dependent on its host. The gut microbiota performs a variety of tasks, including immune system support, pathogen defence, and nutrition extraction from meals. The development of sickness is associated with changes in the microbial composition, dysbiosis, and a reduction in the diversity of gut microbiome [1]. Pregnancy is known to cause a variety of physiological changes, one of which is development of glucose intolerance and hyperglycaemia. Figure 1 shows these putative GDM mechanistic pathways and the microbiota pattern and functioning.

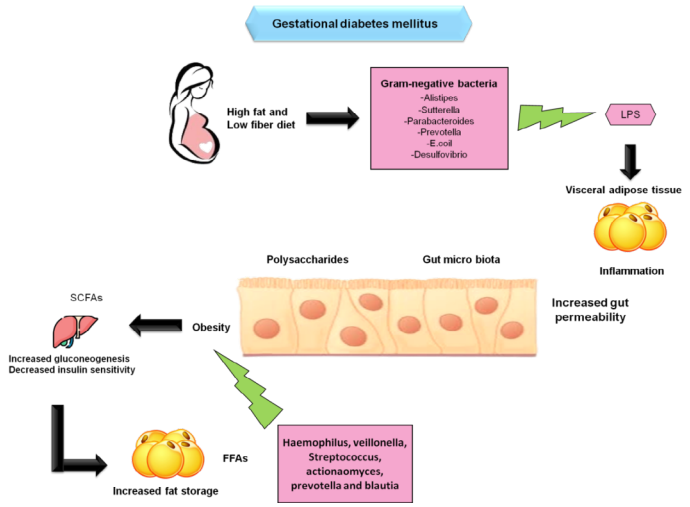

Figure 1: Overview of GDM.

GDM is connected with hormone changes that affect insulin sensitivity and pancreatic β-cell dysfunction, even though the actual etiology of the illness is uncertain [2]. Among the most frequent complications during pregnancy is GDM. It has impacted around 14% of births worldwide in recent years as the prevalence of GDM has increased. Pregnancy complications associated with GDM include shoulder dystocia, macrosomia, cesarean sections, and neonatal hypoglycemia, which can have a negative impact on both the mother and the unborn child [3]. A maternal glucose metabolism abnormality and juvenile obesity in later life were found to be substantially correlated with GDM. To prevent GDM from developing, it is important to identify probable risk factors for the disease.

Pathogenesis of GDM

Initially identified during the third and second trimesters of pregnancy, GDM is a complex condition typified by hyperglycemia [4]. It is hypothesized that women who are unable to adjust to insulin resistance acquire GDM, although the path physiological reasons behind this development remain mostly unclear. Pregnancy causes a reduction in insulin sensitivity, a flexible reaction to satisfy the growing child's physiological demands [5]. The hormones produced by the mother and placenta during pregnancy are the causes of the reduction in insulin sensitivity, such as prolactin, cortisol, estrogen, progesterone, and human placental lactogen (hPL). To preserve normoglycemia, the beta (β)-cells of the pancreas secrete more insulin [6]. Nevertheless, in certain females, the pancreatic β-cells aren't able to keep up with the growing insulin need, which results in glucose intolerance and the onset of GDM [7].

Risks of Gestational diabetes mellitus

Numerous interconnected cellular and molecular mechanisms impact the complex process of pregnancy. Numerous physiological changes, such as those related to hormones, the immune system, microbes, and metabolism, take place during pregnancy. These changes are all closely controlled to support the maintenance of homeostasis and guarantee the delivery of a healthy child [8]. Disrupting these physiological processes can result in several pregnancy-related issues that might have detrimental effects on the mother and unborn child. Research on the function of microbiota in reproductive health and related alterations throughout pregnancy and the neonatal period has gained momentum [9]. GDM is associated with an increased risk of adverse both immediate and future health outcomes for mother and her offspring. Among short-term problems moms face are caesarean deliveries, preeclampsia, increased susceptibility to infections, and gestational hypertension. Premature delivery, fetal growth restriction, macrosomia, and newborn metabolic dysfunction are among the conditions that are more common in the offspring of mothers with prenatal diabetes mellitus [10]. The aim of this extensive study is to determine the composition of the gut microbiota in women with GDM. A substantial portion of the pathophysiology of GDM is also determined by the microbial communities.

Methodology

The systematic review is created with Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) standards to ensure that the evaluation procedure is thorough and accessible.

Data source and Research system

This largest analysis is produced using the PRISMA process under discussion. The Medical Subject Headings (MeSH) keywords and free texts found in titles and abstracts are used to search the databases of Scopus, Web of Science, and MEDLINE/PubMed. Figure 2 illustrates how to include any criteria that restricted participant language, age, research design, and publication year in the search method to minimize unintentional exclusions.

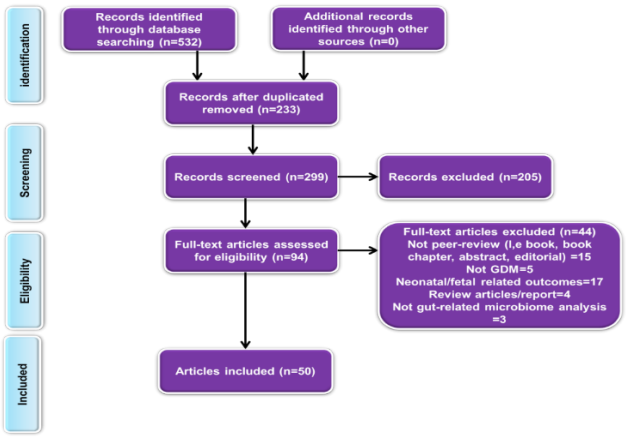

Figure 2: PRISMA flow diagram.

Selection criteria

These investigations examined the structure of gut microbiota for women with GDM as an entire group. The whole text of every article that wasn't disqualified based only on its title or abstract is gathered. Each article achieved the inclusion requirements after that is independently reviewed by the reviewers. After debating and settling any disagreements on which research to keep or discard, the reviewers decided to continue that includes the study. A third clinical examiner made decisions about any issues that were not addressed by the other reviewers. Article exclusion criteria were recorded.

Data extraction

The following details will be documented: the analysis duration, the participants' ethnicity, the size and composition of the recruitment sample, the sample location, and kind of microbiome that is studied, the procedure employed and requirements used to identify moms with GDM, and any changes in the microbiome profile when compared to the group of healthy controls.

Eligibility criteria

Original studies with women who received a GDM diagnosis at some point were scored for inclusion and involving an analysis of the gut microbiota. Abstracts from conferences, reviews, and case studies were not included. Intervention studies were also disregarded, save for information about baseline samples obtained earlier in the procedure.

Inclusion criteria

The human-based research included case control, cross-sectional, cohort, and prospective observational research examining the microbiota of GDM pregnant patients.

Exclusion Criteria

Evaluations and systematic reviews, clinical trials, animal experiments, case studies, conference articles, editor's letters, and publications unrelated to the subject of the study were among the categories of articles that were excluded. The modifications that occurred in the oral, placental, and gut microbiomes of pregnant women that acquired GDM are the findings of interest that are related with the different participants.

Result

A total of 532 articles were found when the databases were searched. Scopus provided 204 articles, Web of Science provided 160, and PubMed provided 168. Following the elimination of duplicates, 233 titles and abstracts were left for the initial screening. 205 were rejected because the study did not match the inclusion requirements, and the remaining 94 were evaluated. Following a review of the entire manuscript, 44 of these papers were removed for not matching the inclusion criteria; as a result, 50 articles were included for data extraction. Table 1 displays the precise differences in gastrointestinal microbiota indices with control groups.

Variations worldwide in intestinal microbiota indicators		Reference
The gut microbiome four genus-level biomarker categories		**[11]**
A typical group of expectant mothers	Clostridiales and Clostridium	
Only ultra-recombinant	Rehnella	
Ultra GDM recombined	*clostridium_sensu_stricto_3, and Terrisporobacter obscuribacteralejun, Deinococcus*	
Exclusive group of GDM	Ruminococcaceae_UCG014	

Characteristic gut microbiota during 24 weeks of pregnancy		**[12]**
exclusive group of GDM	*c_Deltaproteobacteria, f_Desulfovibrionaceae, and Terrisporobacter O_Desulfovibrionales,*	
Typical group of expectant women	*g-Ruminococcus*	
Typical gut microbiota during 37 weeks of pregnancy		
Ultra-recombined alone	*o_Enterobacterials and f_Enterobacteriaceae*	
Ultra GDM recombined	*g_pyramidobacter and f_Dethiosulfovibrionacae g_Eubacterium,*	
GDM group at 28 weeks of pregnancy	*f_Lachnospiraceae↑ in the g_Blautia*	**[13]**
	Lachnospiraceae↓, p_Bacteroidales ↓	
Both underweight and normal pregnancy women	*Clostridia ↑, Bacteroidia ↑*	**[14]**
GDM team	*Barnesiella ↓ , Blautia↓*	
	Genera Acidaminococcus ↑ , Clostridium ↑ , Megasphaera ↑ , Allisonella↑	
GDM team	*g_Bacteroides↑*	**[15]**
Pregnancy's third trimester	*Bifidobacterium ↑ , Peptococcus↑*	
Abnormal OGTT	*Erysipelotrichaceae UCG-003↑*	**[16]**
Abnormal FGP	*genera Enterococcus↑*	
Average blood glucose (BG)	*order Fusobacteriales ↑ , f_Prevotellaceae ↑ , g_Sutterella↑*	

(Note: g - genus, o - order, f - family, c- class, p - phylum)

Table 1: Differences in intestinal microbiota markers across groups.

Fasting blood glucose

The impact of GDM supplementation on pregnant women with GDM's fasting blood glucose (FBG) values is examined in four trials [17]. Comparing the pro-biotic-treated groups to the non-GDM-treated groups, FBG levels were shown to have decreased significantly in two of the four studies [18-22]. Pro-biotic supplements were given to patients with GDM for an equivalent intervention period using a combined evaluation that had a low risk of bias, as shown in Figure 3. Even though each study has a different calculated mean difference, it must be interpreted as an average intervention effect. Significant inter-study heterogeneity was also found (I^2= 80%, $p < 0.001$).

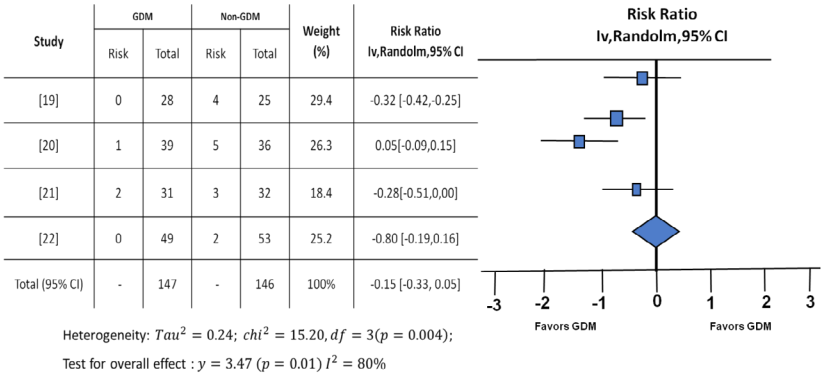

Figure 3: Effect of GMD fasting plasma glucose (mmol/L) in gestational diabetic pregnant patients.

Homeostasis model assessment-Insulin resistance (HOMA-IR)

The insulin resistance of participants is measured by computing the HOMA-IR utilizing insulin and fasting glucose levels in four trials [23]. The research used GDM supplements and compared the insulin resistance of intervention and control groups revealed no differences, significant decreases in insulin resistance were observed in three trials involving women captivating GMD [24-28]. Figure 4 show that GDM $95\%\ (CI\ -1.24, -0.14)$ supplementation has a statistically significant impact favouring it over non-GDM $(p\ =\ 0.01)$. Between-study heterogeneity was found in significant amounts across trials $(I^2\ =\ 80\%, p\ <\ 0.01)$.

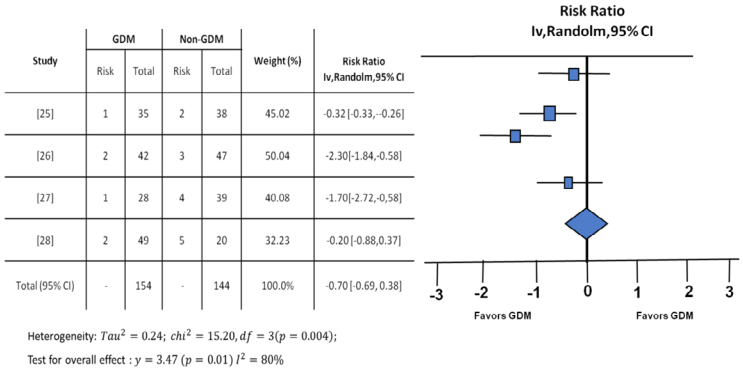

Figure 4: Effect on HOMA-IR of pregnant women with gestational diabetes.

Low-density lipoproteins (LDL)-Cholesterol

The GDM group showed a substantial attenuation of the typical increase in LDL and total cholesterol [29-31] that is typically found during the late stages of pregnancy (both $p < 0.05$). As seen in Figure 5, the study found that there is a substantial decrease in cholesterol the GDM group, yet the overall cholesterol remained unchanged $(p\ =\ 0.25)$ and LDL cholesterol $(p\ =\ 0.05)$ with the groups under treatment and control.

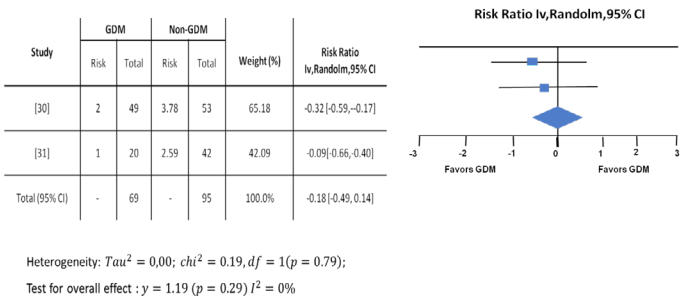

Figure 5: Effect on LDL cholesterol $(mmol/L)$ in gestationally diabetic pregnant women.

Gestational Weight Gain

The previous two weeks included a weight gain of an eight-week intervention and was significantly lower in the GDM group ($0.85 \pm 0.16\ kg\ vs. 1.26 \pm 0.21\ kg$,) than in the non-GDM group. This difference was significant even after correcting for daily energy intake $(p < 0.05)$. In the last three studies, there were no differences in the rise of gestational weight with both control and intervention groups [32]. Additionally, two investigations found no discernible changes in the birth weights of babies delivered to women that obtained the antibiotics and those moms received the non-GDM [33].

GDM-affected women's gut microbiomes

Among several categories of expectant mothers with GDM, a distinct pattern of microbiome modifications is identified into comparison women that failed to develop in the control groups, even though each study analysis was conducted at different times during the early and late phases of pregnancy. *Proteobacteria, Actinobacteria, Fusobacteria, Verrucomicrobia*, and *Firmicutes* have all been shown to have significant changes in mothers with GDM's gut microbiome.

Regarding the *Firmicutes*, several studies reported a rise in their frequency, often manifesting as a rise in the ratio of *Firmicutes* to *Bacteroidetes*. Pregnant women with GDM had a markedly altered gut microbiota overall, with the phylum Firmicutes showing the highest increase. The phylum Bacteroidetes exhibited a similar discrepancy, with most studies showing an increase, showing no difference in the studied groups, and one showing a decline. The prevalence of phylum Proteobacteria varied among the pregnant GDM patients of gut microbiomes [34].

According to [35], the actinobacteria phylum was expanded; nevertheless, in a few other investigations, its expression was shown to be reduced. There is an increase in *Fusobacteria* and primarily *Verrucomicrobia*. Table 2 demonstrates that the phylum Bacteroidetes were more common in women with GDM's gut microbiota, *Firmicutes*, and *Verrucomicrobia*, but lower expression of the phylum actinobacteria. For the most part, women with GDM have enriched gut microbiota in *Actinomyces*, *Bacteroides, Blautia, and Prevotella genera*, whereas *Bifidobacterium* and other genera were deficient.

Microbiome	**Gut microbiota of GDM-affected women**		
Risks	**Increased**	**Variable**	**Decreased**
Phylum	Firmicutes Bacteroidetes Verrucomicrobia	Proteobacteria	Actinobacteria
Class	Gammaproteobacteria	-	-
Genus	Blautia Desulfovibrio Bacteroides Lachnospiraceae Actinomyces	Collinsella Eubacterium Lactobacillus Rothia	Bifidobacterium
Family	Enterobacteriacea Coriobacteriacea Micrococcaceae Ruminococcaceae Leuconostocaceae	-	--
Order	Coriobacteriales Actinomycetales	-	-

Species	Bacteroidescaccae Bacteroides massiliensis Bacteroides thetaiotaomicron	-	Bacteroidesvulgatus Lactobacillus rogosae Prevotellacopri

Table 2: GDM patients of gut microbiota in female patients.

Oral microbiota alterations in GDM-affected women

Firmicutes is a smaller phylum, according to the study [36]. As demonstrated in Table 3, the pattern regarding alteration is less evident when compared to the women with GDM's gut microbiota, since Phyla and genera remained the same. A wide range of modifications to the families and genera were noted in the remaining studies. For example, there was a rise in the genera Enterobacteriaceae, Black-pigmented bacteria, actinomycetes, Christensenellaceae, Ruminococcaceae, and Bacterosis bacilli, while there was a fall in the genera Lactobacilli, Bifidobacterium, and oral streptococci [37].

Microbiome	**GDM patients' oral microbiomes**		
Risks	**Decreased**	**Variable**	**Increased**
Phylum	Firmicutes	Proteobacteria	-
Class	-	-	-
Order	-	-	-
Family	-	-	Enterobacteriaceae Christensenellaceae Ruminococcaceae Veillonellaceae
Genus	oral streptococci Bifidobacterium Lactobacilli	-	Actinomycetes Capnocytophaga Leptotrichia Prevotella
Species	-	-	-

Table 3: Changes in oral microbiota of GDM patients.

Vaginal microbiome changes of women with GDM

Table 4 indicates that the mother's status with GDM has an impact on the vaginal microbiota, even though the quantity of articles may not be adequate to reach an assessment. According to [38], there is a drop in the constitutional ratio of vaginal Linersclone and an association between the presence of GDM for *Lactobacillus fructivorans*, *Lactobacillus listeri*, and *Lactobacillus amylovorus*.

Although there is an increase in the phyla Firmicutes and Proteobacteria, difference is not statistically significant. Additionally, [39] showed that the GDM group had greater alpha diversity. The author found no differences in the vaginal microbiota between the control groups. In addition, a research investigation found that women with gestational diabetes had different microbiological compositions in their oral, vaginal, and rectal cavities compared to those with healthy pregnancies. These changes are demonstrated by a skewed predominance for several genera.

Microbiome	vaginal microbiota of GDM patients	Risks	Genus	Family	Phylum	Species
		Increased	Veillonella Bacteroides Enterococcus Brevibacterium Lactobacillus Fusobacterium	Enterobacteriaceae Sutterellaceae Lachnospiraceae Aerococcaceae	Proteobacteria Firmicutes	Lactobacillus amylovorus Lactobacillus

Table 4: Changes in the vaginal microbiome of GDM patients.

The gut microbiota's metabolic function in the development of GDM is summarized in Table 5. Regardless of their GDM state, pregnant women of gut microbial distribution throughout the first trimester were the same as stable non-pregnant females. The diversity of Actinobacteria and Proteobacteria rose throughout the later stages of pregnancy, whereas Faecalibacterium decreased.

Reference	Gut microbiome in GDM	Metabolic outcome				
		Insulin	blood glucose (BG)	Total cholesterol (TC)	Adiposity	Adipokine
[40]	Proteobacteria	-	↑	↑	↑	-
[41]	Blautia	-	↑	-	-	-
[42]	Faecalibacterium	-	↑↓	↑	↓	-
[43]	Actinobacteria	-	↑	↑	-	-
[44]	Collinsella	↑	-	-	-	-

(Note: ↑=increased abundance, ↓=decreased abundance)

Table 5: Gut microbiota types and their effects on GDM metabolic factors.

Discussion

Pregnancy causes changes in several systems, including the microbiome. During the gestational period, the microbial communities exhibit a discernible pattern. It's unknown if these modifications are a typical result of the physiological responses that occur throughout pregnancy and if they represent a separate manifestation that contributes to the physiological state. The research primarily focuses on the modifications to the microbiota linked to GDM, as demonstrated by findings, in comparison to normal groups, GDM patients display a particular signature [45]. Although there is a drop in their abundance in several studies, the bulk studies revealed an enrichment in the *phylum Firmicutes* and *Bacteroidetes*, accounting for the primary alterations observed [46]. This modification is accounted by the recognized role of Bifidobacteria in the intracellular consumption of short oligosaccharides, a breakdown of carbohydrates, and fermentative metabolism [47]. Furthermore, a consistent result across all research has a large rise in the genus Blautia. This species is linked to metabolic illnesses, Body Mass Index (BMI), and glucose intolerance; this discovery is noteworthy because of the supported information.

The expected rise in LDL and total cholesterol levels during pregnancy appears to be mitigated by the GDM treatment [48]. The VLDL cholesterol and triglyceride levels were significantly reduced, while LDL-cholesterol levels neared significance. Beneficial gut bacteria have a positive effect on lipid metabolism by producing secondary bile acids, which are unavailable for hepatic recirculation. The circulating cholesterol and replacement bile acids must be produced by the liver [49]. The current investigation found no statistical significance in a pooled analysis involving LDL-cholesterol information for GDM-affected women from both trials. It's possible that trials lasting longer than eight weeks produced results with improved impact sizes.

Probiotic supplementation is associated with considerable decreases in insulin resistance in women with GDM, which might lessen the need for insulin later in pregnancy [50]. In addition to dietary adjustments and increased physical activity, Metformin and insulin are prescribed as part of the current GDM treatment plan to achieve the desired blood glucose levels.

Strengths and limitations

Despite several obstacles, a definitive relationship of GDM and a pattern of microbiome changes were established, even though the changed signature pattern is considerably noticed in our systematic evaluation. All of the studies suggest that there is a genuine relationship between GDM and the microbiota in mothers and their offspring, despite these disadvantages. This point is also covered in earlier research that demonstrated a microbiome linked to GDM and a study showed a rise in the GDM genera of *Collinsella* and *Blautia*. There were inconsistent data and no microbiome patterns specific to GDM were determined. The development of techniques to change the microbiome might influence preventing and lessening the possible impacts of GDM. However, additional evidence is required, and fragmentary studies should take this result into account in their upcoming investigations.

Conclusion

This research focused particular attention on gestational diabetes mellitus, a frequent condition that has unintended consequences for both women's health. The assessment of modifications to the microbiota of pregnant GDM patients is one method that is mentioned. To avoid altering every natural gut flora, which raises the risk of illness, pregnant individuals at risk of developing GDM are recommended to eat fewer high-fat meals and more foods high in fibre. The findings of this extensive study indicate a clear relationship with microbial communities and GDM. Pregnant women's gut, oral, and vaginal tracts all showed distinct patterns of microbiome changes. Despite certain limitations, these findings are intriguing and promising for the development of human microbiome-focused techniques to treat and modulate the maternal microbiome in next-generation GDM and non-GDM patients. The results and effectiveness of these therapy approaches should be evaluated in future research.

Additional Information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical Statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans in this study.

The authors declared that no commercially available immortalized human and animal cell lines were used in the present study.

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Author Contributions

All authors have contributed equally.

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