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Exploring the influence of microbiota on gestational diabetes and its potential as a biomarker

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Gestational diabetes mellitus (GDM) represents a significant health concern during pregnancy, impacting both maternal and fetal well-being. While conventional diagnostic protocols typically rely on blood glucose levels in the latter stages of pregnancy, there is a pressing need for early detection methods to mitigate potential risks. A plethora of glucose-based or non-glucose-based biomarkers have been investigated for their potential to predict GDM in early pregnancy. Though specific biomarkers showed promise in predicting GDM, their clinical usage has been constrained by the lack of validation and limitation in translating them into routine clinical use. This review aims to highlight and discuss the potential and practical utility of existing biomarkers and emergent biomarkers, such as microbiomes, in diagnosing GDM. A comprehensive analysis of recent studies reveals significant alterations in the composition and diversity of microbiota among women with GDM, suggesting their potential utility as predictive markers for this condition. For instance, distinct microbial profiles characterized by an increased abundance of *Eisenbergiella*, *Tyzzerella* 4, and *Lachnospiraceae* NK4A136, alongside decreased levels of *Parabacteroides*, *Parasutterella*, and *Ruminococcaceae* UCG 002, correlated with fasting blood glucose levels, hinting at their relevance in early GDM detection. Furthermore, proposed microbiota-targeted panels demonstrated promising predictive accuracy. Beyond gut microbiota, recent investigations have also explored the potential of oral microbiota as predictive biomarkers for GDM. Studies have highlighted the discriminatory capacity of specific oral microbes, such as *Streptococcus* in saliva and *Leptotrichia* in dental plaque, in distinguishing GDM from healthy pregnancies. Moreover, the examination of gut microbiota-derived metabolites has shown promising results in serum-based GDM prediction. These findings collectively underscore the potential of microbiota and its metabolites as valuable biomarkers for the early detection of GDM. However, further research is warranted to elucidate the mechanistic links between microbial dysbiosis and GDM pathogenesis, ultimately facilitating the development of targeted therapeutic interventions and personalized management strategies.

KEYWORDS

fasting plasma glucose (FPG), oral glucose tolerance test (OGTT), World Health Organization (WHO), American Diabetes Association (ADA), National Institute for Health and Care Excellence (NICE), International Association of Diabetes and Pregnancy Study Groups (IADPSG), International Federation of Gynecology and Obstetrics (FIGO)

1 Introduction

Gestational Diabetes Mellitus (GDM) is characterized by varying degrees of severe glucose intolerance with onset or first seen during pregnancy (American Diabetes Association, 2020b). GDM often develops between the 24th and 28th week of gestation. In middle and later pregnancy, GDM is one of the most prevalent maternal complications (Guariguata et al., 2014; Simjak et al., 2018; Kim et al., 2021). GDM is estimated to affect 10%–25% of all pregnancies globally, and its prevalence depends on diagnostic guidelines (Lauring et al., 2018), screening procedures (Nguyen et al., 2018), and obesity (Huvinen et al., 2018). The prevalence of GDM has risen in recent decades in parallel with Westernized living and conceiving at an older age, accompanied by an economic boom (Simjak et al., 2018). Specific racial and ethnic groups, including Hispanics, Asians, and Black women, reported higher odds of developing GDM than non-Hispanic Whites (CDC, 2020; Gardner et al., 2022). GDM is typically asymptomatic but is associated with adverse maternal outcomes like preeclampsia (Yogev et al., 2010), postpartum hemorrhage, and increased cesarean deliveries (O'Sullivan et al., 2011). It also leads to undesirable infant outcomes such as macrosomia, neonatal hypoglycemia (HAPO Study Cooperative Research Group et al., 2008), perinatal mortality (Wendland et al., 2012), and large gestational age (Saravanan et al., 2020). GDM can lead to long-term consequences in mothers, such as an increased risk of type 2 diabetes (Hakkarainen et al., 2016), metabolic syndrome (Hakkarainen et al., 2018), and cardiovascular diseases (Fraser et al., 2012). Additionally, there is a significant risk of recurrent GDM in subsequent pregnancies, with estimates ranging from 29–80% (Schwartz et al., 2016). The children of mothers with GDM also face long-term health risks, including a higher incidence of obesity, type 2 diabetes, and neurodevelopmental disorders (Farahvar et al., 2019). These consequences highlight the importance of early detection and proper management of GDM to minimize health impacts on both mother and child.

Various countries use different diagnostic approaches to assess the prevalence of GDM due to the lack of uniform criteria for its diagnosis. Currently, most GDM diagnoses are made in the later stages of the second trimester (Rani and Begum, 2016), putting the vulnerable fetus at risk for intrauterine metabolic abnormalities and epigenetic modifications (Elliott et al., 2019; Chu and Godfrey, 2020). Hence, early prediction and diagnosis of GDM, preferably prior to the onset of elevated blood sugar levels, including during pre-pregnancy, are crucial. This timely identification would facilitate proactive measures to mitigate complications and health hazards linked with GDM. The identification of GDM biomarkers during early pregnancy and even pre-conception could enhance existing clinical risk assessments, pinpointing high-risk individuals who could benefit from tailored strategies to mitigate GDM development. Advancements in metagenomics have allowed the study of the human microbiota, providing valuable insights into its diagnostic and therapeutic potential (Martin et al., 2014; Malla et al., 2018). Quantitative analysis of biological samples using next-generation sequencing methods has yielded extensive data on the role of microbiota as a diagnostic tool across various diseases (Qin et al., 2012; Yu et al., 2017). Exploring microbiota as a novel biomarker holds promise for the future diagnosis of GDM. This review aims to discuss and evaluate existing screening and diagnostic strategies for GDM. Additionally, we provide insights into emerging biomarkers, with a particular focus on microbiota, that exhibit potential for predicting GDM.

1.1 Screening strategies of GDM

The detection of GDM involves a screening process followed by necessary diagnostic measures, with methods and diagnostic thresholds varying among countries (International Diabetes Federation, 2019; American Diabetes Association, 2020a). Three main approaches to GDM screening exist: universal, two-step, and selective. Universal screening involves testing all pregnant women, regardless of symptoms or glycemic status, with a non-fasting 50 g glucose challenge test (GCT) to assess the likelihood of GDM (Tieu et al.). Two-step screening includes the 50 g GCT followed by a 3-hour 100g oral glucose tolerance test (OGTT) for those exceeding the GCT threshold (Vandorsten et al., 2013; Cundy et al., 2014). Selective screening examines women with specific risk factors, such as high body mass index (BMI), family history of GDM, smoking history, and age at pregnancy (Tieu et al.). In 2010, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) proposed a one-step approach using a 2-hour, 75 g OGTT for all pregnant women at 24–28 weeks (International Association of Diabetes and Pregnancy Study Groups Consensus Panel et al., 2010). This approach has gained acceptance by organizations like the World Health Organization (WHO), the American Diabetes Association (ADA), the International Federation of Gynecology and Obstetrics (FIGO), and the Australasian Diabetes in Pregnancy Society (ADIPS). However, not all major health organizations worldwide, including the American College of Obstetricians and Gynecologists (ACOG) and the National Institute for Health and Care Excellence (NICE), have endorsed the IADPSG screening and diagnostic approach. Due to the array of recommendations available, there is a lack of consensus on the screening and diagnosis of GDM. The decision of to screen for GDM or not, as well as the choice of screening approach, continues to be a subject of controversy.

2 Biomarkers for GDM screening

Multiple laboratory assays have been utilized for screening GDM, examining both direct and indirect hyperglycemic markers. Direct hyperglycemic biomarkers include fasting plasma glucose (FPG), GCT, or OGTT. In addition, indirect hyperglycemic biomarkers include glycosylated hemoglobin A1c (HbA1c) and more current biomarkers, many of which have been explored through proteomic or metabolomic studies. Nonetheless, the optimal approach for GDM detection has not been definitively established.

2.1 Glucose markers

Glucose serves as a critical biomarker in the screening, diagnosing, monitoring, and management of GDM. Over the past

decade, several guidelines have been proposed or updated to improve diagnostic accuracy and global consistency. WHO guidelines emphasized predictive accuracy rather than endorsing a specific gold standard. Typically, GDM diagnosis is confirmed through a 75 g or 100 g OGTT, with most guidelines recommending testing between 24 and 28 weeks of gestation (International Association of Diabetes and Pregnancy Study Groups Consensus Panel et al., 2010; Nankervis et al., 2014; American Diabetes Association, 2015; Imoh et al., 2017) (Table 1). However, the exact association between various OGTT parameters and pregnancy outcomes is still unknown (Feng et al., 2017) and may vary among populations (Farrar et al., 2016). Furthermore, the OGTT has limitations such as poor reproducibility (Davidson, 2002; Munang et al., 2017), dependence on ethnicity (Bonongwe et al., 2015), and time-intensive nature, as it necessitates fasting and a commitment of 2 hours to complete the test (Buckley et al., 2012). Moreover, the OGTT does not account for maternal BMI when determining the glucose load to administer (Bonongwe et al., 2015). Side effects such as vomiting, nausea, and diarrhea can also occur following OGTT administration (ACOG Practice Bulletin No. 180, 2017).

Compared to GCT and OGTT, FPG testing was reported to be more patient-friendly, rapid, economical, and reproducible (Agarwal and Dhatt, 2007). Several countries have supported using an FPG concentration of 92 mg/dL as a cut-off for increased blood sugar during the first trimester (International Association of Diabetes and Pregnancy Study Groups Consensus Panel et al., 2010; American Diabetes Association, 2015; Imoh et al., 2017). ADA and IADPSG recommended an FPG concentration ≥ 92 mg/dl, while NICE and WHO suggested an FPG concentration ≥ 100 mg/dl and 92–125 mg/dl, respectively, for diagnosing GDM (International Association of Diabetes and Pregnancy Study Groups Consensus Panel et al., 2010; NICE, 2015; American Diabetes Association, 2015; Imoh et al., 2017). However, researchers have highlighted the need for a precise cut-off of FPG for the first trimester (Sacks et al., 2002) as the current cut-offs are not relevant at earlier gestational stages (Sacks et al., 2018). In addition, the sensitivity and specificity of FPG for screening GDM showed significant regional variations (Agarwal et al., 2011; Zhu et al., 2013a; Trujillo et al., 2014), and its low specificity makes it unsuitable as a standalone screening test for early pregnancy (Riskin-Mashiah et al., 2010; Zhu et al., 2013b).

In addition to OGTT and FPG, HbA1c is also an acceptable method for early pregnancy diabetes screening, as recommended by the ADA and IADPSG (International Association of Diabetes and Pregnancy Study Groups Consensus Panel et al., 2010; American Diabetes Association, 2016). However, the American College of Obstetricians and Gynecologists disapproves of HbA1c as a standalone screening test due to its low sensitivity in identifying early hyperglycemia (ACOG Practice Bulletin No. 190, 2018). While HbA1c is considered precise and accurate in non-pregnant women (Jia, 2016), studies have shown that it is subpar as a screening test for GDM (O'Connor et al., 2012). Furthermore, the diagnostic potential of HbA1c in early pregnancy and its interpretation are still uncertain, as pregnancy-specific thresholds for identifying early GDM have not been established (Göbl et al., 2014; Shinar and Berger, 2018). Hence, the validity of HbA1c during pregnancy as a diagnostic tool for early GDM remains debatable.

2.2 Non-glucose biomarkers

Despite advancements in healthcare and updated screening approaches, the diagnosis of GDM is still arguable. Challenges such as limited sensitivity, specificity, invasiveness, racial/ethnic variations, and testing costs have hindered the prediction of GDM. To address these challenges, numerous studies have investigated non-glucose biomarkers as potential diagnostic tools for GDM. These biomarkers include inflammatory markers like C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6), as well as adipocyte-derived markers such as adiponectin, leptin, and visfatin. Additionally, other biomarkers such as pregnancy-associated plasma protein A (PAPP-A),

TABLE 1 Global guidelines using FPG and OGTT for diagnosing GDM.

Establishments	Countries recommended	FPG	1 hour 75 g OGTT (post-meal)	2 hours 75 g OGTT (post-meal)	Age of gestation	References
		mg/dl	mg/dl	mg/dl	weeks	
WHO	Multiple countries	92–125	180	153–199	20–28	Imoh et al., 2017
ADA	USA/North America	≥92	≥180	≥153	24–28	American Diabetes Association, 2015
NICE	United Kingdom	≥100		≥140	24–28	NICE, 2015
IADPSG	Multiple countries	≥92	≥180	≥153	24–28	International Association of Diabetes and Pregnancy Study Groups Consensus Panel et al., 2010
ADIPS	Australasia	≥92	≥180	≥153	24–28	Nankervis et al., 2014
FIGO	Multiple countries	≥92	≥180	≥153	24–28	Hod et al., 2015

FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; WHO, World Health Organization; ADA, American Diabetes Association; NICE, National Institute for Health and Care Excellence; IADPSG, International Association of Diabetes and Pregnancy Study Groups; FIGO, International Federation of Gynecology and Obstetrics.

placental growth factor (PLGF), insulin-resistant markers, urinary markers like alanine, L-tryptophan, and serotonin, genetic markers, growth factors, glycoproteins, hormones, microRNAs, single nucleotide polymorphisms (SNPs), and DNA methylation have been explored.

However, the clinical utility of these biomarkers is still under investigation. Inflammatory biomarkers, such as CRP, are affected by factors such as limited clinical data and variations in ethnicity and immunological assays (Amirian et al., 2020). Adiponectin has shown a moderate correlation with predicting GDM, while visfatin and leptin levels have produced inconsistent results (Iliodromiti et al., 2016). Low levels of PAPP-A have been suggested as a link to GDM and insulin resistance (Ramezani et al., 2020), although conflicting findings exist (Savvidou et al., 2012; Syngelaki et al., 2015). PLGF, despite some studies indicating its potential as predicting GDM during the first trimester of pregnancy (Eleftheriades et al., 2014), lacks consistent evidence to validate its use as a dependable biomarker (Mosimann et al., 2016; Maymon et al., 2019). Reduced levels of sex hormone-binding globulin have shown associations with obesity and insulin resistance, hinting at its potential as a GDM biomarker in the first trimester (Zhang T. et al., 2018); however, its diagnostic significance is influenced by factors such as BMI, ethnic disparities, and family history (Corcoran et al., 2018).

Furthermore, urinary markers like 3-hydroxybutanoic acid, and specific amino acids, such as serotonin, valine amino acid, and L-tryptophan, have been found to increase in GDM cases during the 12^{th} and 26^{th} weeks of gestation (Leitner et al., 2017). Yet, further evaluation is warranted to determine their precise predictive and clinical significance. Genetic markers such as microRNAs, SNPs, and DNA methylation have also shown promise (Yahaya et al., 2020); however, contradictory reports (Jamalpour et al., 2018; Tagoma et al., 2018) highlight the need for further studies to determine their clinical usefulness. It is also important to note that most biomarkers have been evaluated in limited case-control studies without additional prospective confirmation, emphasizing the need for more extensive research.

2.3 Microbiota in GDM

Recent research indicates that the gut microbiota plays a significant role in the etiology of metabolic illnesses, such as diabetes (Brunkwall and Orho-Melander, 2017), cardiovascular disease (Tang et al., 2017), and obesity (DiBaise et al., 2008). Microbiota often plays a pivotal role in developing and shaping the immune and endocrine systems (Mohajeri et al., 2018; Rastelli et al., 2019). Advancements in metagenomics have provided a deeper understanding of the human microbiome, which comprises bacteria, archaea, and eukaryotes (Marchesi, 2010; Rajilić-Stojanović and De Vos, 2014). Alterations in microbiota composition have been observed in women with GDM throughout pregnancy (Liu et al., 2017) (Table 2). Specifically, the gut microbiota exhibits increased α diversity and reduced β diversity in the first trimester, while this pattern reverses in the third trimester, characterized by reduced α diversity and increased β diversity. The α diversity measures species richness and evenness within a single sample, β diversity quantifies differences in species composition between different samples or communities (Ionescu et al., 2022; Tang et al., 2022). These measures help in identifying potential alterations in microbial communities associated with GDM.

The dysbiosis or imbalance in gut microbiota diversity starts early in pregnancy, with decreased diversity observed in women with GDM. Reduced gut microbiota abundance in GDM has been associated with insulin resistance and inflammation (Le Chatelier et al., 2013). Numerous investigations have provided insights into the significant alterations in microbiome diversity in women with GDM. For example, Kuang et al. (2017) observed a higher abundance of *Parabacteroides distasonis* and *Klebsiella variicola* in GDM. They also reported a strong correlation between blood glucose tolerance levels and the ratio of overall abundances of GDM-enriched to control-enriched metagenome linkage groups. These findings suggest that the alteration of the microbiome may be directly linked to the pathogenesis of GDM.

Furthermore, Crusell et al. (2018) reported a higher abundance of phylum Actinobacteria and specific genera such as *Collinsella*, *Rothia*, and *Desulfovibrio* in the GDM women during the third trimester. These women also exhibited increased enrichment in *Faecalibacterium* and *Anaerotruncus* species, while species annotated to *Clostridium sensu stricto* and *Veillonella* showed reduced enrichment. Certain operational taxonomic units (OTUs), like *Christensenella*, have been linked to higher glucose levels (Crusell et al., 2018), whereas *Akkermansia* has demonstrated potential in enhancing insulin sensitivity (Crusell et al., 2018) and regulating metabolic syndromes (Christiansen, 2013; Dao et al., 2016). Remarkably, GDM women maintained these altered microbiota months after postpartum (Crusell et al., 2018), indicating a potential long-term impact on metabolic health. Additional studies have shown an increased abundance of *Collinsella* and *Blautia* and decreased abundance of *Sutterella* in GDM women (Crusell et al., 2018; Cortez et al., 2019; Li G. et al., 2021). Moreover, the ratio of Firmicutes/Bacteroidetes was reported to be higher in GDM women (Li G. et al., 2021). These findings underscore the potential impact of gut microbiota on GDM pathogenesis and highlight the need for further investigation in this field. Furthermore, Cortez et al. (2019) revealed an increased abundance of *Ruminococcus*, *Eubacterium*, and *Prevotella* genera, along with a reduced abundance of *Akkermansia*, *Bacteroides*, *Parabacteroides*, *Roseburia*, and *Dialister* in the third trimester of GDM women. Wei et al. (2022) found an increased abundance of *Ruminococcus bromii*, *Clostridium colinum*, and *Streptococcus infantis* in GDM women at 24–28 weeks of gestational age. Notably, *S.infantis* was associated with a higher risk of GDM (Wei et al., 2022). Moreover, GDM women exhibited a reduced abundance of genera such as *Megasphaera*, *Barnesiella*, and *Blautia* in both the first and third trimesters. Conversely, the genera *Acidaminococcus*, *Clostridium*, and *Allisonella* showed higher abundance in GDM women during these trimesters (Abdullah et al., 2022). Ye et al. (2023) demonstrated that microbiota and its short-chain acids play a role in the development of GDM, with reduced abundance of several genera (*Faecalibacterium*, *Prevotella*, and *Streptococcus*) and species (*Bacteroides coprophilus*, *Eubacterium*

TABLE 2 Abundance of microbiota in GDM.

Study by	Study location	GDM/ Non-GDM women	Age in years		Diagnosis criteria	Age of Gestation	Sample	Microbiota in GDM women
			GDM	Non-GDM				
Ye et al., 2023	China	50/54	31.74 ± 5.45	30.20 ± 4.77	IADPSG	24–28 weeks	Stool	Decrease abundance of *Bacteroides coprophilus*, *Eubacterium siraeum*, *Faecalibacterium prausnitzii*, *Prevotella copri*, and *Prevotella stercorea*
Pinto et al., 2023	Israel	44/350	33.1 ± 3.77	31.2 ± 4.43	Two-step screening	10–15 weeks	Stool	Decreased abundance of *Prevotella*
Wei et al., 2022	China	15/18	30.10 ± 3.5	26.10 ± 3.6	IADPSG/ WHO	24–28 weeks	Stool	Increased abundance of *Ruminococcus bromii, Clostridium colinum*, and *Streptococcus infantis*
Abdullah et al., 2022	Malaysia	12/26	30.42 ± 3.8	30.62 ± 4.2		<13 weeks >28 weeks	Stool	Reduced abundance of genera *Megasphaera*, *Barnesiella*, and *Blautia* Increased abundance of *Acidaminococcus*, *Clostridium*, and *Allisonella*
Li G. et al., 2021	China	23/29	29.80 ± 2.19	29.0 ± 1.88	ADA	>28 weeks	Stool	Increased abundance of *Blautia, producta*, *Clostridium spiroforme*, *Collinsella aerofaciens*, *Coprococcus catus*, *Eubacterium dolichum*, *Pyramidobacter piscolens*, *Ruminococcus callidus*, and *Ruminococcus gnavus*
Hu et al., 2021	China	201/201	28.2 ± 4.5	27.90 ± 4.0	IADPSG	6–25 and 24–28 weeks	Stool	Increased abundance of Enterobacteriaceae, *Ruminococcaceae* spp., and *Veillonellaceae* spp
Xu et al., 2020; Rastelli et al., 2019	China	30/31	33.7 ± 4.7	32.3 ± 4.3	WHO	24–28 weeks	Stool	Increased abundance of *Gammaproteobacteria* and *Haemophilus*
							Saliva	Increased abundance of *Selenomonas* and *Bifidobacterium*, and reduced abundance of *Fusobacteria* and *Leptotrichia*
Cortez et al., 2019	Brazil	36/42	35.07 ± 3.75	28.23 ± 5.68	WHO	28–36 weeks	Stool	Increased richness of *Ruminococcus*, *Eubacterium* and *Prevotella* and Reduced richness of *Akkermansia*, *Bacteroides*, *Parabacteroides*, *Roseburia*, and *Dialister*.
							Vaginal	Increased abundance of *Bacteroides*, *Veillonella*, *Klebsiella*, *Escherichia-Shigella*, *Enterococcus*, and *Enterobacter*
Crusell et al., 2018	Denmark	50/161	34.4 ± 4	33.3 ± 4.6	Two-step screening	27–33 weeks	Stool	Increased abundance of *Collinsella*, *Rothia* and *Desulfovibrio*
Wang et al., 2018	China	77/98			ADA	24–28 weeks	Saliva	Increased abundance of *Proteobacteria* and reduced abundance of firmicutes and *Leptotrichia*
Kuang et al., 2017	China	43/81	30.5 ± 3.3	28.8 ± 3.1	ADA	21–29 weeks	Stool	Increased abundance of *Parabacteroides distasonis*, *Klebsiella variicola* Decreased abundance of *Bifidobacterium, Eubacterium, Roseburia* spp.

WHO, World Health Organization; ADA, American Diabetes Association; IADPSG, International Association of Diabetes and Pregnancy Study Groups.

siraeum, *Faecalibacterium prausnitzii*, *Prevotella copri*, and *Prevotella stercorea*) observed in GDM women. Furthermore, Xu et al. (2020) found that during the third trimester of pregnancy, the gut microbiome of GDM women had higher β-diversity and an increased abundance of Gammaproteobacteria and Haemophilus. Additionally, they observed reduced α-diversity, elevated levels of *Selenomonas* and *Bifidobacterium*, and decreased levels of *Fusobacteria* and *Leptotrichia*. They further identified a significant correlation between maternal blood sugar levels and the oral microbiome, particularly in relation to *Streptococcus*, *Leptotrichia*, and *Veillonella*, suggesting a potential link between the oral microbiome and glucose tolerance in later stages of pregnancy (Xu et al., 2020).

Wang et al. (2018) reported significant oral microbiome alteration in GDM, with increased *Proteobacteria* but reduced Firmicutes and *Leptotrichia* (Wang et al., 2018). Moreover, Hu

et al. (2021) noted a higher prevalence of *Enterobacteriaceae*, *Ruminococcaceae* spp., and *Veillonellaceae* spp. very early in pregnancy (at 6–15 weeks of gestation) of GDM women. Majority of the research findings highlight an increased abundance of *Proteobacteria*, *Neisseria* (Wang et al., 2018; Li X. et al., 2021), *Prevotella* (Ganiger et al., 2019; Crusell et al., 2020), and *Capnocytophaga* (Yao et al., 2019; Li X. et al., 2021) in GDM. In contrast, a reduced abundance of *Streptococcus* (Yao et al., 2019; Crusell et al., 2020; Li X. et al., 2021), Firmicutes and *Leptotricia* (Wang et al., 2018; Li X. et al., 2021) is consistently observed across multiple studies investigating GDM women. Inconsistent findings were also noted in the study conducted by Xu et al. (2020) where they reported a reduced abundance of Neisseria in GDM. GDM is often associated with adverse perinatal outcomes as well as dysbiosis in vaginal flora (Hirji et al., 2012; Goncalves et al., 2016). It is widely accepted that pregnant women with GDM have an increased susceptibility to Candida colonization in the vagina (Guggenheimer et al., 2000; Hirji et al., 2012). Zhang X. et al. (2018) identified *Lactobacillus listeri*, *Lactobacillus amylovorus*, and *Lactobacillus fructivorans* as abundant in GDM but absent in healthy pregnant women. They further reported *Lactobacillus acidophilus* being the most abundant among *Lactobacillus*, followed by *Lactobacillus crispatus* and *Lactobacillus inersclone* in GDM women compared to healthy pregnant women (Zhang X. et al., 2018). Nevertheless, regardless of whether women had GDM or were healthy during pregnancy, they did not notice significant differences in the abundance and diversity of vaginal flora between the 28–30 weeks and 37–40 weeks gestation periods. Notably, *Lactobacillus* emerged as the dominant bacteria during both stages of pregnancy (Zhang X. et al., 2018). Cortez et al. (2019) reported an increased abundance of vaginal microbiomes such as *Bacteroides*, *Veillonella*, *Klebsiella*, *Escherichia-Shigella*, *Enterococcus*, and *Enterobacter* in GDM women (Cortez et al., 2019). The studies highlighted above emphasize the substantial role of microbiota in GDM, showcasing altered diversity and composition that impact metabolic health during pregnancy. These alterations, occurring notably in the first and third trimesters, may influence perinatal outcomes. Further investigation is needed to comprehend these alterations fully, offering insights for diagnostic and therapeutic strategies aimed at managing GDM and enhancing maternal and fetal outcomes. Collectively, these findings contribute to our understanding of GDM pathogenesis, suggesting a potential link between gut, oral, and vaginal microbiota and the development of GDM.

2.4 Microbiota as predictors of GDM

Various studies have revealed significant alterations in the composition and diversity of microbiota, suggesting their promising role as predictors of GDM (Table 3). Ma et al. (2020) observed an increased relative abundance of *Eisenbergiella*, *Tyzzerella* 4, and *Lachnospiraceae* NK4A136 in women with GDM. Conversely, their microbiota was predominantly dominated by *Parabacteroides*, *Megasphaera*, and *Eubacterium eligens*. Furthermore, fasting blood glucose levels were positively correlated with an increased abundance of *Eisenbergiella* and *Tyzzerella* 4, while *Parabacteroides*, *Parasutterella*, and *Ruminococcaceae* UCG 002 showed the opposite trend. The authors suggested that dysbiosis in early pregnancy might be associated with the development of GDM. Their study identified five microbiota-targeted panels (*Parabacteroides*, *Ruminococcus* 2, *Ruminococcaceae* UCG-014, *Alloprevotella*, and uncultured-*Ruminococcaceae*) that could potentially serve as predictors of GDM, with an area under the curve (AUC) of 0.696 (Ma et al., 2020). Zheng Wei et al. (2020) identified a moderately good performance of a three-bacteria component consisting of *Coprococcus*, *Intestinimonas*, and *Veillonella* in predicting GDM in the first trimester. Additionally, they proposed a potential association between the reduced abundance of *Coprococcus* (a butyrate producer) and *Streptococcus* (a lactate producer) and the development of insulin resistance and GDM during both the first and second trimesters. Furthermore, they hypothesized that the progression of GDM might be facilitated by a stable gut microbiota composition or a lack of typical dynamic

TABLE 3 Microbiota as predictors of GDM.

Study by	GDM/Non-GDM women	Age of gestation	Age of GDM women in years	Sample	AUC	Microbiota in GDM women
Li X. et al., 2021	44/67	3rd trimester	31.5 ± 4.55	Saliva	0.83	*Streptococcus*
				Dental Plaque	0.83	*Lautropia* and *Neisseria*
Ma et al., 2020	98/98	10–14 weeks	31.0 ± 3.0	Stool	0.696	*Parabacteroides*, *Ruminococcus* 2, *Ruminococcaceae* UCG-014, *Alloprevotella*, and uncultured -*Ruminococcaceae*
Zheng et al., 2020	31/130	1st trimester	32.58 ± 4.1	Stool	0.743	*Coprococcus*, *Intestinimonas*, and *Veillonella*
Xu et al., 2020	30/31	24–28 weeks	33.7 ± 4.7	Stool	0.66	*Hemophilus*
				Saliva	0.70	*Leptotrichia*
Mokkala et al., 2017	15/60	≤17 weeks	18–45	Stool	0.73	*Ruminococcaceae*

AUC, Area under the curve; GDM, Gestational diabetes malleates.

changes (Zheng et al., 2020). Sililas et al. (2021) found that the Firmicutes/Bacteroidetes ratio serves as a more sensitive marker of severe GDM than a specific microbe. On the other hand, Mokkala et al. (2017) observed that an increased relative abundance of the *Ruminococcaceae* family correlated with higher odds of a positive GDM diagnosis, along with a significant positive correlation between *Ruminococcaceae* and OGTT results. They noted that the *Ruminococcaceae* family exhibited an AUC of 0.73 for predicting GDM, suggesting that alterations in gut microbiota composition may influence the onset of GDM by affecting glucose metabolism through inflammatory mechanisms (Mokkala et al., 2017).

Apart from gut microbiota, recent studies have also implicated oral microbiota as potential predictors of GDM. Li X. et al. (2021) demonstrated that *Streptococcus* in saliva (AUC=0.83) and *Lautropia* and *Neisseria* in dental plaque (AUC=0.83) could efficiently distinguish both GDM and healthy pregnant women, highlighting their potential as predictors of GDM.

Xu Yajuan et al. (2020) reported that oral microbes such as *Leptotrichia* (AUC=0.70) or gut microbes such as *Haemophilus* (AUC=0.66) could serve as potential biomarkers to predict GDM status. In a separate investigation conducted by Gao et al. (2022), it was found that gut microbiota-derived metabolites hold promise as potential serum biomarkers for predicting GDM. Valeric acid, in particular, demonstrated the highest predictive potential with an AUC of 0.831 for GDM diagnosis. A combination of metabolites panel (isobutyrate, isovalerate, valerate, caproic acid, GUDCA, THDCA + TUDCA, and LCA-3S) could distinguish GDM patients from healthy women with a highest AUC of 0.890.

These findings collectively highlight the potential of microbiota and its metabolites as non-invasive biomarkers for early GDM diagnosis. Future research is needed with focus on longitudinal studies to elucidate microbiota dynamics during pregnancy. Additionally, mechanistic investigations are crucial to uncover the underlying pathways linking microbiota alterations and GDM development. Validation studies are also necessary to confirm the reliability of microbiota-based biomarkers. Furthermore, integrating these biomarkers with clinical parameters, conducting large-scale clinical trials, and exploring broader clinical applications are essential steps to fully leverage microbiome potential in improving GDM prediction, management, and maternal–child health outcomes.

2.5 Microbiota as a dietary intervention in GDM

Dietary interventions, including probiotics, prebiotics, and synbiotics, present a promising avenue for altering the diversity and richness of the gut microbiota. (Zheng et al., 2020) and potentially reducing the risk of GDM. Microbial metabolites play a significant role in glucose regulation through intestinal gluconeogenesis (De Vadder et al., 2016). In women with GDM who followed dietary recommendations, there was a decrease in the abundance of Bacteroides species along with improved glycemic control (Ferrocino et al., 2018). In a clinical trial, the administration of daily supplements containing *Lactobacillus rhamnosus* HN001, at a dosage of 6 x 10^9 colony forming units (CFU), between weeks 14 to 16 of pregnancy has demonstrated correlations with reduced incidence and recurrence rates of GDM. This effect appears to be particularly notable among older pregnant women and those with a history of GDM (Wickens et al., 2017). Additionally, a clinical trial conducted by Kijmanawat et al. (2019) found that GDM women who took probiotics containing *Lactobacillus* and *Bifidobacteria* in the second trimester demonstrated advantages for glucose metabolism, fasting plasma glucose, insulin fasting, and insulin resistance. Moreover, the administration of a combination of probiotics, including *Lactobacillus acidophilus* LA-5, *Bifidobacterium* BB-12, *Streptococcus thermophilus* STY-31, and *Lactobacillus delbrueckii bulgaricus* LBY-27, led to a reduction in fasting blood glucose levels (Dolatkhah et al., 2015).

Furthermore, studies on symbiotic supplements containing various strains of bacteria (such as *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium bifidum*) along with inulin have demonstrated improvements in very-low-density lipoprotein cholesterol and insulin sensitivity among GDM women (Ahmadi et al., 2016). However, some reports have indicated inconsistency in the efficacy of dietary interventions involving microbiota (Pellonperä et al., 2019; Shahriari et al., 2021). Further research is warranted to fully explore the potential of dietary supplement interventions in modulating gastrointestinal microecology during pregnancy. The field is still in its early stages and requires additional investigation.

3 Conclusion

GDM impacts a significant percentage of women during pregnancy, and the incidence of GDM is anticipated to increase as obesity prevalence rises worldwide. If accurately predicted in the early stages of pregnancy and effective measures implemented, the clinical course of GDM with its accompanying gestational complications and long-term maternal and fetal health risks could be mitigated. Although there have been advancements in the study of accurate biomarkers for diagnosing GDM, none have proven high clinical utility and validity. The microbiome provides an exciting insight into the biology of metabolic disorders, increasing the likelihood of novel biomarkers for clinical application in GDM and their possible use as targeted therapeutics. The processing of enormous metagenomics datasets has the potential to provide more accurate models of GDM, even in the earliest stages of pregnancy. In addition, diagnosing GDM via microbiota assessment for dysbiosis is simple and pragmatic. Obtaining stool and salivary samples from pregnant women is more manageable than blood collection via venipuncture after an oral glucose challenge load. Doctors, nurses, and pregnant women can collect oral and stool samples. In several trials, it is encouraging to see that a small number of bacteria can produce an acceptable level of discrimination, allowing for the development specialized bacterial probes for GDM detection.

Furthermore, well-designed prospective clinical trials are necessary to define and develop the ideal biomarkers. Thanks to these novel biomarkers, our understanding of the pathophysiology and progression of GDM will expand and deepen. The obvious and necessary goal is improved outcomes in maternal–fetal health on a global scale.

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