European Journal of Nutrition
https://doi.org/10.1007/s00394-021-02483-6

REVIEW

Impacts of gut microbiota on gestational diabetes mellitus: a comprehensive review

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Received: 21 September 2020 / Accepted: 8 January 2021

Abstract

Background Gestational diabetes mellitus (GDM) is a condition that seriously threatens mother and child health. The incidence of GDM has increased worldwide in the past decades. In addition, the complications of GDM such as type 2 diabetes (T2DM) and neonatal malformations could negatively affect the living quality of mothers and their children.

Aim It has been widely known that the imbalance of gut microbiota or called 'gut dysbiosis' plays a key role in the development of insulin resistance and chronic low-grade inflammation in T2DM patients. However, the impacts of gut microbiota on GDM remain controversial. Here, we aim to comprehensively review the alterations of gut microbiota in GDM mothers and their offspring.

Results The alterations of Firmicutes/Bacteroidetes (*F*/*B*) ratio, short-chain fatty acid (SCFA)-producing bacteria, bacteria with probiotics properties and gram-negative lipopolysaccharide (LPS)-producing bacteria play a vital role in the development of GDM. The beneficial roles of gut microbiota modification (probiotics, synbiotics and lifestyle modification) as a treatment of GDM were found in some, but not all studies.

Conclusion In the near future, gut microbiota modification may be considered as one of the standard treatments for GDM. Moreover, further studies regarding the specific gut microbiota that are associated with the early development of GDM are required. This may contribute to the novel diagnostic markers for early stages of GDM.

Keywords Gut microbiota · Gut dysbiosis · Gestational diabetes mellitus · Insulin resistance · Probiotics · Synbiotics

Introduction

Gestational Diabetes Mellitus (GDM) is one of the most common types of pregnancy complications [1]. In contrast to type 2 diabetes (T2DM), GDM emphasizes the first detection of hyperglycemia during pregnancy, which is becoming a global health problem in recent years. The prevalence of GDM is as high as 31% in European countries, while 1.5 in 10 pregnant women were diagnosed with GDM in Southeast Asia [2]. Women with GDM are more likely to have comorbidities with other pregnancy complications such as pre-eclampsia, postpartum infection, preterm delivery, shoulder dystocia, metabolic syndrome, and cardiovascular diseases [3–5]. In addition, an infant born from the GDM mother is at a very high risk of developing larger size for the gestational age, fetal malformations, diabetic fetopathy, and neonatal hyperinsulinemia [6–8]. Several studies also found that children of GDM mother had a higher risk of impaired glucose tolerance (IGT), T2DM, metabolic syndrome, and even autism later in life [9–11].

The mucosal surface and lumen of gastrointestinal, respiratory, reproductive and urinary tracts is colonized by beneficial communities of microbes called as "microbiota" [12–14]. Among these diverse microbial habitats, the gastrointestinal tract, especially the distal colon, is populated with the largest density of microbiota, which is defined as

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Published online: 29 January 2021

"gut microbiota". Interactions between host cells and gut microbiota result in shaping host metabolism and immune response [15, 16]. Imbalanced population of normal gut microbiota or gut dysbiosis has been linked to several non-communicable diseases such as metabolic syndrome, allergic diseases, some types of cancer, and neurodegenerative diseases [17–20]. Considering gut microbiota and pregnancy, Koren and colleagues [21] firstly reported a direct link between gut dysbiosis and inflammation, adiposity, as well as insulin resistance in late pregnancy. After that, several studies also demonstrated the role of gut microbiota in pregnancy and its complications, including GDM [22, 23].

To specifically focus on the association between gut microbiota and GDM, we comprehensively reviewed the alterations of gut microbiota in GDM mothers and their offspring. Additionally, the potential influence of modulation of gut microbiota composition as a treatment of GDM were discussed in this review article.

Search method and selection criteria

"GDM" or "Gestational diabetes" or "Gestational diabetes mellitus" or "Pregnancy hyperglycemia" or "Pregnancy glucose intolerance" or "Pregnancy insulin resistance" and "Gut microbiota" or "Gut microbiome" or "Gut bacteria" or "Gut dysbiosis" or "Intestinal microbiota" were used as keywords for literature searches from the PubMed database since January 2000 until December 2020. All relevant literatures in English, including clinical observation studies, and clinical trials were selected. Because we only focused on the changes in gut microbiota during GDM and the impact on the outcome of their newborns, any studies regarding gut microbiota analysis prior to GDM diagnosis were excluded.

Alterations of gut microbiota in GDM compared to normal pregnancy

Alterations of gut microbiota in women with GDM compared to their non-GDM counterparts are listed in Table 1. Gut dysbiosis in GDM women was mainly characterized by changes in microbiome diversity, including alpha- and beta-diversity, i.e. within individuals and inter-individual species diversity, respectively. Moreover, various types of abnormal bacterial composition were also exhibited in GDM, including the changes at phylum, genus, and species levels. All these changes were reported at both mid-gestation (14–27 weeks) and late gestation (28–42 weeks).

Previous studies reported a reduction in alpha-diversity in the GDM group, when compared to that of normoglycemic women at both mid- and late gestation [24–26]. The reduction in alpha-diversity was also correlated with increased blood glucose level [25]. These results were consistent with other studies in obese, IGT and T2DM patients [27, 28]. However, some prior studies demonstrated no difference in alpha-diversity between the GDM and the non-GDM groups at late gestation [29–33]. This might be due to the overweight status of the control groups [29]. In contrast, another study observed an increase in alpha-diversity in the third trimester of GDM women, when compared to that of the control group [34]. The inconsistent results might be due to the too small sample size in each study, as well as some variation among studies such as different sample sources and analysis methods. A previous study compared the PCR results from the selection of different 16SrRNA regions of the gut microbiota in the same healthy individual [35]. They found that the richness of gut microbiota was higher using a primer for V1-V3 regions, when compared with using a primer for V3-V5 regions [35]. This finding suggested that the different primers or analytical methods may affect the experimental results. However, there is still no evidence of the direct comparison among different analysis methods in GDM patients. Therefore, a future study with a larger sample size, wider range of microbiome analysis, and adjustment of confounding factors is required. Regarding beta-diversity, previous studies used UniFrac/Bray–Curtis distances analysis and found significant separation in beta-diversity between GDM and non-GDM individuals during their second and third trimesters [24, 25, 30, 31]. While another two studies showed no difference in the beta-diversity between GDM and non-GDM women in late pregnancy [29, 34]. The inconsistency of the results might be related to the difference in inclusion criteria, sample sizes and methods of analysis. Therefore, either a large-population study or a meta-analysis adjusting for those confounding factors is necessary.

At the phylum level, an increase in Firmicutes/Bacteroidetes (*F*/*B*) ratio in late pregnancy were exhibited in the GDM group when compared with non-GDM [34]. Previous studies indicated that a higher *F*/*B* ratio was associated with obesity [36] and an aggravation of low-grade inflammation [37].

At the genus level, the elevated numbers of gram-negative bacteria, including *Parabacteroides*, *Prevotella*, *Haemophilus* and *Desulfovibrio* were observed in the intestine of GDM when compared with those of non-GDM women in both mid- and late pregnancy [24, 25, 29, 31, 34]. These increased bacteria were also reported to be positively associated with a higher blood glucose on an individual level [24, 25, 29, 34]. One of the outer membrane components of gram-negative bacteria, lipopolysaccharides (LPS), is considered as an endotoxin that can contribute to low-grade inflammation and insulin resistance [38, 39]. Consistently, LPS biosynthesis and transport system were positively correlated with blood glucose from an oral glucose tolerance test (OGTT) on an individual level [24]. Meanwhile, a reduction was found in

Table 1 Alterations of gut microbiota in GDM women compared with non-GDM women

Participants/age (years old)/GW (weeks)/*N*/method	Major findings						Interpretation	References
	Metabolic parameters	Gut microbiota				Correlation		
		Profiles		Diversity				
		Increase	Decrease	α	β			
GDM women/30.5 ± 3.3/26.2 ± 1.6/43 Non-GDM/28.8 ± 3.1/25.9 ± 1.6/81 Whole-metagenome shot-gun sequencing	↑OGTT Pathway ↑Membrane transport ↑Energy metabolism ↓ Amino acid Metabolic pathway ↓ Weight gain	Genus *Parabacteroides* *Megamonas* *Phascolarctobacterium* Species *Bacteroides sp.3_1_19* *Streptococcus agalactiae* *Lachnospiraceae bacterium*	Genus *Ruminiclostridium* *Roseburia* *Fusobacterium* *Haemophilus* *Clostridium* Species *Bifidobacterium bifidum* *Eubacterium siraeum* *Alistipes shahii*	↓	S	Positive between OGTT and *Parabacteroides,* Megamonas, *Lachnospiraceae bacterium*, *Streptococcus agalactiae*, *Bacteroides sp.3_1_19*, PTS system pathway, LPS biosynthesis and transport systems Negative between OGTT and *Eubacterium*, *Alistipes* No correlation between OGTT and *Bifidobacterium bifidum*	The enrichment of gram-negative bacteria and depletion of butyrate-producing bacteria are associated with hyperglycemia and chronic inflammation in GDM	[24]
GDM women/not provided/39.04/74 Non-GDM/not provided/39.33/73 PCR 16 s rRNA (V3-V4)	↑OGTT	Genus *Fusobacterium* *Prevotella*	Genus *Faecalibacterium*	–	–	Negative between *Faecalibacterium/Fusobacterium* ratio and OGTT No data provided between OGTT and *Prevotella*	*Faecalibacterium/Fusob-acterium* ratio was found deceased in GDM and related with increased blood glucose	[22]
GDM women/29.3 ± 0.9/31.2 ± 0.5/11 Non-GDM/28.2 ± 0.8/32.7 ± 0.3/11 PCR 16s rRNA (V3–V4)	↑ FPG ↑ 2-h PG ↔BMI ↔TG, TC ↔LDL, HDL	Phylum Verrucomicrobia Genus *Akkermansia*	Genus *Faecalibacterium*	↓	S	Negative between FPG and alpha-diversity TG and *Faecalibacterium* No correlations between blood glucose, insulin, lipids and *Akkermansia*	A decrease in alpha-diversity and *Faecalibacterium* in GDM women were associated with abnormal glucose and lipid metabolism	[25]
GDM with hyperlipidemia women/29.1 ± 0.7/31.8 ± 0.8/12 Non-GDM/28.2 ± 0.8/32.7 ± 0.3/11 PCR 16 s rRNA(V3-V4)	↑FPG ↑2-h PG ↑TC, TG ↑LDL ↓HDL ↔BMI	Genus *Streptococcus* *Veillonella* *Prevotella Haemophilus* *Actinomyces*	Genus *Faecalibacterium*	↓	S	Positive between TC and *Streptococcus*, *Veillonella*, *Haemophilus*, *Actinomyces* Negative between FPG and alpha-diversity TG and *Faecalibacterium* No correlations between blood glucose, lipids and *Prevotella*	An increase in *Streptococcus*, *Veillonella* and *Prevotella*, as well as a decrease in alpha-diversity and *Faecalibacterium* were associated with abnormal glucose and lipid profiles in GDM with hyperlipidemia	[25]

Table 1 (continued)

Participants/age (years old)/GW (weeks)/*N*/method	Major findings						Interpretation	References
	Metabolic parameters	Gut microbiota				Correlation		
		Profiles		Diversity				
		Increase	Decrease	α	β			
GDM women/34.4 ± 4.4/28.7 ± 1.4/50 Non-GDM/33.3 ± 4.6/28.4 ± 1.1/161 PCR 16 s rRNA(V1-V2)	↑OGTT ↑Insulin, HOMA-IR ↑HbA1c ↑Pre-pregnancy BMI ↓Insulin sensitivity Matsuda Index ↓Insulin secretion Disposition index	Phylum Actinobacteria Genus *Collinsella* *Desulfovibrio* *Blautia* *Rum inococcus2*	Genus *Bacteroides* *Faecalibacterium* *Ruminococcus* *Isobaculum*	↔	NS	Positive between OGTT and beta-diversity, *Collinsella*, *Dorea*, *Blautia*, *Prevotella* hsCRP and *Bacteroides* Negative between OGTT and *Bacteroides* Insulin sensitivity and *Akkermansia*, *Blautia* Insulin secretion and *Blautia* Inconsistence correlations between blood glucose and species of *Faecalibacterium*, *Ruminococcus*	*Bacteroides*, *Blautia*, *Collinsell*a, *Prevotella* played the vital role of abnormal glucose metabolism, impaired insulin sensitivity in GDM	[29]
GDM women/32–38.5/38.6–39.7/23 Non-GDM women/30–35/39.0–40.6/26 PCR 16 s rRNA(V3-V4)	↑OGTT Pathway ↑PPP pathway ↓SCFA Pathways ↔BMI	Species *Bacteroides dorei* *Bacteroides sp.3_1_3FAA*	Species *Alistipes putredinis* *Lactobacillus casei*	↔	S	Positive between OGTT and *Bacteroides dorei*, *Bacteroides sp.3_1_3FAA* Negative between OGTT and *Alistipes putredinis* No correlation between OGTT and *Lactobacillus casei*	An increase in two species of *Bacteroides* and a decrease in *Alistipes putredinis*, *Lactobacillus casei* were associated with abnormal glucose metabolism in GDM	[30]
GDM women/33.7 ± 4.7/38.3 ± 0.7/30 Non-GDM women/32.3 ± 4.3/38.5 ± 0.8/31 Whole-metagenome shot-gun sequencing	–	Genus *Haemophilus*	Genus *Alistipes* *Rikenellaceae*	↔	S	Positive between hsCPR and *Escherichia* HbA1c and *Clostridium*, *Megasphaera* Negative between hs CPR and *Akkermansia* No correlations between blood glucose, insulin, lipids and *Haemophilus*, *Alistipes*, *Rikenellaceae*	Gut dysbiosis in the third trimester of GDM may related to inflammation	[31]

Table 1 (continued)

Participants/age (years old)/GW (weeks)/*N*/method	Major findings						Interpretation	References
	Metabolic parameters	Gut microbiota				Correlation		
		Profiles		Diversity				
		Increase	Decrease	α	β			
GDM women/35.07 ± 3.75/32.45 ± 7.04/26 Non-GDM women/28.23 ± 5.68/33.89 ± 1.97/42 PCR 16 s rRNA(V4)	↑OGTT ↑HbA1c	Phylum Firmicutes Genus *Ruminococcus Collinsella* *Lachnospiraceae* *Dorea*	Phylum Bacteroides Genus *Eubacterium rectale*	↑	NS	–	Increased *F*/*B* ratio, *Collinsella*, and decreased *Eubacterium* was found in GDM	[34]
GDM women/32.8 ± 3.3 /25.55 ± 1.17/45 Non-GDM women/32.8 ± 3.9 /25.68 ± 1.26/45 PCR 16 s rRNA(V3-V4)	↑OGTT ↑Serum IL-6, IL-8 ↑ Serum TNF-α ↔TC, TG, LDL ↔BMI	Genus Blautia Faecalibacterium	Phylum Bacteroides Genus *Akkermansia* *Odoribacter* *Butyricimonas* *Christensenellaceae R-7 group*	↓	S	Positive between OGTT, IL6, TNF-α and *Faecalibacterium* Negative between OGTT and *Akkermansia*, *Odoribacter*, *Butyricimonas*, *Christensenellaceae R-7 group* Inconsistence correlations between OGTT and *Blautia*	An increase in *Faecalibacterium* and decrease in *Akkermansia*, *Odoribacter*, *Butyricimonas*, and *Christensenellaceae R-7 group* were associated with increased blood glucose and inflammatory cytokines in GDM	[26]
GDM women/ 33.95 ± 4.7 /25.6 ± 1.0/36 Non-GDM women/30.8 ± 4.8/25.9 ± 1.1/16 PCR 16 s rRNA(V3-V4)	↑OGTT ↑ BMI ↔TC, TG, LDL, HDL ↓PPAR signaling pathway	Genus *Blautia* *Eubacterium_hallii_group*	Genus *Faecalibacterium* *Phascolarctobacterium* *Roseburia*	↔	S	Positive between OGTT and *Blautia*, Eubacterium_hallii_group PPAR signaling pathway and Faecalibacterium Negative between OGTT and Faecalibacterium PPAR signaling pathway and Blautia Inconsistence correlations between OGTT and *Phascolarctobacterium*, *Roseburia*	An increase in *Blautia*, *Eubacterium_hallii_group* and decrease in *Faecalibacterium* were associated with increased blood glucose in GDM. Gut dysbiosis may be involved in the pathological of GDM through PPAR signaling pathway	[32]
GDM women/32.58 ± 4.1/24.5 ± 0.5/31 Non-GDM women/31.79 ± 3.70/24.5 ± 0.5/103 PCR 16 s rRNA(V3-V4)	↑OGTT ↔TC, TG, LDL, HDL	Genus *Holdemania* *Megasphaera* *Eggerthella*	Genus *Streptococcus* *Coprococcus* *Flavonifractor*	↔	NS	–	An increase in *Holdemania*, *Megasphaera*, *Eggerthella* and decrease in *Streptococcus*, *Coprococcus*, *Flavonifractor* were found in GDM	[33]

Table 1 (continued)

GDM gestational diabetes mellitus, *N* sample size, *Method* the method that used for gut microbiota analysis, ↑ increased in GDM women when compared with non-GDM, ↓ decreased in GDM women when compared with non-GDM, ↔ shown no statistical difference between the two groups, – no data provided, *GW* gestational weeks, *OGTT* oral glucose tolerance test, *HOMA-IR* homoeostasis model assessment of insulin resistance, *HbA1c* glycated hemoglobin, *BMI* body mass index, *NS* non-significant, *S* statistically significant separation, *LPS* lipopolysaccharide, *PTS* phosphotransferase system, *PCR* polymerase chain reaction, *FPG* fasting plasma glucose, *2-h PG* 2 h postprandial glucose, *TG* triglyceride, *TC* total cholesterol, *LDL* low-density lipoprotein, *HDL* high density lipoprotein, *PPP* pentose phosphate pathway, *SCFA* short-chain fatty acids, *hs-CRP* high sensitive C-reactive protein, *IL-6* interleukin 6, *IL-8* interleukin 8, *TNF-α* tumor necrosis factor alpha, *PPAR* peroxisome proliferator-activated receptor

the relative abundance of SCFA-producing genus *Faecalibacterium*, *Ruminococcus*, *Roseburia*, *Coprococcus*, *Akkermansia*, *Phascolarctobacterium*, and *Eubacterium* in GDM women, when compared with non-GDM at their second and third trimester [22, 24–26, 29, 32–34]. These alterations were reported to be associated with increased blood glucose on an individual level [22, 24–26, 29, 32–34]. The SCFAs can combine with G protein-coupled receptors (GPR) 41 and GPR 43 to promote the secretion of peptide tyrosine tyrosine (PYY) and glucagon-like peptide (GLP)-1 from enteroendocrine cells [40, 41]. This helps regulate insulin release and promote glucose metabolism [42]. SCFAs also plays vital role in strengthening the intestinal barrier, as well as decreasing inflammation and oxidative stress by activating the peroxisome proliferator-activated receptor (PPAR) pathway [43–46]. A study revealed that there were abnormalities in the SCFA pathway, as indicated by a reduction in acetate, butanoate, and propanoate in GDM women when compared with normoglycemic ones in late gestation [30]. Moreover, aromatic amino acids (AAA)-degrading bacteria such as *Clostridium*, *Fusobacterium*, *Eubacterium* were found decreased in GDM women, when compared with those of the non-GDM group [24, 34]. In addition, indoles—a product of aromatic amino acids by bacteria—were also reported to be able to promote the release of GLP-1 through the aryl hydrocarbon receptor (AhR) pathway [47–49]. Indoles can also strengthen the intestinal mucosal barrier [50]. Wang and colleagues [22] reported that *Faecaibacterium* (SCFA-producing genus)/*Fusobacterium* (gram-negative AAA-degrading bacteria) ratio was reduced in women with GDM at late-gestation, compared with that of non-GDM. Additionally, previous studies observed that the genus *Collinsella*, *Blautia*, *Megamonas* and *Dorea* were increased in GDM patients in late pregnancy [24, 29, 34]. These elevated genera have also been reported to related with a higher blood glucose on an individual level [24, 29, 34].

At the species level, previous studies reported an increase in *Bacteroides* (*sp.dorei, sp.3_1_3FAA, sp.3_1_19*) and a reduction in SCFA-producing species *Bifidobacterium bifidum* and *Lactobacillus casei* in GDM patients, when compared with non-GDM at mid- and late gestation [24, 30]. These alterations were also related to elevated blood glucose levels [24, 30]. These results suggested that some specific *Bacteroides* species were increased in GDM. Regarding *Bifidobacterium* spp. and *Lactobacillus* spp., these two bacteria have been considered as probiotics that alleviate insulin resistance by decreasing systemic inflammation, regulating immune function, and improving intestinal mucosal permeability [51–54].

In summary, the gut dysbiosis of GDM is characterized by changes in alpha-diversity (five out of ten studies), a change in beta-diversity (seven out of ten studies), an increase in gram-negative bacteria (five out of 11 studies)

and some gram-positive bacteria (five out of 11 studies) such as *Collinsella*, *Blautia*, *Megamonas*, and *Dorea*, as well as a reduction in SCFA-producing bacteria (eight out of 11 studies), and a decrease in bacteria with probiotics properties (two out of 11 studies). Most of these articles were reported a correlation between the changes in these specific microbiota and elevated blood glucose (night out of ten studies). In fact, two previous studies reported the alterations of gut microbiota at the first trimester of pregnant women who were subsequently diagnosed with GDM at their second trimester, when compared to that of pregnant women who did not develop GDM [33, 55]. Therefore, changes in gut microbiota at early pregnancy can be considered as a potential diagnostic tool for GDM or may be a cause of GDM. On the other hand, prior studies revealed that the gut microbiota composition of women who were diagnosed with GDM at their first trimester was not different from those of women without GDM at the same gestational age [26, 56], suggesting the gut dysbiosis may be a consequence of GDM. Hence, the argument that gut microbiota is a cause or a consequence of GDM, remains controversial and needs further studies.

Alterations of gut microbiota in GDM at different time points

Alterations of gut microbiota in GDM individuals in late gestation (28–42 weeks), compared with their baseline at mid-gestation (14–27 weeks) are summarized in Table 2. These include alterations of alpha- and beta-diversity, as well as changes in phylum and genus levels.

A higher alpha-diversity in late pregnancy of GDM individuals when compared to that of their mid-gestation was observed in two previous studies [23, 57]. Ferrocino et al. believed that an increase in alpha-diversity correlated with gestational weight gain [57]. However, this requires further validation. Furthermore, Ferrocino and colleagues reported a significant separation in beta-diversity at late gestation of GDM patients when compared with their second trimester [57]. This result supported the findings in normal pregnancy, in which there was a dramatic expansion of beta-diversity during the third trimester [21].

At the phylum level, an increase in Firmicutes, a decrease in Bacteroides, and an increase in *F*/*B* ratio were revealed at late gestation of GDM women, when compared to their levels at mid-gestation [23, 57]. These results were also associated with weight gain in their third trimester [57].

Consistent with the results at phylum level, the genera belonging to phylum Firmicutes such as *L-Ruminococcus*, *Blautia*, and *Lachnospiraceae* were increased, while those belonging to Bacteroides such as a butyrate producer *Rikenellaceae* were decreased in late pregnancy of GDM individuals, when compared with their baseline at mid-pregnancy [57]. Notably, an increased abundance of *L-Ruminococcus*, *Blautia*, and *Lachnospiraceae* were correlated with higher oligosaccharides intake [57].

In summary, dynamic changes in the gut microbiota composition from mid- to late gestation were manifested by an increase in alpha-diversity (two out of two studies), a change in beta-diversity, as well as an increased *F*/*B* ratio (two out of two studies) from the mid-gestation baselines. Most of which were associated with maternal blood glucose, maternal BMI, and maternal oligosaccharides intake (one out of two studies). Interestingly, Ye et al. [32] reported that the dynamic changes in gut microbiota composition from the first trimester to the third trimester of non-GDM was greater than those of GDM individuals. Another previous study also revealed that the dynamic changes in the gut microbiota of GDM were associated with increased inflammatory status from the first trimester to the second trimester [26]. In addition, *Coprococcus catus* was found increased in GDM at the third trimester (mean gestational age of 35.2 weeks) when compared with their first trimester (mean gestational of 13.9 weeks) [56]. However, the mechanisms that are responsible for the difference of dynamic changes between non-GDM and GDM have not been determined, and therefore future studies identifying these mechanisms are needed to be established. Furthermore, Fugmann et al. [58] suggested that gut microbiota dysbiosis and insulin resistance existed in pre-GDM women after 3–16 months delivery. This supports the fact that women with GDM have a high risk of developing T2DM later in their life.

Alterations of gut microbiota in offspring of GDM mothers

Previous studies regarding the changes in gut microbiota in the offspring of GDM mothers when compared with those of normoglycemic mothers are listed in Table 3. These include changes in alpha-diversity, phylum, and genus levels.

Prior studies exhibited a reduction in alpha-diversity in neonates of GDM mother when compared with those of mothers without GDM [23, 59]. Regarding beta-diversity, a previous study reported a significant separation in the beta-diversity between the offspring of GDM and non-GDM mothers [59].

At the phylum level, the abundance of Actinobacteria was greater in neonates of GDM mothers, and these were also associated with increased level of maternal fasting glucose [59]. Meanwhile, Bacteroidetes were reduced in the 1-day-old neonates of GDM mothers, which negatively correlated with the maternal fasting glucose [59]. On the other hand, another previous study revealed a higher abundance of Bacteroidetes in 1-week old infants of GDM mothers, when compared with those of non-GDM mothers [23]. The

Table 2 Alterations of gut microbiota in GDM patients at late gestation, when compared with their baseline at mid-gestation

Participants/age (years old)/GW (weeks)/*N*/method	Major findings						Interpretation	References
	Metabolic parameters	Gut microbiota				Correlation		
		Profiles		Diversity				
		Increase	Decrease	α	β			
GDM women/35.5 ± 3.8/38/41 Baseline/35.5 ± 3.8/24–28/41 PCR 16 s rRNA(V3-V4)	↑BW, BMI ↑TG, TC ↑Oligosaccharide intake Pathway ↑Carbohydrate metabolism ↑Biosynthesis of amino acids ↓Fatty acid metabolism ↔FPG, Insulin ↔HOMA-IR, HbA1c ↔CRP	Phylum Firmicutes *F/B* ratio Genus *Blautia* *Faecalibacterium* *Butyricicoccus* *Coprococcus* *L-Ruminococcus* *Lachnospiraceae*	Phylum Actinobacteria Bacteroidetes Genus *Bacteroides* *Rikenellaceae* *Collinsella*	↑	S	Positive between ΔInsulin and *Collinsella*, *Coprobacillus*, *Blautia* ΔHOMA-IR and *Collinsell*a, *Butyricimonas* ΔCRP and *Sutterella* LPS biosynthesis and *Sutterell*a, *Bacteroides* Oligosaccharides and L-*Ruminococcus*, *Lachnospiraceae* Negative between ΔFPG and Faecalibacterium No correlations between blood glucose, insulin, lipids and Rikenellaceae	An increasing in alpha-and beta-diversity, *F/B* ratio, *Faecalibactirum*, *Blautia*, and decreasing *Bacteroides* and *Collinsella* were found in the late pregnancy in GDM women	[57]
GDM women/37.1 ± 4.5/38/29 Baseline/37.1 ± 4.5/24–28/29 PCR 16 s rRNA(V3-V4)	–	Phylum Firmicutes *F/B* Ratio	Phylum Bacteroidetes	↑	–	–	The development of GDM led to gut dysbiosis as indicated by increasing alpha-diversity, *F/B* Ratio, Firmicutes and declining Bacteroidetes	[23]

GDM gestational diabetes mellitus, *N* sample size, *Method* the method that used for gut microbiota analysis, *PCR* polymerase chain reaction, ↑ increased in GDM women at late gestation when compared with their baseline at mid-gestation, ↓ decreased in GDM women at late gestation when compared with their baseline at mid-gestation, ↔ shown no statistical difference between the two groups, – no data provided, *GW* gestational weeks, *Y* years, *BW* body weight, *BMI* body mass index, *TG* triglyceride, *TC* total cholesterol, *FPG* fasting plasma glucose, *HOMA-IR* homoeostasis model assessment of insulin resistance, *HbA1c* glycated hemoglobin, *CRP* C-reactive protein, *F* Firmicutes, *B* Bacteroidetes, *S* statistically significant separation, *LPS* Lipopolysaccaride, Δ delta (final values – baseline values), *OGTT* oral glucose tolerance test

inconsistent results between these two studies might be due to different ages of the neonates. Therefore, a further study regarding a dynamic change of gut microbiota in the offspring of GDM mothers is needed.

At the genus level, opportunistic pathogens including *Escherichia* and *Parabacteroides* increased, while the probiotic (*Lactobacillus*) decreased in the neonates of GDM individuals [23, 59]. Additionally, a positive correlation between the abundance of *Clostridium* in infants and maternal BMI was reported [59]. Moreover, the abundance of *Ruminococcu*s in infants was found positively correlated with maternal oligosaccharide intake and negatively correlated with maternal saturated fatty acids intake [23]. Notably, a literature reported that the abundance of *Lactobacillus iners* was increased in meconium of newborns from GDM mothers, which emphasized that the colonization of some species was influenced by maternal GDM status [22].

All these studies suggested that gut microbiota composition in the offspring of GDM mothers was characterized by a reduction in alpha-diversity (two out of three studies), increased Actinobacteria (two out of three studies), *Escherichia* and *Parabacteroides* (two out of three studies), as well

as decreased Bacteroidetes (one out of three studies) and bacteria with probiotic properties (two out of three studies), when compared to the offspring of non-GDM mothers. Most of which were associated with maternal blood glucose, maternal BMI, as well as maternal oligosaccharides and saturated fatty acids intake (two out of three studies).

Gut microbiota modification as a treatment of GDM

Gut microbiota modification as a treatment of GDM are summarized in Table 4. This gut microbiota modification includes probiotics and synbiotics.

Probiotics are living organisms that display benefits to the host in a proper amount, and have been widely studied in insulin resistance and T2DM [60–63]. Randomized controlled trials (RCTs) gave a combination capsule of *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium bifidum*, with or without *Lactobacillus fermentum* at the dose of 2×10^9 CFU/g daily to GDM women at mid-gestation [64, 65]. Six weeks after treatment, an amelioration of insulin resistance and improved lipid metabolism were observed when compared to those of GDM received a placebo [64, 65]. These were indicated by a reduction in blood glucose, insulin, homoeostasis model assessment of insulin resistance (HOMA-IR), and very low-density lipoprotein cholesterol (VLDL) level [64, 65]. A higher PPAR-γ gene expression and a lower level of pro-inflammation cytokines were also exhibited after probiotic supplementation [65], suggesting that probiotics alleviate insulin resistance and chronic inflammation at least through the PPAR pathway. Interestingly, a recent study reported that a treatment with probiotics—*B. animalis* (1×10^{10} CFU/day) plus *L. rhamnosus* (1×10^{10} CFU/day)—for 21 weeks could decrease the abundance of an inflammation-associated species—*Bacteroides ovatus*—[66] in obese GDM women, when compared with that of placebo group [56].

Synbiotics are a combination of probiotics and prebiotics, considered to enhance more benefits for health effects more than using each one alone [67]. GDM patients in their second trimester were prescribed with either a placebo or a synbiotic capsule that consisted of *L. acidophilus* (5×10^{10} CFU/g), *L. plantarum* (1.5×10^{10} CFU/g), *L. fermentum* (7×10^9 CFU/g), *L. gasseri* (2×10^{10} CFU/g) and 38.5 mg of fructooligosaccharide (FOS) for 6 weeks [68]. Thereafter, the positive effects of synbiotics on the regulation of oxidative stress and lipid metabolism were exhibited, as indicated by an increase in total antioxidant capacity (TAC), increased high density lipoprotein (HDL) level, and reduced low-density lipoprotein (LDL) level [68]. However, synbiotics showed no beneficial effect on the improvement of insulin sensitivity in those GDM women, which might be due to higher fat and calorie intake in the treatment group when compared with the placebo group [68]. Another daily synbiotic supplement at mid-gestation that consists of *L.acidophilus, L.casei, and B.bifidum*, at the dose of 2×10^9 CFU/g each plus 0.8 g of inulin for 6 weeks also alleviated insulin resistance and oxidative stress, as indicated by lower level of insulin, HOMA-IR, and higher level of quantitative insulin sensitivity check index (QUICKI) and TAC when compared to placebo group [69, 70]. Moreover, the neonates of GDM mothers exhibited better neonatal outcomes following the synbiotic supplement, as indicated by decreased incidence of postnatal hyperbilirubinemia and postnatal hospitalization [70].

In summary, probiotics and synbiotics play a vital role in the improvement of insulin sensitivity (three out of five studies) and lipid metabolism (three out of five studies) as well as decreased oxidative stress (two out of five studies) in GDM patients via the modification of gut microbiota composition. From two meta-analysis studies, it was revealed that probiotics and synbiotics could alleviate insulin resistance and chronic inflammation, but these treatments could not reduce neither blood glucose nor the incidence of GDM, when compared with the placebo group [71, 72]. Similarly, another study reported that probiotics supplementation did not reduce the incidence of GDM in overweight women [73]. A study observed that either probiotics alone or probiotics plus fish oil could alter the gut microbiota composition in non-GDM, but not in GDM individuals [56]. Therefore, the supplementation of probiotics or synbiotics for women with GDM remains controversial. A previous study found some changes in gut microbiota composition of GDM at the third trimester after 10 weeks of lifestyle modifications, when compared with those of GDM patients who did not follow the recommendations [57]. These changes including an increase in butyrate-producing genus (*Faecalibacterium*) as well as a reduction in gram-negative genera (*Alistipes and Bacteroides*) [57]. Additionally, a previous study suggested that dietary modification and exercise interacted each other to alter the gut microbiota composition of pregnant rats [74]. Interestingly, moderate exercise before and during pregnancy was found to be more beneficial in regulating gut dysbiosis and metabolic function in GDM rats than the exercise only during pregnancy [74]. Underscoring the importance of early lifestyle interventions on GDM. However, clinical studies investigating the effects of exercise on the gut microbiota of GDM patients have never been conducted.

Table 3 Alterations of gut microbiota in the offspring of GDM mothers, when compared with the offspring of non-GDM mothers

Participants/age (years)/*N*/method	Major findings					Interpretation	References
	Metabolic parameters	Gut microbiota			Correlation		
		Profiles		Diversity			
		Increase	Decrease	α β			
New-born from GDM mother/–/20 New-born from non-GDM mother/–/14 PCR 16 s rRNA(V4)	↔ Wt. at birth ↔ Ht. at birth	Phylum Actinobacteria Proteobacteria	Phylum Bacteroidetes Genus *Prevotella* *Lactobacillus*	↓ S	Positive between MFG and Actinobacteria, Acinetobacter MPB/MAW/MAB and *Clostridium* Negative between MFG and Bacteroidetes, *Prevotella* Maternal age and *Lactobacillus* No correlations between maternal glucose, BMI, age and Proteobacteria	An increase in Actinobacteria, Proteobacteria and a decrease in Bacteroidetes, *Lactobacillus* in newborns were closely related to GDM status of their mothers	[59]
New-born from GDM mother/–/29 New-born from non-GDM mother/–/19 PCR 16 s rRNA (V3–V4)	–	Phylum Actinobacteria Bacteroidetes Genus *Escherichia* *Parabacteroides*	Genus *Staphylococcus* *Ralstonia* *Lactobacillus* *Enterobacteriaceae*	↓ –	Positive between MOI and *Ruminococcus* Negative between MSFA intake and *Ruminococcus* Δ HbA1c and *Clostridiales* No correlations between maternal food intake, glucose, HbA1c and *Escherichia*, *Parabacteroides*, *Lactobacillus*	The opportunistic pathogens increased, and probiotics decreased in newborn related with diet and GDM status of their mother	[23]
New-born from GDM mother/–/24 New-born from non-GDM mother/–/24 Whole-metagenome shot-gun sequencing	–	Species *Lactobacillus iners*	–	– S	No data provided between Maternal blood glucose, insulin, BMI and *Lactobacillus iners*	*Lactobacillus iners* was found increased in newborn of GDM mother when compared with those of Non-GDM mother	[22]

GDM gestational diabetes mellitus, *N* sample size, *Method* the method that used for gut microbiota analysis, *PCR* polymerase chain reaction, ↓ decreased in offspring of GDM mothers when compared with the offspring of non-GDM mothers, ↔ shown no statistical difference between the two groups, – no data provided, *Wt* weight, *Ht* height, *MFG* maternal fasting glucose, *BMI* body mass index, *MPB* maternal pre-pregnancy BMI, *MAW* maternal antepartum weight, *MAB* maternal antepartum BMI, *S* statistically significant separation, *MOI* maternal oligosaccharide intake, *MSFA* maternal saturated fatty acids intake, *HbA1c* glycated hemoglobin

Table 4 Gut microbiota modification as a treatment of GDM

Participants/*N*/Method	Intervention/dose/duration (weeks)/GW (weeks)/*N*	Major findings						Interpretation	References
		Metabolic parameters	Gut microbiota				Correlation		
			Profiles		Diversity				
			Increase	Decrease	α	β			
Double-blind RCT GDM women/60 –	Probiotics *L. acidophilus*, *L. casei*, *B. bifidum*/2×10^9 CFU/g/day/6/24–28/30 Placebo/–/6/24–28/30	↑QUICKI ↓FPG, Insulin ↓HOMA-IR ↓VLDL ↔ Nutrient intakes ↔ BW, ΔBW, BMI, ΔBMI ↔ HOMA-B, TC, LDL, HDL	–	–	–	–	–	Probiotic consumption alleviated high blood glucose, insulin resistance and benefited to insulin sensitivity and VLDL in GDM women	[64]
Double-blind RCT GDM women/48 –	Probiotics *L. acidophilus*, *L. casei*, *B. bifidum*, *L. Fermentum*/2×10^9 CFU/g/day/6/24–28/24 Placebo/–/6/24–28/24	↑QUICKI ↑NO, TAC, HDL ↑PPAR-γ, TGF-β ↑VEGF ↓FPG, Insulin ↓HOMA-IR ↓TG, TC, VLDL ↓TNF-α, MDA ↔ Nutrient intakes ↔ BW, BMI, ΔBMI ↔ LDLR, IL-1, IL-8	–	–	–	–	–	Probiotic supplementation showed beneficial effects on glycemic control, lipid metabolism, anti-inflammation, antioxidation in patients with GDM	[65]
Double-blind RCT GDM women/31 Whole-metagenome shot-gun sequencing	Probiotics *B. animalis*, *L.rhamnosus* + Medium-chain fatty acids/1×10^{10} CFU + capric acid C8 54.6% and caprylic acid C10 40.3%/day/21/13.9 ± 2.0/20 Placebo/microcrystalline cellulose + medium-chain fatty acids/day/21/13.9 ± 2.0/11	–	↔	Species *Bacteroides ovatus*		–	–	Long term of probiotics consumption reduced the *Bacteroides ovatus* in overweight GDM when compared with placebo group	[56]
Double-blind RCT GDM women/70 –	Synbiotics *L. acidophilus, L. casei, B. bifidum* + inulin/2×10^9 CFU/g + 800 mg/day/6/24–28/35 Placebo/–/6/24–28/35	↑QUICKI, ↓Insulin, HOMA-IR/B ↓TAG, VLDL ↔ FPG ↔ Nutrient intakes ↔ BW, BMI, ΔBMI ↔ TC, LDL, HDL	–	–	–	–	–	Synbiotic consumption was benefited to insulin sensitivity, TAG and VLDL, however, it did not affect FPG and other lipid profiles	[69]

Table 4 (continued)

Participants/*N*/Method	Intervention/dose/duration (weeks)/GW (weeks)/*N*	Major findings						Interpretation	References
		Metabolic parameters	Gut microbiota				Correlation		
			Profiles		Diversity				
			Increase	Decrease	*α*	*β*			
Double-blind RCT GDM women/60 –	Synbiotics *L. acidophilus, L. casei, B. bifidum* + inulin/2×10^9 CFU/g + 800 mg/day/6/–/30 Placebo/–/6/–/30	↑TAC, GSH ↓Hs-CPR, MDA ↓Newborns' hyperbilirubinemia (%) ↓Newborns' hospitalization (%) ↔ Nutrient intakes ↔ BW, ΔBW, BMI, ΔBMI ↔ NO	–	–	–	–	–	Synbiotic intake were increased TAC, GSH and reduced hs-CRP, MDA in GDM women, and decreased the incidence of newborn's hyperbilirubinemia and hospitalization	[70]

GDM gestational diabetes mellitus, *N* sample size, *Method* the method that used for gut microbiota analysis, ↑ increased in the intervention group when compared to the control group, ↓ decreased in in the intervention group when compared to the control group, ↔ shown no statistical difference between the two groups, – no data provided, *GW* gestational weeks, *L* Lactobacillus, *B* Bifidobacterium, *RCT* randomized controlled trial, *FOS* fructooligosaccharide, Δ value changes from their baseline, *TAC* total antioxidant capacity, *HDL* high density lipoprotein, *BP* blood pressure, *LDL* very low-density lipoprotein, *TC* total cholesterol, *TG* triglyceride, *FPG* fasting plasma glucose, *HOMA-IR/B* homoeostasis model assessment of insulin resistance/β cell function, *QUICKI* quantitative insulin sensitivity check index, *BMI* body mass index, *CFU* colony-forming unit, *NO* nitric oxide, *PPAR* peroxisome proliferator-activated receptor, *TGF-β* transforming growth factor beta, *VEGF* vascular endothelial growth factor, *VLDL* very low-density lipoprotein-cholesterol, *TNF-α* tumor necrosis factor alpha, *MDA* malondialdehyde, *BW* body weight, *LDLR* low-density lipoprotein receptor, *IL-1/8* interleukin-1/8, *GSH* total glutathione, *hsCPR* high sensitive C-reactive protein, *TAG* Triacylglycerol

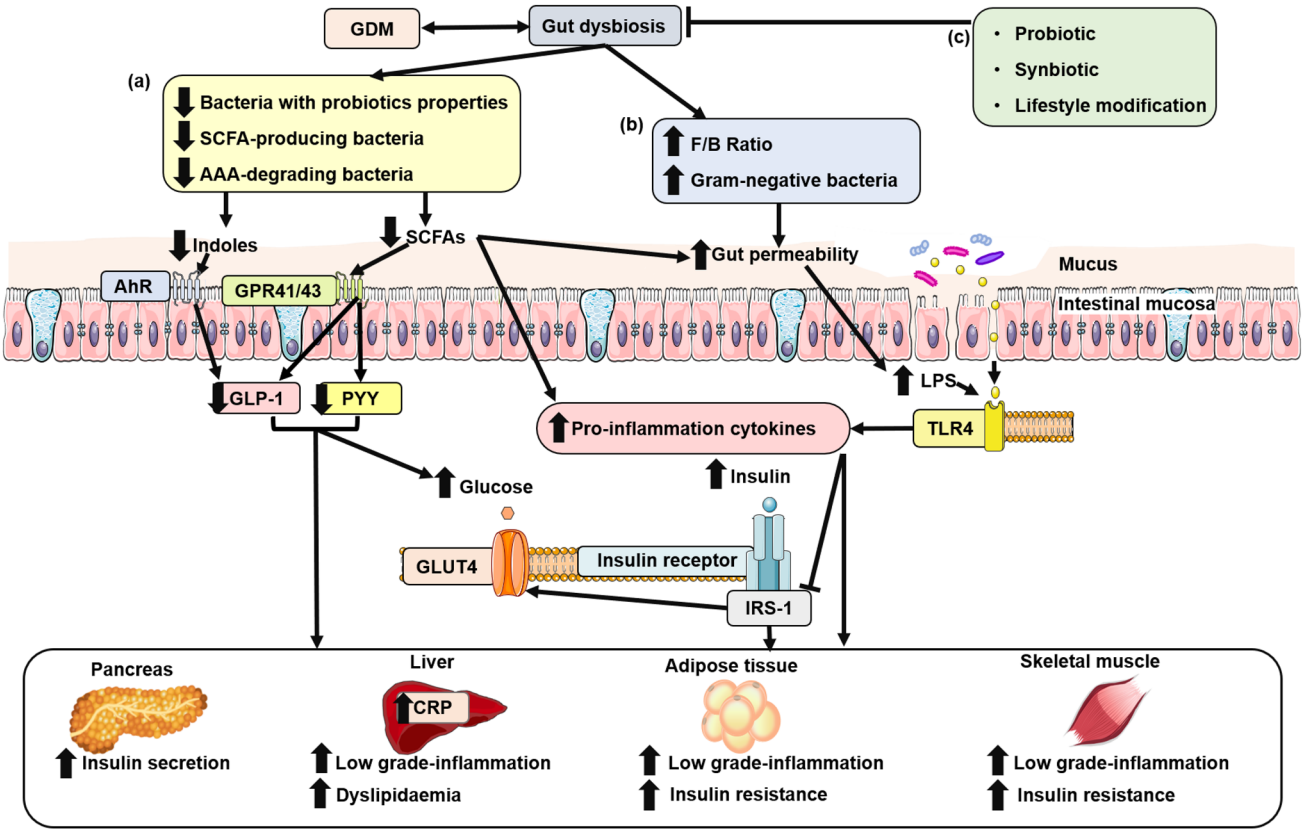

Fig. 1 The relationship between gut microbiota dysbiosis and GDM. The gut microbiota dysbiosis in GDM includes **a** reduction in bacteria with probiotics properties, SCFA-producing bacteria and AAA-degrading bacteria. The lower level of SCFAs and indoles in the intestine leads to decreased GLP-1 and PYY secretion. Resulting in impaired insulin selection and glucose metabolism. Meanwhile, the decrease in SCFAs and causes increased gut mucosal permeability and pro-inflammation cytokines. **b** Higher *F/B* ratio and gram-negative bacteria. Higher *F/B* ratio is associated with low-grade inflammation. Gram-negative bacteria lead to increasing gut mucosal permeability and LPS level. LPS accelerates pro-inflammatory cytokine production by affecting the TLR4 pathway, resulting in abnormal expression and phosphorylation of downstream regulators of insulin signaling IRS-1 and GLUT4. These contribute to low-grade inflammation and insulin resistance in adipose tissue and skeletal muscle, as well as increased CRP production by the hepatocytes. **c** Probiotics, synbiotics and lifestyle modification alleviate chronic low-grade inflammation and insulin resistance in GDM women, possibly by regulating gut microbiota. *GDM* gestational diabetes mellitus, *SCFA* short-chain fatty acid, *AAA* aromatic amino acids, *GLP-1* glucagon-like peptide-1, *PYY* peptide tyrosine tyrosine, *AhR* aryl hydrocarbon receptor, *GLUT4* glucose transporter type 4, *F/B ratio* Firmicutes/Bacteroidetes ratio, *LPS* lipopolysaccharides, *TLR4* toll-like receptor, *IRS-1* including insulin receptor substrate 1, *CRP* C-reactive protein

Conclusion, future direction and clinical application

The relationships between gut microbiota and GDM are illustrated in Fig. 1. Based on the current evidence, gut dysbiosis in GDM patients is characterized by changes in alpha- and beta-diversity, an increase in *F*/*B* ratio and gram-negative bacteria, a reduction in the relative counts of the bacteria with probiotics properties, and decreased SCFA-producing bacteria. Most of which are associated with elevated blood glucose. Although there were evidence suggesting the alterations of gut microbiota composition in GDM when compared to the non-GDM group, the trend of the alterations in some bacteria were inconsistent. For example, even though a SCFA-producing bacterium Bacteroidetes plays a beneficial role in the gut, it is considered as a gram-negative bacterium that can produce a pro-inflammatory marker—LPS [75]. Therefore, it is not surprising that some studies reported that some species belong to Bacteroidetes phylum was elevated in GDM and was positively correlated with high blood glucose [24, 31]. In other words, Bacteroidetes can be either increased or decreased in GDM. Other examples are genus *Faecalibacterium* and genus *Blautia*, in which the abundance of both genera can be either increased or decreased in GDM, depending on their subgenus [29]. Thus, it is necessary to study the role of subgenus in GDM in the future. Importantly, different methods of analyses can lead to the inconsistent findings among studies. PCR can be more economical and efficient, but whole gene shot-gun sequencing can go deep to a subgenus. In addition, there is no consensus

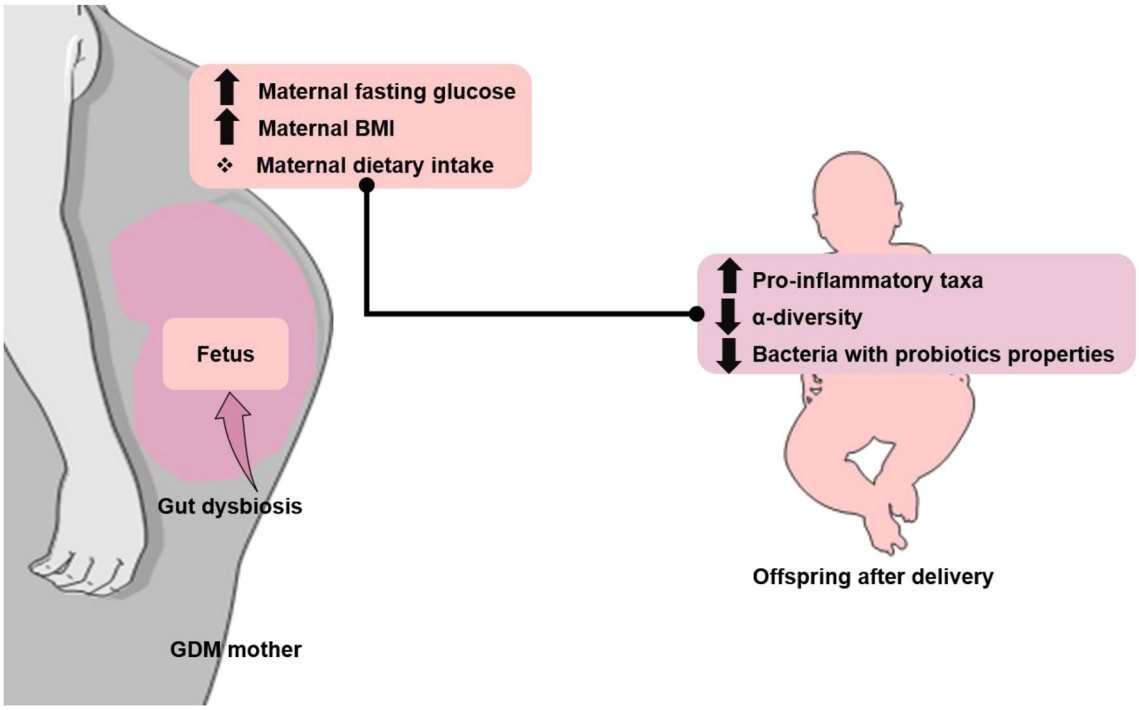

Fig. 2 Factors influencing gut microbiota of the offspring from GDM mother. Abnormal maternal parameters such as increased fasting blood glucose level and maternal BMI lead to the dominance of pro-inflammatory bacteria, decreased α-diversity and bacteria with probiotics properties in fetal gastrointestinal tract. Moreover, maternal dietary intake also alters the composition of gut microbiota in their newborns. *BMI* body mass index, *GDM* gestational diabetes mellitus

on the selection of 16SrRNA region in PCR. Currently, most studies have selected V3–V4 variable region, but some studies believe that V1–V2 region is more representative. Therefore, future comparative studies on different regions of 16S rRNA in gut microbiota may be helpful to establish the most appropriate method for gut microbiota analysis in GDM. Furthermore, based on the characteristics of the analysis method, the β-diversity was just described as "difference" or "no difference" in most of the articles. Indeed, only few articles specified the β-diversity as "increasing" or "decreasing". This makes the description vague and may limit the interpretation.

The alterations of gut microbiota in offspring of the GDM mother include increased opportunistic pathogens, a reduction in alpha-diversity and decreased bacteria with probiotics properties, as depicted in Fig. 2. The colonization of gut microbiota in newborns is closely related to the delivery pattern. Previous studies found that the composition of gut microbiota of newborns delivered naturally is similar to that of their mothers' vaginal microbiomes, whereas this association was not observed in cesarean section delivery [76]. In addition, the gut microbiota of newborns is affected by the feeding pattern. Indeed, previous studies reported that breast-fed babies exhibited more abundance of Actinobacteria than the non-breast-fed babies, suggesting that breast milk may promote colonization of Actinobacteria in the gut of newborns [23]. Given that there have been only few studies in this area, the key factors affecting the composition of gut microbiota in newborns of GDM mother have not yet been established. Therefore, the effects of the composition of gut microbiota, blood glucose, BMI, and dietary intake of the mothers on the gut microbiota of their newborns are needed to be further investigated.

As previously summarized in Table 4, probiotics, synbiotics, and lifestyle modifications can help reduce blood glucose, insulin resistance, and oxidative stress in GDM in some, but not all studies. It is important to note that only few of these prior studies provided data regarding the daily dietary intake of GDM individuals. Diet is well known to play a crucial role in the alterations of gut microbiota composition [77]. Previous studies suggested that dietary habits led to different gut predominant bacteria, which resulted in different responses to specific diets [77]. Moreover, increase, as well as a reduction in *Faecalibacterium* were observed in GDM patients who failed to control their glucose level by diet modification, when compared to those of GDM individuals whose glucose regulation was successful by diet control at second trimester [32]. According to this result, the effects of diet on the gut microbiota in GDM require further investigation.

Although the findings among several previous studies were controversial, it is generally accepted that gut microbiota plays a key role in GDM during pregnancy. However, there were only few studies investigating about the alterations of gut microbiota composition in GDM prior to pregnancy and the postpartum period of GDM women. Furthermore, maternal BMI, diet, sex hormone levels, the dosage of insulin therapy, and defecation habit during pregnancy may affect gut microbiota of GDM. Therefore, future studies regarding the gut microbiota composition that cover those factors at pre-pregnancy, early pregnancy, mid- and late pregnancy, as well as postpartum period are necessary. Additionally, our report is neither a systematic review nor meta-analysis, and thus the study quality and risk of bias are not assessed. Therefore, future systematic reviews or meta-analyses may help better understanding the relationship between gut microbiota and GDM. Moreover, the future placebo-controlled randomized trials with large-sample size regarding the effects of probiotics and synbiotics supplementation on GDM are required. After the consistent outcomes are established, gut microbiota modification may be considered as one of standard treatments for GDM. Moreover, further studies determining the specific gut microbiota associated with the early development of GDM are required. All of these future studies may contribute to novel diagnostic and therapeutic paradigms for GDM.

Acknowledgements This work was supported by Senior Research Scholar Grant from the National Research Council of Thailand (S. C. C.); the NSTDA Research Chair Grant from the National Science and Technology Development Agency Thailand (N. C.), the Chiang Mai University Center of Excellence Award (N. C.) and the Thailand Research Fund Grants MRG6280014 (C. T.). The authors would like to thank Dr. Parameth Thiennimitr for his editorial assistance.

Author contributions LH: conception, planning, carrying out and writing up of the work. CT: planning, writing up of the work. NC: conception, final approval of the version to be published. SCC: conception, planning, writing up of the work, final approval of the version to be published.

Compliance with ethical standards

Conflict of interest The authors declared that there is no conflict of interest.

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