From gut dysbiosis to placental dysfunction in maternal obesity: A common soil for gestational complications

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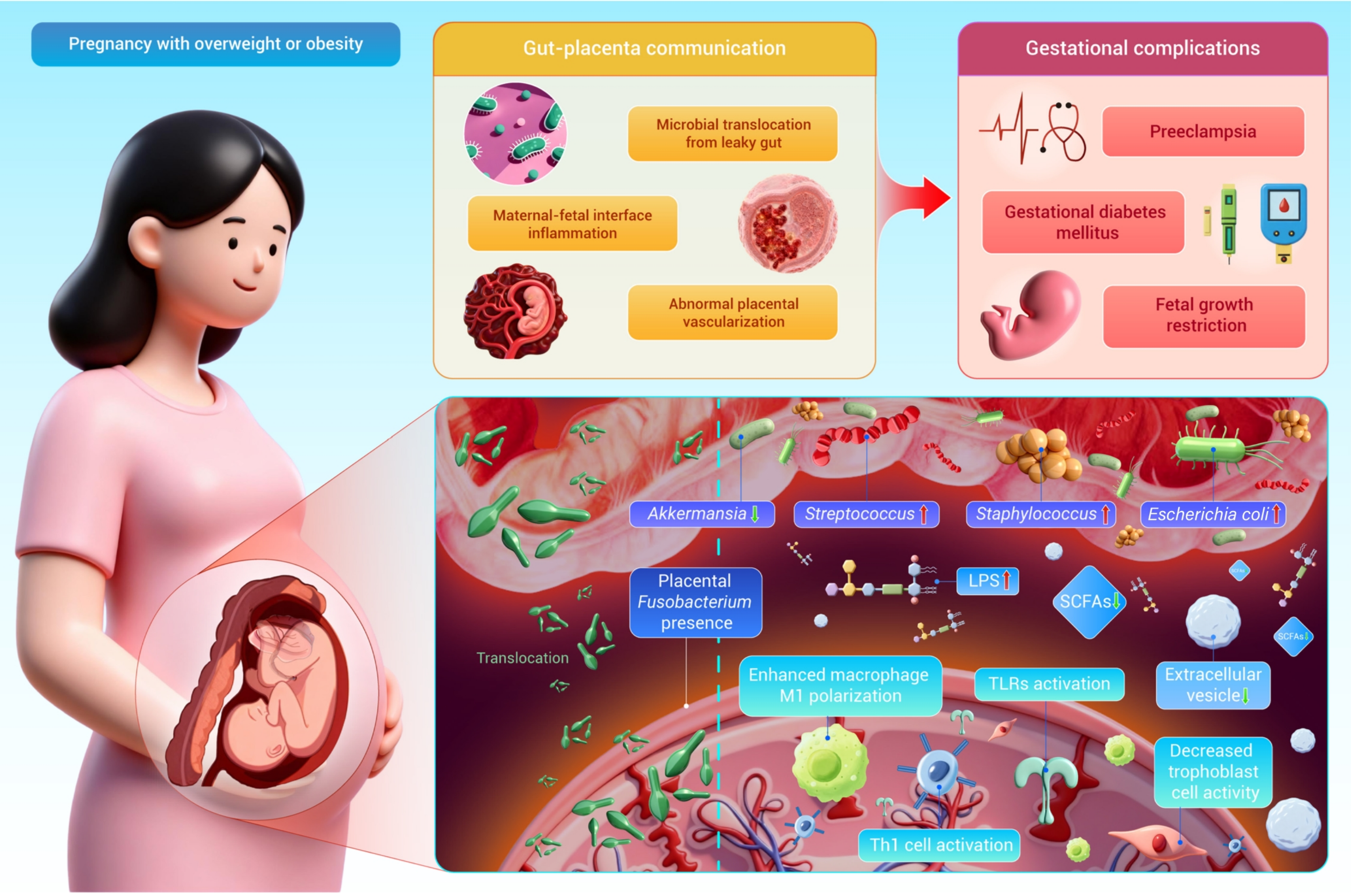
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Maternal obesity increases the risk of gestational diabetes, preeclampsia, and fetal growth restriction.
- This review explores the 100 years of the gut-placenta axis and its role in placental health and pregnancy.
- Obesity-related gut dysbiosis forms a “common soil” linking placenta dysfunction to pregnancy complications.

From gut dysbiosis to placental dysfunction in maternal obesity: A common soil for gestational complications

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Maternal obesity constitutes a risk factor for gestational complications and adverse pregnancy outcomes. While insulin resistance, metabolic syndrome, and inflammation are recognized contributors, the clinical heterogeneity among these disorders suggests the involvement of systemic, cross-organ interactions. Among these, the gut-placenta axis has become a mechanistic bridge linking maternal metabolism with placental development and fetal health. This review examines the evolution of the gut-placenta axis over the past 50 years and looks forward to its clinical translation in the next 50 years. The obesity-related gut microbiota alterations and their associations with placental dysfunction are summarized. We propose that obesity-induced gut dysbiosis establishes a shared pathophysiological foundation, or "common soil", characterized by microbial translocation, inflammation at the maternal-fetal interface, and abnormal placental vascularization. From this shared foundation emerge diseases including gestational diabetes mellitus (GDM), preeclampsia (PE), and fetal growth restriction (FGR). Current microbiota-targeted interventions have demonstrated partial metabolic improvements but limited clinical efficacy, highlighting the need for better experimental models, optimal timing, and targeted delivery. Ultimately, targeting this common soil may enable a transition from association to prevention, and transform obesity-related pregnancy complications from adverse outcomes into preventable conditions.

INTRODUCTION

Maternal obesity, typically defined as excessive adiposity with a body mass index (BMI) > 25 kg/m^2, is a significant global public health issue.[1] Recent projections indicate that by 2050, more than 80% of women in 60 countries and regions will be overweight or obese.[2] This study also suggests that by that time, China will have 627 million overweight or obese individuals, the highest number globally. This demographic shift would generate a serious burden on the global obstetric health system.

In 2024, a Swedish cohort study including 1,164,783 pregnancies from various regions demonstrated that overweight and obesity contributed significantly to adverse pregnancy outcomes, including gestational diabetes mellitus (GDM, 52.1%, 95% CI: 51.0-53.2), preeclampsia (PE, 26.5%, 95% CI: 25.7-27.3), infant mortality (12.7%, 95% CI: 9.8-15.7), severe maternal morbidity (8.5%, 95% CI: 6.0-11.0), and preterm birth (5.0%, 95% CI: 4.4-5.7).[3] A systematic review of 1,309,136 pregnancies suggested that with rising maternal BMI, the incidence of adverse pregnancy outcome in women increases from 34.7% (BMI < 18.5) to 61.1% (BMI > 40).[4] Moreover, a meta-analysis indicated that obesity exacerbates the risk of gestational complications, as seen in GDM, which elevates the risk of large-for-gestational-age infants (OR 3.22, 95% CI: 2.17, 4.79) and macrosomia infants (OR 3.71, 95% CI: 2.76, 4.98) by three- to fourfold.[5] These associations suggest that maternal obesity acts as a common risk factor for multiple gestational complications, likely driven by shared mechanistic pathways.[6] While chronic inflammation, insulin resistance, and excess gestational weight gain (GWG) are commonly implicated, these factors alone fail to account for the clinical heterogeneity observed in obese pregnancies.[7] For instance, only a subset of women with overweight or obesity developed PE or GDM despite similar metabolic profiles, suggesting additional systemic contributors beyond traditional risk factors.[3,8]

Recent studies have demonstrated the gut-placenta axis as a significant pathway linking gut microbiota to maternal and fetal health, where gut dysbiosis might initiate a cascade of events, including placental inflammation and impaired placental angiogenesis.[9-11] However, few works have synthesized these findings into an integrated framework explaining how maternal obesity drives placental pathology. Drawing from the "common soil" hypothesis established in cardiovascular and metabolic research, we propose that obesity-related gut dysbiosis establishes a chronic inflammatory-metabolic environment that serves as a common soil for placental dysfunction.[12,13] This common soil, defined by microbial translocation, maternal-fetal interface inflammation, disrupted microbial metabolites, and abnormal placental vascularization, represents a shared pathological foundation underlying multiple gestational complications. This framework considers gestational complications as interconnected outcomes of a gut-placenta axis, and supports the study of microbiota-based strategies.

This review also traces the evolution of the gut-placenta axis over the past five decades. We summarize current evidence on how maternal obesity alters gut microbial composition and function, and how these changes influence placental pathology. Emphasis is placed on gut microbiota-regulated signaling networks and shared placental pathological foundations in gestation complications. Current microbiota-targeted interventions for preventing gestational complications in women with maternal obesity are evaluated. Finally, we identify existing problems and propose next-generation strategies.

FIFTY YEARS BEHIND AND FIFTY YEARS AHEAD: INSIGHTS INTO THE GUT-PLACENTA AXIS

The gut-placenta axis describes how maternal gut microbiota influence placental immune balance, nutrient transport, angiogenesis, and trophoblast development, primarily through microbial translocation, metabolites, and immune modulation.[14] This section reviews key milestones in gut-placenta axis research, spanning theoretical developments, experimental models advances, and clinical translation, and considers future directions in this area.

Theoretical shifts

The concept of the gut-placenta axis emerged in the 1970s, when studies first linked *Listeria monocytogenes* infection to placental inflammation.[15-17] Since 2007, research have revealed that microbiota-derived lipopolysaccharides (LPS) contribute to adverse pregnancy outcomes through placental trophoblast.[18,19] Aagaard and colleagues further advanced this field by identifying possible placental microbial, challenging the "sterile womb" hypothesis.[20] However, subsequent debates raised concerns about contamination and the origin of these microbes.[21] Since 2017, fecal microbiota transplantation (FMT) research has steadily indicated that the gut dysbiosis causally induces placental inflammation and vascular dysfunction in models of malaria, PE, fetal growth restriction (FGR), and GDM.[22-25] More recently, depletion of maternal microbiota was shown to impair placental angiogenesis and fetal growth.[10] Intriguingly, paternal gut dysbiosis also affected placental development by altering sperm quality.[26] The theoretical development of the gut-placenta axis in the past 50 years is summarized in Table 1.

Table 1. Milestones in the development of the gut-placenta axis theory over the past 50 years.

Year	Summary	Key Findings	Reference
1970	Listeria and pregnancy loss	*Listeria monocytogenes* infection induces placental inflammation, necrosis, and miscarriage.	15
1981-1990	Vitamin D and the placenta	Vitamin D was identified as the first nutrient mediating gut-placenta nutrient transfer.	27
1992	Appendicitis and placental abruption	Appendicitis was linked to placental abruption via inflammatory pathways.	28
2004-2008	*Listeria* placental invasion	Mechanistic analysis of *Listeria monocytogenes* placental translocation and infection.	29,30
2009	Lipopolysaccharides (LPS) and preterm birth sex differences	Gut-derived LPS triggers sex-specific tumor necrosis factor-α (TNF-α) upregulation in trophoblasts, influencing implantation, pregnancy maintenance, and adverse outcomes.	31
2014	Placental microbiome in preterm birth	First large-cohort study using 16S rRNA and metagenomics to detect placental microbiota linked to preterm birth.	20
2014	Probiotics and preterm birth	*Lactobacillus rhamnosus* GR-1 supernatant alleviates LPS-induced preterm birth and placental inflammation in mice.	32
2017	Placental and oral microbiota	Placental microbiota shows higher phylogenetic similarity to oral than gut microbiota from early pregnant women with overweight and obesity.	33
2019	Gut microbiota and malaria in pregnancy	Transplanting malaria-resistant gut microbiota affects *Plasmodium chabaudi* infection severity, placental vascularization, monocyte infiltration, and inflammation in mice.	22
2020	Gut dysbiosis links to gestational complications	Gut microbiota is speculated to affect gestational complications.	9,23
2020	Bacterial translocation in preeclampsia (PE)	Gut-derived bacteria translocate to the placenta in PE patients, elevating total bacterial load, *Fusobacterium*, and inflammatory cytokines.	23
2020	Placental microbiome controversy	Debate over the robustness of human placental microbiome evidence and bacterial transfer to the fetal gut.	34
2022	Short-chain fatty acids (SCFAs) depletion in PE	PE patients show gut dysbiosis with reduced SCFAs-producing bacteria.	24
2023	Gut microbiota and fetal growth restriction (FGR)	Maternal gut microbiota depletion leads to FGR and placental vascular dysfunction in germ-free mice.	10
2023	Propionate and placental inflammation	Propionate via G protein-coupled receptors 41/ protein kinase B (GPR 41/AKT) signaling enhances placental macrophage autophagy, M2 polarization, and mitigates PE-induced inflammation.	24
2023	Lachnospiraceae and gestational diabetes mellitus (GDM)	Lachnospiraceae mitigates GDM-induced insulin resistance and placental inflammation.	25
2023	*Akkermansia muciniphila* extracellular vesicles (EVs) and spiral artery remodeling in PE	*Akkermansia muciniphila* EVs activate epidermal growth factor receptor/phosphoinositide 3-kinase/protein kinase B (EGFR/PI3K/AKT) signaling to remodel spiral arteries and alleviate PE in a mouse model.	35
2023	Placental microbiome skepticism	Lack of evidence for viable and replicating microbes in healthy placenta questions the placental microbiome concept.	21
2024	Galectin-3 (Gal-3) and placental metabolism	Maternal Gal-3 deficiency alters gut microbiota, leading to placental glucose metabolism disruption and fetal growth restriction.	36
2024	Paternal gut microbiota and sperm quality	Paternal gut dysbiosis impairs leptin signaling, alters testicular metabolites, and damages sperm RNA, affecting placental colonization.	26
2024	Bisphenol A, gut dysbiosis, and placenta	Gut dysbiosis mediates Bisphenol A-induced placental apoptosis, oxidative stress, and FGR.	37
2024	Trimethylamine-N-oxide (TMAO) and PE	TMAO from gut microbiota induces oxidative stress, inflammation, and PE symptoms, reversible by TMAO inhibitors.	38
2025	Gut microbiota and FGR recovery	*Butyricimonas* and *Lactobacillus murinus* improve placental efficiency, fetal growth, and gut function in FGR mice models.	11,39
2022-2025	SCFAs and FGR	SCFAs improve FGR outcomes, placental inflammation, and vascularization via GPCRs pathways.	10,24,25,39

Together, these findings solidify the gut-placenta axis concept and illustrate how gut microbiota influence placental health through immune and vascular pathways.

Experimental models and technological advances

Since the first in vitro placental trophoblast model was established in 1999, various cell lines have been developed to study gut microbiota-derived metabolites on placental cells. However, conventional 2D models lack the complexity to simulate trophoblast invasion or spiral artery remodeling.[40] 3D trophoblast organoids preserve cellular heterogeneity and functional architecture, offering more physiologically relevant platforms for investigating maternal-fetal interactions.[41] Notably, a 2023 study used a G-protein-coupled receptor (GPCR)-targeted single-guide RNA library in mouse trophoblast organoids combined with CRISPR-Cas9 screening to identify regulators of placental function.[42] Human trophoblast stem cell-derived placental organoids now allow transplacental permeability studies of microbial metabolites.[43] Future models may integrate placental and intestinal organoids in microfluidic systems to simulate the gut-placenta-fetus axis.[41] Animal models also contributed significantly. A murine model of *Listeria monocytogenes* placental infection was first introduced in 2007,[44] and *Lactobacillus*

Table 2. Experimental models and technological advances in gut-placenta axis research.

Year	Summary	Key Findings	Reference
1999	First in vitro trophoblast model	Established the first in vitro trophoblast cell model.	[47]
2007	Murine model for listeriosis	Developed a versatile murine model for human listeriosis.	[44]
2009	Probiotics mitigate trophoblast inflammation	Probiotics (*Lactobacillus rhamnosus* GR-1) supernatant alleviates LPS-induced trophoblast inflammation in a mouse model.	[31]
2014	Placental microbiome profiling	Analyzed placental microbiome of 320 pregnant women using 16S rRNA sequencing and whole-genome shotgun metagenomics.	[20]
2014	Probiotics reduce lipopolysaccharides (LPS)-induced preterm birth	Probiotics (*Lactobacillus rhamnosus* GR-1) supernatant alleviates LPS-induced inflammation in the preterm birth mice model.	[32]
2018	Single-cell atlas of early placenta	Single-cell RNA-seq mapped the maternal-fetal interface and trophoblast differentiation, advancing understanding of early placental development.	[48]
2018-2020	Trophoblast organoids	Developed long-term, genetically stable human trophoblast organoids.	[49,50]
2020	Gut microbiota induces preeclampsia (PE) symptoms	Fecal microbiota transplantation from PE patients induced PE-like symptoms in mice.	[23]
2023	Multi-omics mapping of trophoblasts	Single-cell transcriptomics, snRNA-seq, spatial transcriptomics, and spatial proteomics mapped human trophoblast differentiation and invasion at the maternal-fetal interface.	[45,51]
2023	CRISPR screening of G protein-coupled receptors (GPCRs) in trophoblasts	High-throughput CRISPR-Cas9 screening using a GPCRs sgRNA library in mouse trophoblast organoids.	[42]
2024	Placental barrier organoid model	Developed a trophoblast stem cell-derived human placental barrier organoid model.	[43]
2024	Placental compound transfer	Organoid model assesses compound transfer across the placenta.	[43]

supernatant was shown to alleviate placental inflammation.[31,32] Germ-free mouse FMT experiments first suggested a causal relationship between microbiota and placental function in malaria, and later extended to other complications.[22] Yet, species-specific placental structures limit translation to humans, and ethical constraints restrict primate model use.[45,46]

As shown in Table 2, for technological advances, shotgun metagenomic sequencing was initially employed to identify the placental microbiome in 320 pregnant women in 2014.[20] Recently, integration of single-cell omics and spatial omics has constructed a map of placental trophoblast differentiation and invasion at the interaction zone between mother and fetus, and they are expected to deepen understanding of gut microbiota-placenta interactions between healthy and gestational complications pregnancies.[45]

Clinical translation

Present studies have noted some microbial biomarkers associated with gestational complications. In patients with PE, the gut microbiota showed an increase in harmful bacteria like *Fusobacterium* and *Veillonella*, and a reduction in beneficial genera such as *Faecalibacterium* and *Akkermansia*.[23] Notably, lowered levels of propionate and higher trimethylamine-N-oxide (TMAO) have been related to PE severity, suggesting their potential as diagnostic biomarkers.[24,38] Similarly, in GDM, the decreased levels of acetate, propionate, and butyrate correlated with elevated placental inflammation.[52] Though limited in humans, FGR-related studies in animal models showed gut dysbiosis, pro-inflammatory trends, and distinct serum metabolic profiles.[53-55]

Large cohort studies proposed that probiotic intake is associated with a reduced risk of PE,[56-57] whereas randomized controlled trials and systematic reviews have shown limited benefits for GDM or overall pregnancy outcomes and even a potential increase in PE risk.[58-60] As shown in Table 3, current evidence indicates that gut microbiota interventions can transiently improve metabolic and inflammatory states during pregnancy, yet clinical outcomes remain inconsistent. Future studies should refine probiotic strain selection, dosage, and intervention timing, and include long-term tracking of outcomes for mothers and infants.[58]

The gut-placenta axis for the next 50 years

Future progress in gut-placenta research will focus on transforming correlative observations into clinical strategies. Three directions appear particularly critical.

First, the short-term goal for the next decade is to establish causality. While emerging studies have begun to reveal causal links between gut dysbiosis and placental dysfunction, future research should explore how gut microbiota interventions, such as microbes, microbial metabolites, or extracellular vesicles, interact with host targets that control angiogenesis, oxidative balance, and inflammation.[68] Therefore, it is essential to develop optimized experimental models and deep metagenomic sequencing. Second, robust clinical validation is essential to translate mechanistic insights into practice. Large-scale randomized controlled trials across diverse populations are required to determine effectiveness, dosage, optimal timing, and long-term safety. Particular attention should be given to strain-specific effects and potential risks, ensuring that microbiota-based interventions are both effective and safe for mothers and their offspring.[69] Third, gut-placenta axis targeted interventions are expected to be developed in the next 50 years. Notably, placenta-targeted delivery of mRNA and bacterial exosomes has been effective in animal experiments and will be a future treatment for pregnancy complications due to placental dysfunction.[35,70] Synthetic biology provides tools for designing engineered probiotics capable of delivering beneficial metabolites or degrading harmful compounds like TMAO.[71] The integration of culturomics, in-depth metagenomics sequencing, and artificial intelligence could enable personalized gut microbiota interventions, optimizing microbial strains, dosages, and intervention windows according to individual profiles.[51,72,73]

OBESITY AND GESTATIONAL COMPLICATIONS

Maternal obesity is a significant risk factor for placenta-related gestational complications, including PE, GDM, and FGR. These disorders reflected a common pattern of placental maladaptation to the obese maternal metabolic syndrome, and gut dysbiosis is a mediator linking to adverse pregnancy outcomes.[63,74,75] This section will examine the interconnections between obesity and these major gestational complications while emphasizing the influence of gut microbiota alterations on their development.

GDM

GDM is characterized by abnormal glucose metabolism first detected during pregnancy, affecting 10-15% of pregnant women globally based on the International Association of Diabetes and Pregnancy Study Groups criteria.[76] A Swedish large-scale cohort study demonstrated that overweight and obesity are its most consistent risk factors, making up 52.1% GDM cases.[3] Recent perspectives have proposed that GDM extends beyond a state of insulin resistance and should be regarded as a placenta-centered disorder, as placental hormones are crucial in inflammation, angiogenesis, and metabolic adaptations during pregnancy.[77]

Table 3. Key biomarkers and clinical translation in gestational complications.

Category	Year	Summary	Key Findings	Reference
Biomarker discovery	2020	Gut microbiota composition alterations in preeclampsia (PE).	PE patients had enriched *Fusobacterium* and *Veillonella*, with depleted *Faecalibacterium* and *Akkermansia* in their gut microbiota.	[23]
	2022	Gut-derived metabolites in PE patients.	Depletion of Short-chain fatty acids (SCFAs, especially propionate) in feces, serum, and placenta of PE patients in late pregnancy.	[24]
	2022	SCFA depletion and gestational diabetes mellitus (GDM) inflammation.	Reduced acetate, propionate, and butyrate in GDM pregnancies correlated with pre-pregnancy body mass index (BMI), gestational weight gain, and placental inflammation.	[52]
	2023	Gut microbiota-metabolite alterations in fetal growth restriction (FGR).	FGR showed distinct fecal and serum metabolomic profiles, with altered metabolites (allantoin, ethanolamine-2-phosphate, lauric acid) linked to gut dysbiosis.	[53]
	2024	Trimethylamine-N-oxide (TMAO) linked to PE severity.	Elevated TMAO levels in PE pregnancies positively correlated with disease progression.	[38]
Clinical translation	2011	Probiotics milk lowers PE risk.	A Norwegian cohort study found the frequency of probiotics milk (*Lactobacilli*) consumption correlated with reduced PE risk in primiparas.	[56]
	2012	Probiotics impact fetal immunity.	A double-blind trial showed probiotics (*Bifidobacterium lactis* and *Lactobacillus rhamnosus* GG) intake for 14 days ahead of a planned cesarean section at full term altered microbial DNA in placenta/amniotic fluid and fetal gut Toll-like receptors (TLRs) gene expression.	[61]
	2018	Probiotics milk reduces preterm birth and PE risk.	A systematic review suggested early probiotics milk (*Lactobacillus and Bifidobacterium*) intake was linked to reduced preterm birth risk, while late pregnancy intake was associated with lower PE risk.	[57]
	2019-2021	No effect of fish oil/probiotics on GDM.	Several randomized, double-blind trials suggest that fish oil and/or probiotics (*Lactobacillus* and *Bifidobacterium*) supplementation did not significantly lower the incidence of GDM in overweight and obese women.	[60,62,63]
	2024	Gut microbiota shifts with lifestyle changes in GDM.	*Bifidobacterium* abundance increased in GDM patients after lifestyle modifications, which negatively correlated with glycemic markers.	[64]
	2024	Probiotics lower the pre-labor rupture of membranes.	Probiotics (*Lactobacillus*) intake from gestational week 16 to 37 lowered the occurrence of pre-labor membrane rupture before term, and pre-labor rupture of membranes.	[65]
	2024	Synbiotics mitigate PE risk.	Daily supplementation with symbiotic (*Lactobacilli*, *Bifidobacteria*, and fructo-oligosaccharide) until delivery reduced systolic/diastolic blood pressure, severe PE, and proteinuria incidence of pregnancies with mild PE.	[66]
	2024	No metabolic impact of probiotics in GDM.	Daily supplementation with a Probiotics mix (*Lactobacillus* and *Bifidobacterium*) until delivery did not alter blood glucose or fetal weight in GDM pregnancies.	[59]
	2023	Prebiotics improve microbiota, with no metabolic effect.	Early pregnancy galacto-oligosaccharide supplementation improved gut microbiota but did not affect glucose metabolism or systemic inflammation of GDM pregnancies.	[67]

Data summarized from representative studies published between 1970 and 2025 exploring the gut-placenta axis in pregnancy.

The gut microbiota alterations in GDM pregnancies have been summarized in the recent review.[78] Several large-scale studies described reduced α-diversity in GDM at various stages,[79,80] but not all cohorts reproduce these changes.[81-83] The variation might result from insulin resistance, ethnicity, and sampling time across cohorts. As suggested in a case-control trial, Shannon index fluctuates dynamically throughout gestation (T1-T3) in healthy pregnancies, while no similar patterns were noticed in GDM pregnancies.[79] Consequently, studies sampling at different trimesters may yield contrasting results when comparing GDM to controls. However, the common finding of these studies was an enrichment of pro-inflammatory taxa such as *Proteobacteria* and *Acidobacteria* in GDM pregnancies, which were related to hyperglycemia and insulin resistance.[83] A Danish cohort study found that individuals exhibit gut microbiota disruptions associated with insulin resistance and excessive gestational weight gain, and these alterations persist beyond 8 months of gestation.[81] Previous findings remained largely correlative, but animal models provided stronger mechanistic evidence bridging gut dysbiosis and GDM. Notably, fecal microbiota from GDM patients across all trimesters (T1-T3), when transplanted into germ-free mice, induced systemic inflammation and insulin resistance, establishing a causal relationship.[83,84] These observations suggest that obesity-related GDM is manifested as insulin resistance and placental inflammation, potentially exacerbated by gut dysbiosis.[25,83,85]

PE

The metabolic and inflammatory disturbances contributing to GDM are also implicated in the pathogenesis of PE, highlighting a shared mechanistic basis.[74] The PE is a maternal syndrome during pregnancy, manifested as the clinical features of hypertension (blood pressure ≥ 140/90 mmHg) and proteinuria (urinary protein ≥ 300 mg/24 h) appearing after 20 weeks of pregnancy.[68] It increases the risks of placental abruption, coagulation disorders, fetal complications, and maternal morbidity and mortality.[86] Established risk factors include prior PE, pre-gestational diabetes, antiphospholipid syndrome, and maternal obesity.[86] Among these, obesity is one of the most studied factors.[38,87] Although obesity is classified as a medium-level risk factor, a Swedish cohort study suggested that overweight and obesity accounted for a considerable part of PE (26.5% [25.7-27.3]).[3,88] A Mendelian randomization study has shown a close relevance between pre-pregnancy BMI and risk of PE.[89]

Compared with GDM, placental damage is more severe and primarily arises from defective spiral artery remodeling, leading to vascular endothelial disorders and multiorgan damage.[90] Despite some negative results, most studies found significant microbial diversity differences between PE and healthy pregnancies, suggesting that PE may exhibit a stronger association with gut dysbiosis than GDM.[91-93] At various sampling times, the gut microbiota diversity of PE pregnancies was substantially decreased compared to that of healthy pregnancies.[23-24,38,94] Especially, human studies identified gut microorganisms closely associated with PE, such as *Streptococcus*, *Bifidobacterium*, *Escherichia-Shigella*, *Akkermansia muciniphila*, *Verrucomicrobia*, and *Fusobacterium*.[23,24,94] However, most findings remain correlative rather than causal. Although human PE cannot be fully replicated in rodents,[95] a landmark study found that transferring gut microbiota from PE patients into rodents partially induced PE-like symptoms (inadequate invasion of placental dysfunction, hypertension, and proteinuria), confirming microbiota could produce effects.[23,24,38] *Akkermansia muciniphila* depletion was consistently observed in PE patients across clinical studies.[23,24,96] Notably, restoring *Akkermansia muciniphila* in PE rodent models alleviated symptoms such as hypertension and proteinuria.[21,23] The detailed receptors and signaling pathways will be discussed later.

FGR

Beyond PE, placental vascular insufficiency caused by maternal obesity can also lead to FGR. The FGR is referred to as the inability of a fetus to achieve its genetic capability for growth, representing a primary reason for stillbirth and newborn health problems around the world.[97] Most FGR cases are attributed to placental insufficiency, which disrupts the transfer of oxygen and nutrients to the fetus.[98] Based on World Health Organization data, 21.9 million live births globally were term small-for-gestational-age (SGA) infants, which are considered typical manifestations of FGR.[99] FGR's complex etiology involves maternal and environmental factors, including impaired intrauterine environment, genetic susceptibility, nutritional deficiencies, and toxin exposure.[99] Unlike PE, which originates from defective spiral artery remodeling, FGR results from impaired nutrient transport and inadequate placental function.[100,101] However, FGR shares several features with PE, such as impaired angiogenesis, hypoxia, and reduced birth weight.[102] A raised ratio of soluble fms-like tyrosine kinase-1 (sFlt-1) to placental growth factor (PlGF) enhances FGR prediction when combined with Doppler ultrasound,[97,101] and dysregulated concentrations of sFlt-1, PlGF, and vascular endothelial growth factor (VEGF) are linked to poor neonatal outcomes and increased PE risk.[103] In overweight or obese mothers, the incidence of SGA infants and gestational hypertension was markedly increased, largely attributable to placental dysfunction.[104,105] Notably, among mothers with BMI ≥ 40, SGA infants faced a 3.15-fold higher stillbirth risk in Australia (95% CI: 2.22-4.47).[106]

In a Turkish cohort, high pre-pregnancy BMI is negatively correlated to both birth weight and fecal microbial α-diversity in the first trimester of pregnancy.[107] However, existing FGR cohorts remain scarce, whereas human studies were underpowered and sampling was limited to a single gestational stage, due to the complexity of FGR etiology.[53,108-110] Future large-scale cohort studies integrating metagenomic analyses are required to uncover how the gut microbiota reprograms metabolism and drives pregnancy pathogenesis.

Most evidence on FGR and gut microbiota was derived from animal studies, where placental nutrient transport regulated by microbiota has been a focus. Germ-free mice exhibited restricted fetal growth and impaired fetal-placental vascularization,[10,111] and microbiota from FGR donors induced structural remodeling of the placental labyrinth and downregulated expression of fatty acid binding protein 3 (FABP3).[53] These defects coincide with a decrease of substances derived from microbiota, including fatty acids, essential amino acids, and bile acids, which are essential for trophoblast metabolism and fetal nutrient uptake, and this is also evidenced by the FGR fetuses' metabolomic profile.[53,100,112] For example, evidence found an aberrant tryptophan metabolism in the gut microbiota of pregnancies with FGR infants,[112] while melatonin supplementation restored fetal growth in animal models, and its mechanism would be demonstrated later.[11] However, the causal relationship between these nutrient reductions and improved placental vascularization is unclear, and this mechanism needs to be further investigated in the future.

In summary, although PE, GDM, and FGR have distinct pathophysiological mechanisms, they share a common association with maternal obesity and gut microbiota dysbiosis. Gut microbial alterations in obesity may represent an upstream driver of these complications.[63]

GUT DYSBIOSIS IN MATERNAL OBESITY

Due to pregnancy-related changes in metabolism, hormones, appetite, and lifestyle during pregnancy, gut microbiota will differ between obese pregnant women and obese non-pregnant women.[113,114] Previous reviews have described the gut microbiota alterations in a healthy pregnancy, but gut dysbiosis in maternal obesity has not been reviewed before.[115] Therefore, it is essential to understand gut dysbiosis in maternal obesity before exploring the potential risks.

Decreased α-diversity in fecal microbiota

The α-diversity is used as a fundamental gut homeostasis indicator, and decreased α-diversity in maternal obesity suggests a fragile gut microbiota ecosystem.[116] An American large-scale cohort study showed that the α-diversity (Chao1 and Shannon indices) in fecal samples collected post-delivery is significantly lower in women with a higher BMI before pregnancy compared to those with a normal BMI.[117] Most studies involving the gut microbiota structure in maternal obesity have reported similar results.[117-119] However, a study by Abdullah et al. in 2022 observed no notable variations, possibly due to population variation, as some participants were also diagnosed with GDM.[120] The gut microbiota alteration in maternal obesity is summarized in Table 4.

High energy harvest efficiency of microbes from carbohydrates

Enhanced carbohydrate energy extraction by gut microbiota is another significant characteristic observed in maternal obesity. It typically manifests as a raised Firmicutes/Bacteroidetes (F/B) ratio and decreased abundance of Bacteroides, resembling the gut microbiota characteristics of non-pregnant individuals with obesity.[107,121] Despite the different sampling times, studies reported increased Firmicutes or decreased Bacteroides in the fecal microbiota of overweight or obese pregnancies.[107,121,122] A large-scale Chinese cohort using metagenomic sequencing identified reduced microbial diversity and decreased abundance of Bacteroides as strongly associated with maternal dyslipidemia.[118] These changes correlated with metabolic disturbances, including insulin resistance, dyslipidemia, and elevated C-reactive protein during pregnancy, linking F/B to glucose metabolism disorder.[118,121] Conversely, due to the differences in diet, digestion, and insulin resistance, some cohort studies have failed to observe this trend, but the F/B was inversely correlated with α-diversity and fasting plasma glucose.[63,79,127] Gut microbes belonging to the Firmicutes phylum normally exhibit a higher carbohydrate utilization efficiency by degrading non-digestible fiber.[116] This structural change may represent a gut microbiota adaptive adjustment to satisfy the rising energy needs of both the mother and the fetus during pregnancy.

Pro-inflammatory gut microbiota composition

As summarized in Figure 1, gut microbiota composition in pregnancies with obesity shows pro-inflammatory and prohypertensive tendencies. The gut microbiota of women with obesity and overweight during pregnancy tends to harbor more potentially pathogenic bacteria, such as Proteobacteria, *Staphylococcus*, *Streptococcus*, *Megamonas*, and *Escherichia coli*, whose abundances are significantly increased compared with pregnant women with normal BMIs.[120,122,128] Pathogenic gut bacteria adhere to epithelial cells and secrete toxins that disrupt barrier integrity, facilitating endotoxin leakage into circulation.[129] This triggers systemic inflammation characterized by elevated cytokines interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), closely linked to placental dysfunction.[75] Moreover, trimethylamine (TMA), derived from choline by *Escherichia coli*, undergoes oxidation to TMAO in the liver, a proinflammatory metabolite known to exacerbate vascular inflammation and hypertension (Figure 1).[130]

Decreased short-chain fatty acids (SCFAs)-producing bacteria and SCFA levels

A consistent feature of maternal obesity is the depletion of *Akkermansia*

Table 4. Overview of changes in gut microbiota linked to maternal obesity in human and animal studies.

Object	Sample source	Sample time	Alterations in gut microbiota composition	Reference
Human	Women with pre-pregnancy overweight (Body mass index, BMI >30)	First trimester	UP: Firmicutes, *Prevotella copri* DOWN: Bacteroides, Proteobacteria	107
	Women with pre-pregnancy overweight (BMI = 25.0-29.9)	First trimester and the third trimester	UP: *Megamonas, Succinatimonas, Dialister* DOWN: *Papillibacter, Oscillibacter, Oscillospira, Blautia, Dorea, Alistipes, Prevotella, Paraprevotella*	120
	Women with pre-pregnancy overweight (BMI 25-29.9) and obesity (BMI > 30)	Third trimester	UP: Firmicutes, Firmicutes/Bacteroidetes, Lachnospiraceae, Leuconostocaceae, Actinomycetaceae, *Faecalibacterium, Coprococcus, Blautia* DOWN: Tenericutes, Desulfovibrionaceae, Bacteroidaceae, *Actinomyces, Bacteroides*	121
	Pregnancy with overweight at 20 weeks of gestation (BMI > 25)	Twenty-four weeks of pregnancy	UP: *Staphylococcus,* Enterobacteriaceae, *Escherichia coli* DOWN: *Bifidobacterium, Bacteroides, Akkermansia muciniphila*	122
	Pregnancy with dyslipidemia in the second or third trimester	Second and third trimester	DOWN: α-diversity, *Bacteroides*, *Clostridia UCG-014*, *Paraprevotella*, *Christensenellaceae* R7 *group*, *Alistipes*, and UCG-002	118
	Women with pre-pregnancy overweight (BMI 25-29.9)	Third trimester	UP: Bacteroidetes, *Bacteroides, Acidaminococcus, Dialister* DOWN: α-diversity, *Phascolarctobacterium*	119
	Pregnancy with pre-pregnancy overweight (BMI 25 29.9) and obesity (BMI > 30)	Four days post-partum	UP: Lachnospiraceae DOWN: α-diversity, Ruminococcaceae, Christensenellaceae, Clostridiaceae, *Faecalibacterium, Bifidobacterium, Parabacteroides*	117
Mice	High-fat diet-fed female C57BL/6J mice	Four weeks postpartum	UP: Bacillota DOWN: Bacteroidota	123
	High-fat diet-fed female Wistar rats	Postnatal day 12	*UP:* unknown Lachnospiraceae, unknown Ruminococcaceae, *Parabacteroides, Butyricicoccus* DOWN: Lactobacillaceae, *Lactobacillus, Enterococcus, Clostridium* sensu stricto 1, *Escherichia–Shigella*	124
	High-fat diet-fed female C57BL/6J mice	Before mating and at embryonic day (E0.5, E10.5, E15.5 and E18.5)	UP: *Clostridium*, Dorea DOWN: *Ruminococcus, Lachnospira, Bifidobacterium, Bacteroides, Coprococcus*	125
	High-fat diet-fed female C57BL/6J mice	At E0.5, E6.5, E10.5 and E14.5	DOWN: Clostridiales, Ruminococcaceae, Lachnospiraceae	114
	High-fat diet-fed female C57BL/6J mice	Gestation day 1	UP: α-diversity, Lachnospiraceae, Rikenellaceae, Ruminococcaceae, *Bacteroides, Prevotella, Mucispirillum, Helicobacter* DOWN: *Bacteroidetes, Bacteroidetes S24-7, Allobaculum, Sutterella*	126

Data summarized from published studies exploring the effects of maternal overweight and obesity on gut microbiota composition. Most studies used 16S rRNA or metagenomics sequencing to assess taxonomic change.

muciniphila, a keystone bacterium essential for mucin degradation, gut barrier maintenance, and SCFA production (Figure 2).[131] This bacterium promoted glucose and lipid homeostasis through GLP-1 secretion and its outer-membrane protein Amuc_1100.[35,132] Moreover, *Akkermansia muciniphila* is depleted in obese pregnant women and in patients with GDM and PE, suggesting that its reduction may represent a shared microbial link connecting maternal obesity with gestational complications.[24,81,133]

The reduced production of SCFAs ties the themes of maternal obesity, gut microbiota, and gestational complications. In an Australian cohort, 205 obese pregnant women, butyrate production and the abundance of *Odoribacter* were both reduced and inversely correlated with systolic blood pressure.[128] Pregnancies with overweight and obesity showed a decreased fecal SCFAs level, and the reduced butyrate is associated with hepatic lipid accumulation.[134] Similar reductions in other SCFAs-producing taxa (Ruminococcaceae, *Parabacteroides*, *Butyricimonas*, *Bifidobacterium*, and *Faecalibacterium*) have been reported.[117,120,122] However, some studies observed elevated acetate levels in pre-pregnancy obesity.[134,135] Acetate often increases in obesity due to altered fiber metabolism and gut ecology, but this rise does not necessarily compensate for the loss of total SCFAs.[136] Yet, the interpretation of such results requires caution, as many studies are cross-sectional and cannot establish causality.

In summary, despite variations across populations, the common theme is that maternal obesity leads to a gut dysbiosis that is prone to metabolic disorders, gut barrier damage, pro-inflammatory signaling, and hypertension. These dysregulated changes set the stage for downstream complications.

CROSS-COMPLICATION SIGNALING NETWORKS REGULATED BY GUT MICROBIOTA

Gut microbiota in pregnant women with obesity, particularly its metabolites, influences signaling networks for gestational complications. As shown in Figure 3, the maternal obesity-induced gut dysbiosis alters key signaling molecules that regulate immune responses, placental vascularization, hypoxia, and oxidative stress, thereby forming pathologies for pregnancy complications.

TLR

LPS-mediated inflammation provides a mechanistic link between obesity and placental pathology. A cross-sectional trial showed that serum zonulin, a biomarker associated with gut barrier function, was positively correlated with circulating triglyceride and LPS levels in women with overweight and obesity.[137] In maternal obesity, gut dysbiosis, marked by a decrease in SCFAs-producing bacteria and enrichment of Gram-negative pathogens, leads to increased translocation of pathogen-related molecular patterns (PAMPs), like

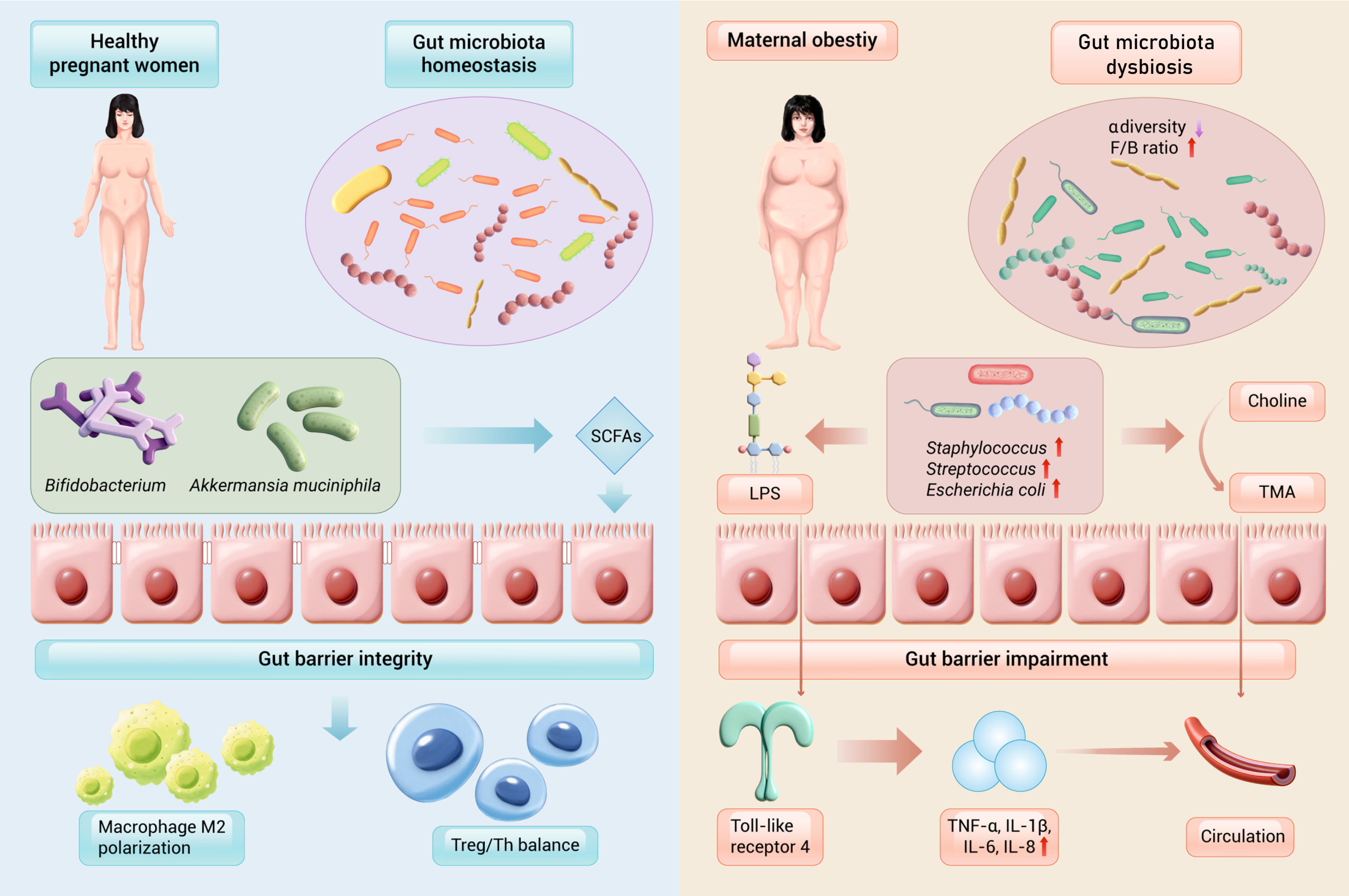

Figure 1. Differences in the gut microenvironment between healthy pregnancies and pregnancies with obesity In healthy pregnant women, the gut microbiota sustains a stable and varied community. Bacteria such as *Bifidobacterium* and *Akkermansia muciniphila*, which are part of the commensal microbiota, help generate short-chain fatty acids (SCFAs) like acetate, propionate, and butyrate, thus strengthening the gut barrier and reducing inflammation. In contrast, maternal obesity disrupts gut microbial composition, characterized by decreased α-diversity, SCFAs-producing bacteria (*Bifidobacterium* and *Akkermansia muciniphila*), and an elevated Firmicutes/Bacteroidetes ratio. The loss of SCFAs production disrupts gut immunity and gut barrier integrity. Furthermore, the increase of potentially pathogenic bacteria, including *Staphylococcus*, *Streptococcus*, and *Escherichia coli*, which activate placental TLR4 signaling and proinflammatory cytokine release, such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), IL-6, and IL-8. Additionally, *Escherichia coli* produces choline-degrading enzymes, which convert choline into trimethylamine (TMA). TMA enters hepatic circulation, where flavin-containing monooxygenases (FMOs) oxidize it to produce trimethylamine N-oxide (TMAO). In maternal obesity, gut dysbiosis and barrier disruption link metabolic imbalance, systemic inflammation, and endothelial dysfunction, thereby leading to the development of gestational complications and adverse pregnancy outcomes. The symbol of "↑" means upregulated, and "↓" means downregulated.

LPS, into the circulation (Figure 3).[137-139] Elevated circulating and fecal LPS in obese and GDM pregnancies activated the toll-like receptor 4 (TLR4)/myeloid differentiation primary response 88 (MyD88)/nuclear factor kappa-B (NF-κB) axis, inducing cytokine release and impairing insulin signaling.[25,140] Then, this response increases insulin receptor substrate 1 (IRS-1) phosphorylation and inhibits protein kinase B (AKT) signaling, thereby worsening insulin resistance in GDM.[122,140] This pathway also inhibits the phosphatidylinositol-3-kinase (PI3K)/AKT signaling required for trophoblast invasion, elevates sFlt-1 expression, and disrupts spiral artery remodeling and placental perfusion.[141,142] In PE pregnancies, elevated plasma and placental LPS levels were associated with the upregulation of microbial LPS biosynthesis genes.[139,143] Loss of *Akkermansia muciniphila*-derived extracellular vesicles might lead to overactivation of placental TLR4 signaling and upregulation of pro-inflammatory cytokines (IL-6, TNF-α) via NOD-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasome disinhibition.[23] Conversely, propionate and butyrate suppressed TLR4/NF-κB-driven inflammation and restored insulin sensitivity via extracellular signal-regulated kinase (ERK) /IRS-1 signaling.[144] In FGR, gut microbiota-induced TLR9 activation stimulated the TNF receptor-associated factor 3/TANK-binding kinase 1/interferon Regulatory Factor 3 (TRAF3/TBK1/IRF3) signaling pathway, further exacerbating the placental inflammatory environment and FGR.[145] The mechanism of TLR has been fully investigated, and future interventions with microbial metabolites targeting TLR4 could be developed. Currently, an animal study suggested that microbiota-related melatonin supplementation restored microbial balance (reducing *Aliivibrio* and increasing *Butyricimonas*), and improved placental angiogenesis and fetal growth via TLR4/Mitogen-activated protein kinase (MAPK)/VEGF pathway.[11]

GPCRs

GPCRs are widely expressed in placental cells, including trophoblasts, endothelial cells, and smooth muscle cells, where they bind with SCFAs to regulate placental cell development, function, and gestational complications.[52] SCFAs, particularly propionate and butyrate, are beneficial metabolites derived from healthy gut microbiota, which activate GPRCs such as GPR41and GPR109A to exert anti-inflammatory, metabolic, and pro-angiogenic effects at the maternal-fetal interface (Figure 3).[24,146]

A large-scale cohort study found reduced butyrate-producing bacteria and lower SCFA levels in obese pregnancies,[128] leading to downregulation of placental GPR41 and 43 signaling, increased histone deacetylase (HDAC) activity, and heightened inflammatory and vascular dysfunction.[25,134,147] Despite distinct mechanisms, this SCFA deficiency, consistently reported in both GDM and PE, exacerbates endothelial dysfunction and placental immune imbalance, representing a key molecular bridge between maternal metabolic stress and placental pathology.[94,148]

Mechanistically, propionate improved the invasion and migration of trophoblasts via the GPR41/AKT pathway, while enhancing M2 macrophage polarization and suppressing M1 polarization-related placental inflammation via the GPR43/signal transducer and activator of transcription 1 (STAT1)

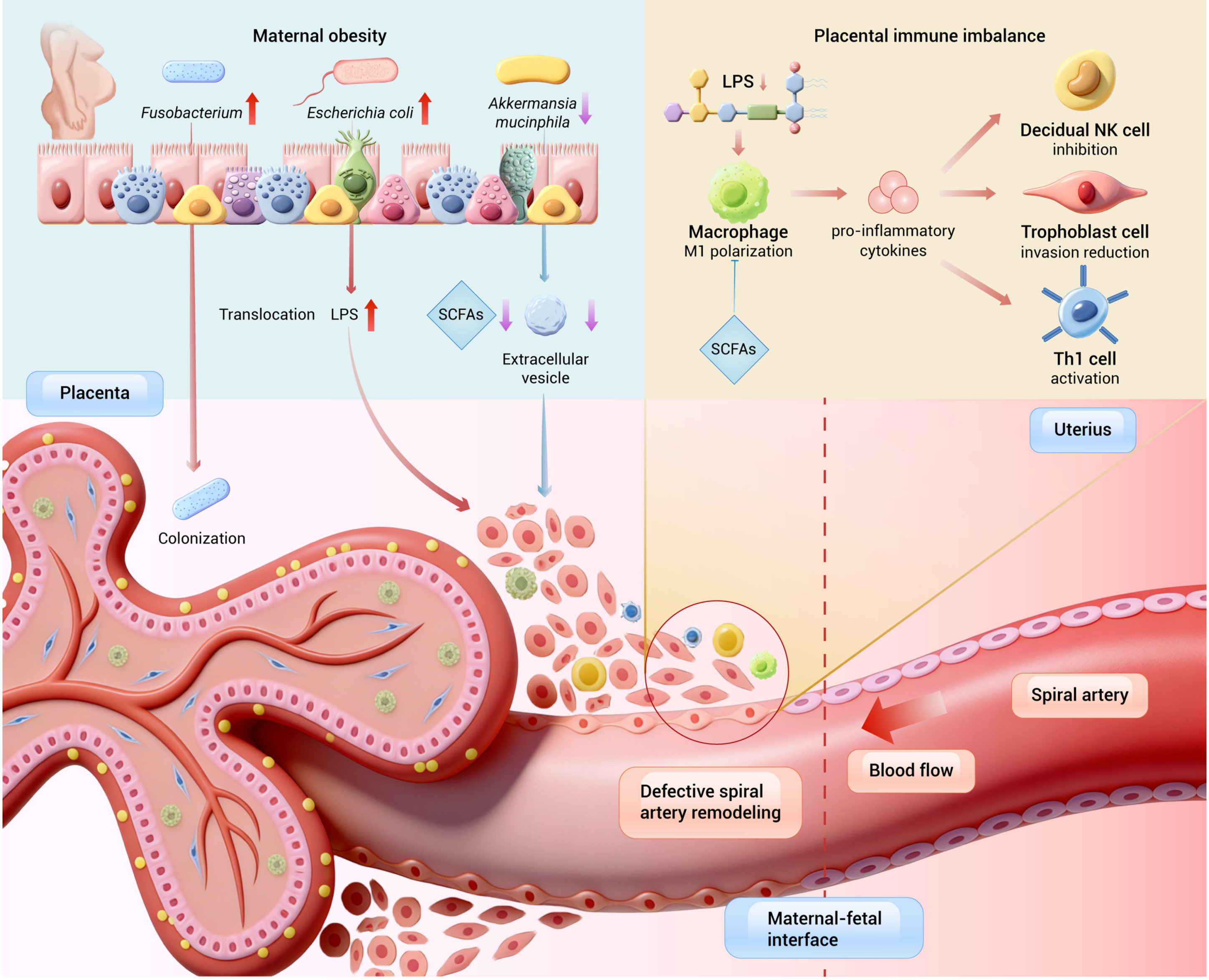

Figure 2. Maternal obesity-induced gut microbiota contributes to the placental immune imbalance and defective spiral artery remodeling Maternal obesity-associated gut dysbiosis, oxidative stress, and systemic inflammation increase gut permeability, facilitating the translocation of microbial components along the gut-placenta axis. Notably, *Fusobacterium* species pass through the compromised gut barrier and reach the placenta, thereby inducing placental inflammation, oxidative stress, and DNA damage. Additionally, bacteria-derived lipopolysaccharide enters the placenta and leads to inflammation in trophoblast cells. Lipopolysaccharide stimulation drives macrophage shift to the pro-inflammatory M1 type and triggers cytokine release, thereby impairing decidual natural killer (NK) cell function and promoting Th1 cell activation. Conversely, the reduced abundance of *Akkermansia muciniphila* contributes to the reduction in short-chain fatty acids (SCFAs) and extracellular vesicles, and this reduction aggravates the macrophage M1 polarization and inflammation. Collectively, these alterations within the gut-placenta axis, compounded by obesity-induced gut dysbiosis, maternal-fetal interface immune imbalance, and impaired remodeling of spiral arteries, link maternal metabolic imbalance to placental dysfunction. The symbol of “↑” means upregulated, and “↓” means downregulated; blue “→” denotes anti-inflammatory effects, red “→” denotes pro-inflammatory effects, and “—|” denotes inhibition.

pathway in PE.[24] In GDM, butyrate acted through GPR109A to reinforce intestinal barrier integrity, suppressed LPS-induced TLR4 activation, and inhibited M1 macrophage polarization in the placenta.[25] Regarding FGR, depletion of intestinal SCFAs triggered deficient placental growth and vascularization through GPR41 and GPR43 in germ-free mice.[10,149]

Together, the disruption of SCFA-GPCRs signaling in obesity represents a key molecular bridge linking maternal gut dysbiosis, metabolic inflammation, and placental vascular dysfunction.[10,24] Its disruption represents a unifying mechanism underlying pregnancy complications associated with obesity, like GDM, PE, and FGR.[150]

Nuclear factor erythroid 2-related factor 2 (NRF2)

Oxidative stress is a common feature in GDM, PE, and FGR, manifested as increased levels of reactive oxygen species (ROS), DNA oxidation, and decreased activity of antioxidant enzymes in the placenta.[151] NRF2 is activated by ROS to restore redox balance, but its response varies across gestational complications. In GDM, NRF2 deficiency impairs β-cell adaptation, contributing to glucose dysregulation.[152] In FGR, chronic hypoxia and nutrient deprivation suppress NRF2 signaling.[153-154] However, in PE, NRF2 is initially upregulated but later silenced through promoter methylation, enhancing susceptibility to ischemia-reperfusion injury and inflammatory cytokine release (TNF-α, IL-6).[155,156]

Notably, women with both GDM and obesity exhibit impaired placental respiratory chain enzyme activity, likely through NRF2/antioxidant response element (ARE) signaling.[157] Bidirectional interactions exist between obesity, gut microbiota, and oxidative stress.[158] Obesity-related gut microbiota imbalance led to reduced butyrate levels, while butyrate supplementation prevented ROS accumulation via nicotinamide adenine dinucleotide phosphate oxidase 2 (NOX2) and p21/NRF2-mediated SOD1 upregulation.[159] Ursodeoxycholic acid (UDCA), a gut microbiota-modulated bile acid, was markedly reduced in the liver and gut of ob/ob mice, while its supplementation enhanced NRF2 nuclear translocation, promoted antioxidant gene

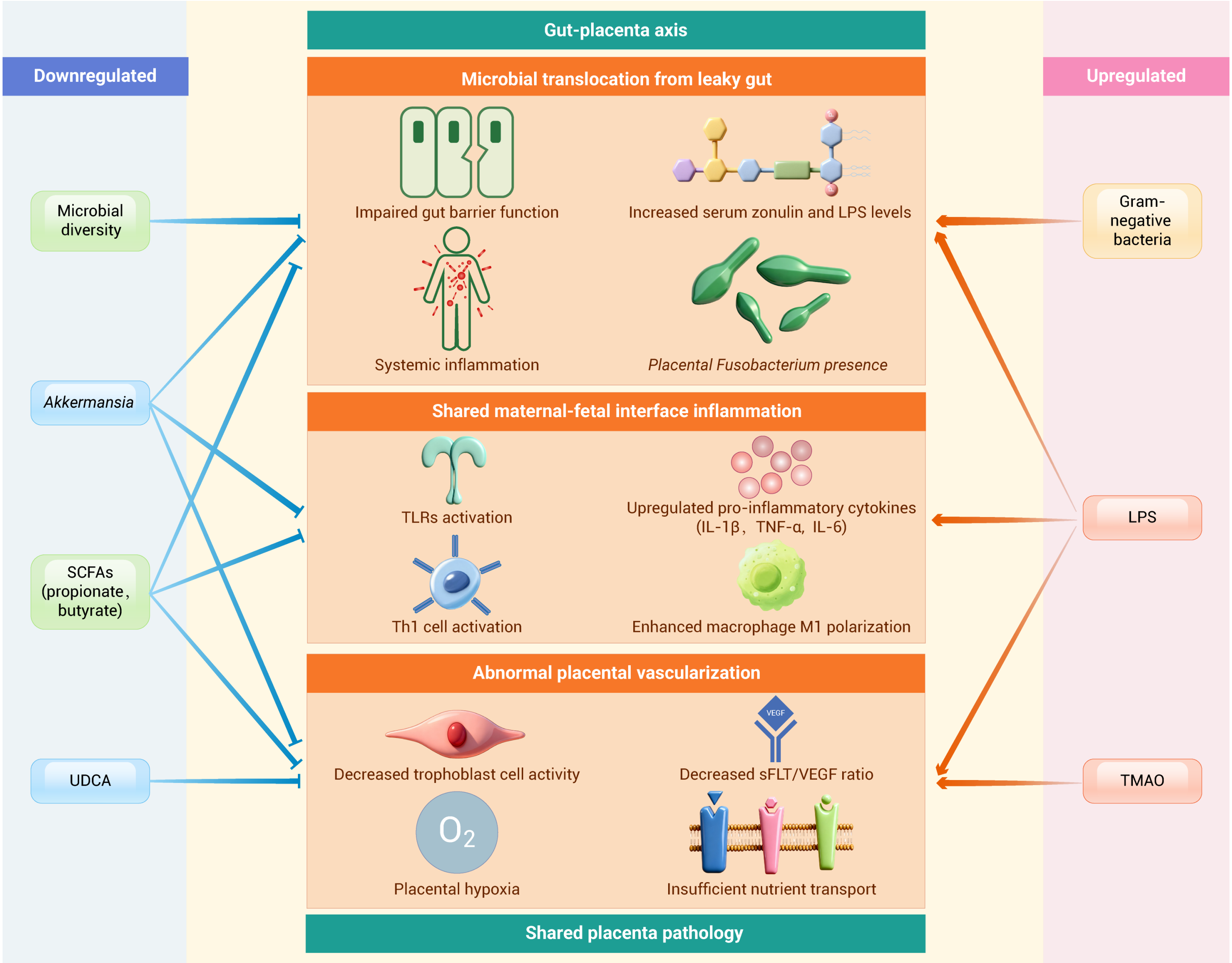

Figure 3. Gut dysbiosis in maternal obesity shapes the shared placental pathologies Maternal obesity reshapes the gut microbiota, manifested as decreased microbial diversity, *Akkermansia muciniphila,* short-chain fatty acids (SCFAs)-producing bacteria, and ursodeoxycholic acid (UDCA) production, and increased Gram-negative bacteria and compounds like lipopolysaccharide (LPS), and trimethylamine N-oxide (TMAO). Through the gut-placental axis, these microbial and metabolic alterations induce a number of pathogenic factors, such as disruption of the integrity of the intestinal barrier, placental Toll-like receptor 4 (TLR4)-associated inflammation, and reduction of trophoblast activity. Such interactions trigger three shared placental pathologies: (1) microbial translocation from leaky gut, (2) inflammation at the maternal-fetal interface, and (3) abnormal placental vascularization. The symbol of "→" denotes activation, and "⊣" denotes inhibition. Abbreviations: IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α; sFlt-1, fms-like tyrosine kinase-1; VEGF, vascular endothelial growth factor;

expression, lowered intracellular ROS, improved insulin sensitivity, and restored *Akkermansia muciniphila* abundance.[160] While NRF2 is crucial in the development of pregnancy complications, the mechanism behind it has not been fully explained.[161] Targeting the NRF2 signaling pathway through antioxidant strategies may broaden the therapeutic possibilities of altering gut microbiota to address pregnancy complications.

VEGF

The VEGF signaling is essential for the development of blood vessels and vascular remodeling in the placenta, involving VEGF-A, PlGF, and sFlt-1.[162] The sFlt-1 competitively binds VEGF-A and PlGF, reducing their interaction with membrane-bound VEGFR-1/2 and thereby impairing placental vascularization and endothelial proliferation through downstream PI3K/AKT and MAPK pathways.[163]

A suppressed VEGF signaling pathway, reflected by elevated sFlt-1 levels or a reduced VEGF/PlGF ratio, is observed in PE, GDM, and FGR.[164-166] This suggests that VEGF suppression-driven placental vascular impairment may be a common pathogenic mechanism, despite etiological differences among these complications. For instance, in PE, sFlt-1 release is primarily a consequence of failed spiral artery remodeling, whereas in GDM, VEGF suppression is linked to hyperinsulinemia and chronic inflammation.[74,86]

A recent study indicated that in the second trimester, pre-pregnancy obesity increased sFlt-1/PlGF ratios, potentially inhibiting VEGF activation.[167] Gut microbiota dysbiosis, particularly in maternal obesity, may contribute to VEGF pathway suppression (Figure 3).[168] Red and processed meat, common in some obesogenic diets, facilitates the breakdown of choline and L-carnitine by intestinal bacteria (*Prevotella*, *Clostridium*, *Lachnospira*, *Escherichia coli*), resulting in the formation of trimethylamine to TMAO.[130] Besides obese individuals, elevated TMAO, frequently seen in GDM and PE pregnancies, correlated with increased plasma sFlt-1, hypertension, and kidney injury in PE pregnancies.[70,169-171] TMAO induced systemic inflammation and inhibited VEGF signaling via Sirtuin 1/AMP-activated protein kinase (SIRT1/AMPK) signaling and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation.[172,173] Additionally, an overgrowth of Enterobacteriaceae promoted LPS release, which activated the TLR4/NF-κB pathway, thereby suppressing VEGF function and inducing sFlt-1 secretion.[174] Novel strategies, such as engineered placenta-targeting VEGF mRNA lipid nanoparticles, have been shown to alleviate PE in mice, offering promising therapeutic potential to

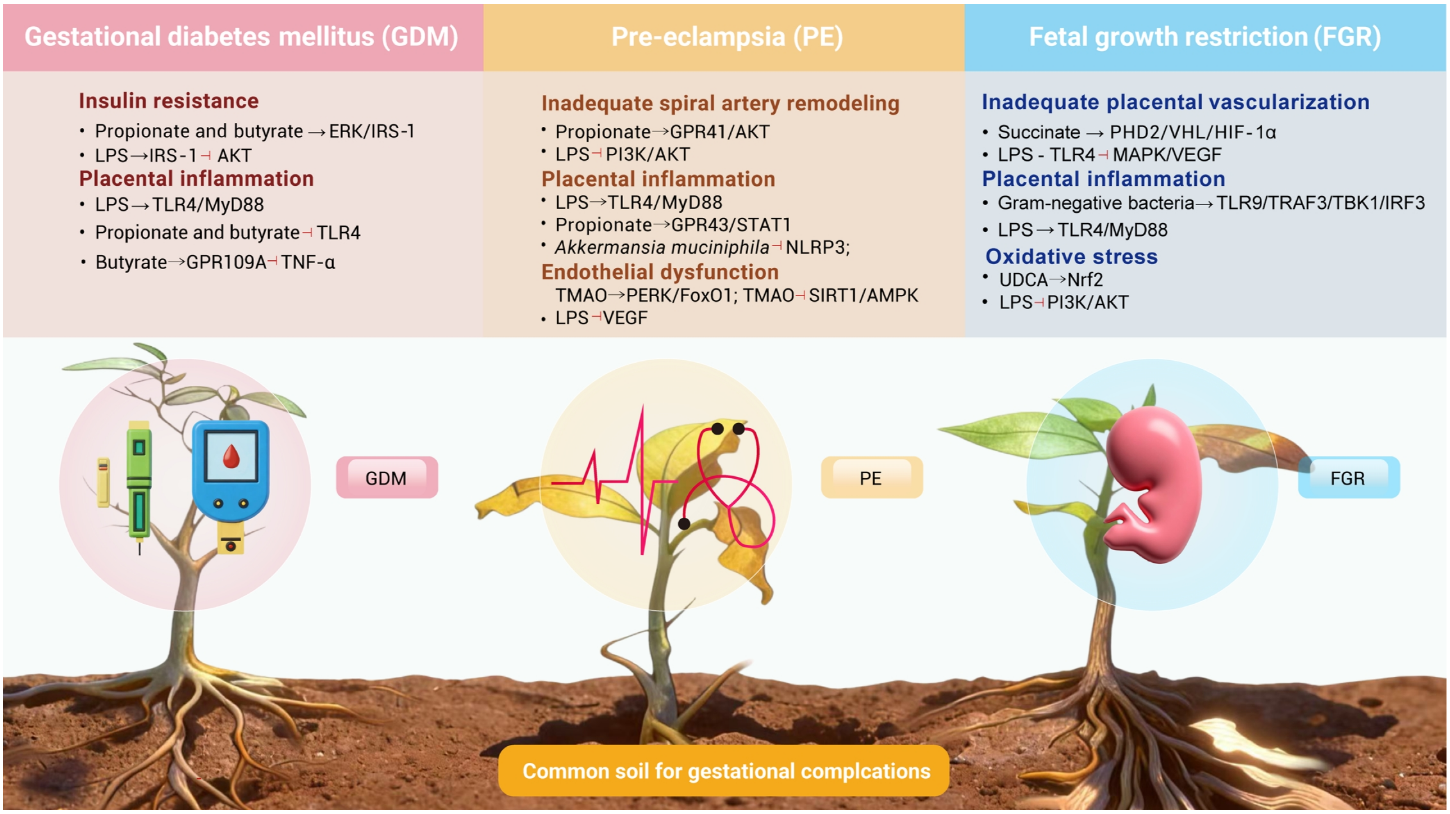

Figure 4. The "common soil" framework of gut-placenta crosstalk in obesity-related gestational complications Three diseased plants symbolize the growth of different gestational complications from the shared pathological "common soil" programmed by maternal obesity. Within this soil, pathogenic activators (LPS, TMAO, gram-negative bacteria) and protective regulators (*Akkermansia*, SCFAs, ursodeoxycholic acid (UDCA)) dynamically shape placental immune and vascular homeostasis. From this adverse soil, complications such as GDM, PE, and FGR emerge. The diverse phenotypes, molecular targets, and associated metabolites are demonstrated: GDM driven by impaired insulin signaling and placental inflammation (LPS-IRS-1/AKT, butyrate-GPR109A); PE characterized by defective spiral artery remodeling and endothelial dysfunction (propionate-GPR41/AKT, TMAO-SIRT1/AMPK); and FGR marked by inadequate placental vascularization and oxidative stress (succinate-HIF-1α, LPS-PI3K/AKT). Collectively, the figure provides a framework that metabolic-immune disturbances in maternal gut microbiota function as a unifying pathogenic substrate leading to diverse pregnancy complications. The symbol of "→" denotes activation, and "⊣" denotes inhibition. Abbreviations: GDM, gestational diabetes mellitus; PE, preeclampsia; FGR, fetal growth restriction; ERK, extracellular signal-regulated kinase; IRS-1, insulin receptor substrate 1; PI3K, phosphatidylinositol-3-kinase; AKT, protein kinase B; MyD88, myeloid differentiation primary response 88; GPR109A, G protein–coupled receptor 109A; TNF-α, tumor necrosis factor-alpha; PERK, PKR-like endoplasmic reticulum kinase; FoxO1, forkhead box O1; SIRT1, sirtuin 1; AMPK, AMP-activated protein kinase; VEGF, vascular endothelial growth factor; GPR43, G protein–coupled receptor 43; STAT1, signal transducer and activator of transcription 1; NLRP3, NOD-like receptor family pyrin domain–containing 3; PI3K, phosphoinositide 3-kinase; Nrf2, nuclear factor erythroid 2–related factor 2; TLR9, toll-like receptor 9; TRAF3, TNF receptor–associated factor 3; TBK1, TANK-binding kinase 1; IRF3, interferon regulatory factor 3; PHD2, prolyl hydroxylase domain-containing protein 2; VHL, von Hippel-lindau protein; HIF-1α, hypoxia-inducible factor 1-alpha; MAPK, mitogen-activated protein kinase.

restore placental angiogenesis in obese pregnancies.[70]

Hypoxia inducible factor (HIF)

Inadequate trophoblast invasion results in defective spiral artery remodeling and abnormal placental development with low perfusion pressure, resulting in a hypoxic environment in the placenta.[7] The HIF-1α is a transcription factor regulating cellular responses in hypoxic environments, and its upregulation is associated with placental vascular dysplasia, inadequate oxygenation of the embryo, and fetal growth retardation in utero.[175]

In late pregnancy, maternal obesity-induced hyperglycemia and hyperinsulinemia elevate fetal metabolic rates and a chronic hypoxic environment, leading to an increased expression of HIF-1α and downstream VEGF and nitric oxide synthase.[176] Animal studies have demonstrated that obesity exacerbates hypoxia at the maternal-fetal interface and gestational hypertension.[177] Conversely, weight loss in PE mice has been shown to alleviate hypoxia symptoms at the maternal-fetal interface.[178] Although hypoxia is a primary driver, HIF-1α expression is also modulated by upstream signals.[179,180] Gut microbiota-derived metabolites modulate hydroxylase domain (PHD) activity by changing the PHD enzyme structure, which is an HIF-1α-degrading enzyme, with succinate receiving the most extensive study.[181] Elevated succinate levels in early pregnancy have been shown to dose-dependently enhance HIF-1α expression via PHD2/von Hippel-Lindau protein (VHL)/HIF-1α in JEG-3 and HTR-8 cells by inhibiting PHD activity.[182] Women with obesity had a decreased abundance of succinate-consuming microbiota, such as Odoribacteraceae and Clostridaceae, leading to elevated succinate levels in the gut.[183,184] Although modulation of the HIF pathway via gut microbiota interventions may offer a potential avenue to enhance placental vascularization and fetal growth, no studies have directly investigated this possibility.

In general, gut microbiota-derived metabolites modulate key molecular targets involved in placental pathologies. In the next part, we will highlight the similar features of each disorder and illustrate how these distinct outcomes arise from a shared pathological foundation.

OBESITY-DRIVEN GUT DYSBIOSIS CULTIVATES A COMMON SOIL FOR PLACENTAL PATHOLOGY

Maternal obesity is considered to be a shared risk factor for multiple gestational complications, including GDM, PE, and FGR. However, direct causal evidence linking obesity to their common placental pathology remains limited. The "common soil" hypothesis, centered on obesity-associated gut dysbiosis, offers a unifying framework to explain the convergent placental phenotypes observed across these disorders. As shown in Figure 4, microbial translocation, maternal-fetal interface inflammation, and abnormal placental vascularization represent interconnected outcomes of obesity-driven gut dysbiosis, together forming the common soil from which diverse gestational complications emerge.

Microbial translocation from leaky gut

The increased intestinal permeability and decreased microbial diversity facilitate the translocation of pro-inflammatory mediators and pathogenic bacteria to the placenta.[137,138] While historically considered sterile, studies using 16S rRNA and metagenomic sequencing have detected microbial DNA and *Streptococcus agalactiae* in placental tissue.[20,185,186] Notably, obese women exhibited altered and less diverse placental microbiota in contrast to individuals with normal weight, suggesting a potential gut-placenta microbial migration due to increased intestinal permeability.[187,188] However, most studies identified microbial DNA rather than live colonization, leaving the immunological implications unresolved.

Bacterial migration to the placenta might be one of the causes of placental inflammation in various gestational complications.[119] As illustrated in Figure 2, obesity-induced gut dysbiosis leads to increased microbial translocation and circulating LPS levels, which drive placental macrophage polarization and trophoblast dysfunction.[24] Similarly, increased microbial fluorescence intensity and elevated levels of microbiota-derived LPS have also been reported in GDM pregnancies.[25,144] Among them, *Fusobacterium*, a mucin-adherent pathogen, is frequently detected in placental studies.[189,190] Oral *Fusobacterium nucleatum* administration triggered placental inflammation and fetal death in animal models.[190,191] The PE-derived microbiota transplanted into germ-free mice increased gut permeability and placental *Fusobacterium* enrichment.[23] Conversely, a similar study using qPCR found no placental microbes despite gut barrier disruption, possibly due to methodological differences (qPCR vs fluorescence in situ hybridization) in sensitivity.[24] *Fusobacterium* species reach the placenta and disrupt the function of immune cells involved in spiral artery remodeling, including macrophages, uterine NK cells, and T helper 1 cells (Figure 2).[192,193] However, a recent study suggested that low biomass *Fusobacterium nucleatum* exposure in vitro enhanced VEGF-A secretion and HIF activation, promoting trophoblast tube formation, whereas high bacterial loads triggered NF-κB-mediated inflammation and impaired trophoblast function.[194] This result challenges the current view of placental immunity, but the tolerance of the endometrium to microorganisms needs to be further verified in human studies.

While some evidence suggests microbial presence, conclusive proof of live colonization in healthy placentas is lacking.[21,190] Discrepancies across studies reveal the demand for stringent contamination controls and advanced detection techniques. If gut microorganisms do reach the placenta, it is crucial to elucidate their migration mechanisms through contamination control, sensitive detection, and deep sequencing methods to improve detection accuracy.[195]

Shared maternal-fetal interface inflammation

In a healthy pregnancy, M2 macrophages normally secrete cytokines and VEGF-A to promote spiral artery remodeling.[196] Macrophage polarization toward the M1 phenotype, imbalanced cytokines, and aberrant activation of the TLR4 pathway are central inflammatory signatures in GDM, PE, and FGR (Figure 4).[144,197] An animal study showed that propionate partially inhibits M1 and restores M2 polarization in PE.[24] However, obesity-driven gut dysbiosis, particularly the depletion of SCFAs, disrupted this balance. Compared to GDM and PE, FGR is more related to LPS-induced inflammation. In the FGR model, gut-derived LPS exacerbated placental inflammation and oxidative stress when gut barrier integrity was compromised, which is a mechanism widely studied in FGR models induced by high-fat diets and environmental stressors such as heat stress, microplastics, and heavy metals.[11,37,198-199]

However, most evidence is from animal models, where outcomes vary. For instance, LPS is often used to induce PE or FGR in rodents, but outcomes vary. LPS administration from gestation days 13.5-16.5 induced PE-like symptoms, while late administration only triggered inflammation without vascular effects.[200-202] These discrepancies suggest that outcomes depend on timing and dosage, and the pathogenesis of these gestational complications is beyond inflammation, limiting the reliability of LPS-induced models.[203]

Abnormal placental vascularization

Abnormal placental vascularization is manifested as defective trophoblast cell migration, sFlt/VEGF inhibition, placental hypoxia, and insufficient nutrient transport, regulated by microbial metabolites (Figure 3). Although placental lesions in GDM, including villous immaturity and fibrinoid necrosis, some studies have reported increased placental angiogenesis, which might indicate compensatory responses to vascular dysfunction, highlighting the complexity of vascular remodeling in GDM.[204,205] Obesity-related vascular pathology is more pronounced in PE and FGR than in GDM.[206,207]

Due to the limits of human placenta availability, human evidence for microbial metabolite-driven placental vascularization remains scarce. Animal data suggest most mechanistic links to this topic. As illustrated in Figure 4, *Akkermansia muciniphila* could release extracellular vesicles to the placenta and activate epidermal growth factor receptor (EGFR)/PI3K/AKT and phosphatase and tensin homolog (PTEN) signaling, promoting trophoblast migration and invasion in PE model.[35] Propionate also increased birth weight in hypoxia-induced FGR, whose mechanism might be associated with metabolic syndrome and early placental vascular development.[208,209] Notably, tryptophan metabolism has been disturbed in obese populations and FGR.[112,210,211] Animal models also showed that tryptophan metabolites produced by gut microbiota, including melatonin and serotonin, are reduced, while kynurenine levels increase, which is related to disrupted placental angiogenesis and nutrient transport in FGR.[212,213] Conversely, melatonin supplementation increased fetal weight and placental nutrient transport in the FGR model by upregulating expressions of VEGF, glucose transporter type 4 (GLUT4), FABP3, and sodium-coupled neutral amino acid transporter 2 (SNAT2).[11,199]

Collectively, these microbiota-mediated disruptions establish a pro-inflammatory, metabolically adverse environment, which is a common soil that increases the susceptibility to diverse gestational complications, including PE, GDM, and FGR. Targeting this axis through microbiota-modulating strategies may provide a unified therapeutic approach for preventing obesity-related placental pathologies and improving pregnancy outcomes.

GUT MICROBIOTA INTERVENTION

Rising BMI across reproductive stages, including pre-pregnancy, gestation, and delivery, is closely linked to increased risks of gestational complications.[3] While preconception weight control is crucial, excessive dietary restriction during pregnancy may harm fetal development.[214,215] Considering the known function of gut microbiota in metabolism, inflammation, and vascular function, the exploration of gut microbiota interventions is expected to help manage maternal obesity and its complications.[216,217]

Probiotic supplementation exhibits mixed results

Microbiota-targeted interventions (probiotics, prebiotics, or dietary modification) have attracted interest for mitigating maternal obesity and gestational complications. Research showed that the gut microbiota of mothers can be reshaped within weeks by enhancing bacterial diversity, *Bifidobacterium* and *Lactobacillus* abundance, and SCFA production.[218,219] These shifts are proposed to improve glucose and lipid metabolism, intestinal barrier integrity, and systemic inflammatory balance in pregnancy, which has been demonstrated in previous chapters.

Despite encouraging data, current results remain mixed and context-dependent (Figure 5). While several randomized controlled trials (RCTs) reported improved glycemic control and insulin sensitivity, most large-scale studies and meta-analyses found no consistent reduction in the incidence of SGA, GDM, and PE.[218,220-222] For instance, the SPRING trial showed no decrease in GDM incidence after *Lactobacillus rhamnosus* and *Bifidobacterium animalis* administration in overweight pregnancies.[62] Similarly, a Cochrane review involving over 1,647 participants concluded that current evidence is insufficient and even suggested a possible rise in PE risk.[58] Some results also observed increased fasting glucose and PE incidence, indicating the potential danger of probiotics.[60,62,223] Conversely, early large observational data point toward potential benefits. The Norwegian mother and child cohort study, which included over 33,000 women, found that habitual intake of probiotic milk was linked to a lower risk of severe PE.[56] Discrepancies across studies are likely due to heterogeneity in participant profiles (enterotype, metabolic status, general vs high-risk cohorts), microbial strains, dosing, intervention duration, and timing (early vs late pregnancy). Mode of delivery and dietary factors, both of which markedly affect maternal and infant microbiota, are frequently uncontrolled, and bacterial colonization or persistence is rarely validated, raising questions about the plausibility of some findings.[62,224] Additionally, methodological variation, including 16S rRNA sequencing, metagenomics, and metabolomics, affected the depth of results. Early or preconceptional supplementation might be more effective, as key metabolic and immune reprogramming occur before mid-gestation.[225]

Taken together, we should be very cautious about the results of current interventions. Current gut microbiota-related interventions offer only modest

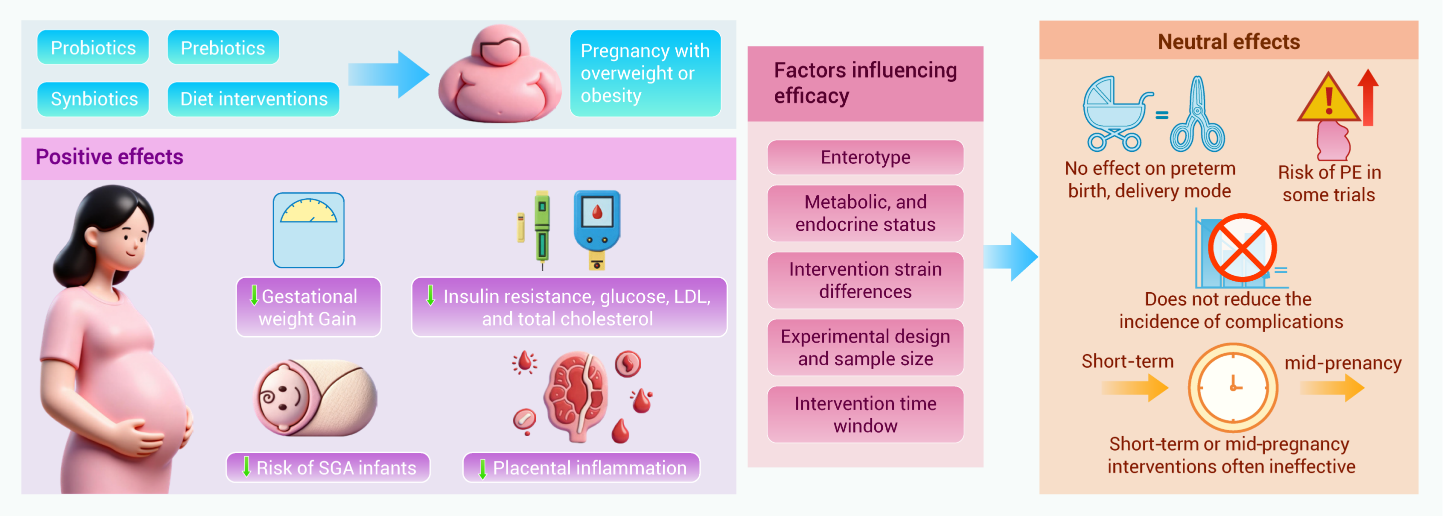

Figure 5. Gut microbiota intervention in maternal obesity: Current evidence and future directions Current evidence shows that probiotics, prebiotics, synbiotics, and diet interventions reduce gestational weight gain, insulin resistance, glucose, low-density-lipoprotein (LDL), and cholesterol levels, placental inflammation, and the risk of small-for-gestational-age (SGA) infants. However, the variability of outcomes is further influenced by different enterotypes, metabolic and endocrine status, microbial strain differences, sample size, and intervention timing. Therefore, their overall efficacy remains inconsistent, as the majority of randomized controlled trials (RCTs) commence during mid-pregnancy and do not reveal any notable alterations in the occurrence of complications and adverse pregnancy outcomes.

metabolic benefits and appear insufficient to prevent gestational complications, whereas earlier or preconception strategies may yield greater maternal and fetal improvements.

Broader applications across preconception to offspring health

Although current microbiota-targeted therapies have not consistently reduced pregnancy complications, long-term interventions seem to generate more effective results. Probiotic supplementation (*Bifidobacterium bifidum*, *Bifidobacterium lactis*, *Lactobacillus acidophilus*) only after GDM diagnosis until delivery yielded no metabolic benefits,[59] while asymptomatic post-GDM women supplemented with *Bifidobacterium* and *Lactobacillus* showed improvements in serum glycated hemoglobin, lipids, and C-reactive protein levels.[226] Meta-analyses confirmed that short intervention duration of probiotic or lifestyle interventions and high metabolic variability during pregnancy have limited effects on major clinical outcomes.[227,228]

Similarly, as shown in Figure 5, there are few clinical studies on probiotics to improve premature birth, stillbirths, and FGR, and probiotics supplementation in pregnancy did not change the occurrence of births before 37 weeks.[229] In contrast, long-term follow-up studies suggested potential intergenerational benefits. For example, in overweight and obese pregnancies, combined probiotic and fish oil supplementation decreased the risk of childhood overweight at 24 months.[224] A double-blind trial found that galacto- and fructo-oligosaccharides (14.2 g/day from < 21 weeks to 6 months postpartum) improved infant gut microbiota and increased fecal *Akkermansia* level.[219] Maternal probiotic intake during the perinatal period was linked to a higher fetal weight and length.[230] These benefits likely reflect immune imprinting and microbial inheritance, though causal mechanisms remain poorly defined.

Collectively, current data reveal that gut microbiota interventions during gestation improve maternal metabolic indices but fail to prevent complications and adverse pregnancy outcomes. Future studies are needed to optimize intervention timing, duration, and personalization, ideally beginning before conception to achieve durable effects on both maternal and offspring health.

EXISTING PROBLEMS AND FUTURE PERSPECTIVES

In this part, we will discuss the current bottlenecks, missed windows, and realistic translational in this area. Figure 6 summarizes the current translational bottlenecks and emerging strategies for microbiota-based interventions in maternal obesity, highlighting the limited placental focus in existing trials and outlining next-generation approaches to develop targeted and personalized microbiota therapies.

Current bottlenecks: The forgotten placenta

Although the placenta is the central organ regulating metabolism, immunity, and vascular homeostasis during pregnancy, it remains an overlooked component in human studies.[205] Its role in PE and FGR is often inferred rather than directly investigated, largely due to limited accessibility to human placental tissues. As a result, current insights into the gut-placenta axis rely heavily on animal models, which, although indispensable, are inherently imperfect. Interspecies differences in gut microbial colonization, placental architecture (labyrinthine vs villous), and gestational duration (21 vs 280 days) significantly constrain their translational value, particularly for understanding PE pathophysiology and placental vascular remodeling.[231]

To address these gaps, the development of more human-relevant experimental systems is urgently needed (Figure 6). Refining placental organoid and humanized models represents a critical goal for the next decade.[232] The next fifty years may witness the emergence of an artificial placenta that supports embryonic development in vitro and prevents placenta-related pregnancy complications. In the near term, human trophoblast organoids using microfluidic devices would better simulate the exchange of maternal-fetal gas and nutrients.[233,234] Additionally, the development of more humanized systems, such as gene-edited mice, mini pigs, and organoid platforms, will be crucial for bridging experimental findings with clinical applications.[235] CRISPR/Cas9-engineered and germ-free mice colonized with humanized microbiota offer powerful tools to bridge interspecies gaps.[42]

Missed windows: Timing of intervention

A recent study suggested that pre-pregnancy weight control enhanced metabolic status and vascular function during pregnancy.[236] However, current public health efforts rarely emphasize pre-conceptional weight management.[237,238] Moreover, relying solely on BMI may be insufficient, as fat distribution and metabolic risk vary across populations.[239] An immediate priority is to develop evidence-based guidelines and clinical programs that promote metabolic optimization before conception, aligning with China's 2025 National Weight Management Policy.[240] Measures, including body fat percentage, adipokine profiles, and patterns of gestational weight gain, could refine risk stratification and facilitate earlier identification and management of high-risk women.[241,242] Despite increasing research interest, gut microbiota interventions during pregnancy-particularly probiotics, have shown limited success in improving gestational complications.[62] Clinically, most probiotic trials have initiated supplementation in mid or late pregnancy, potentially missing the critical early windows for intervention.[243-245] Additionally, beyond pregnancy, the prolonged effect of mothers' microbiota on offspring is important.[78] Maternal-offspring microbiota databases may help reveal how early microbial environments shape fetal growth, immune, and neurodevelopment.[246]

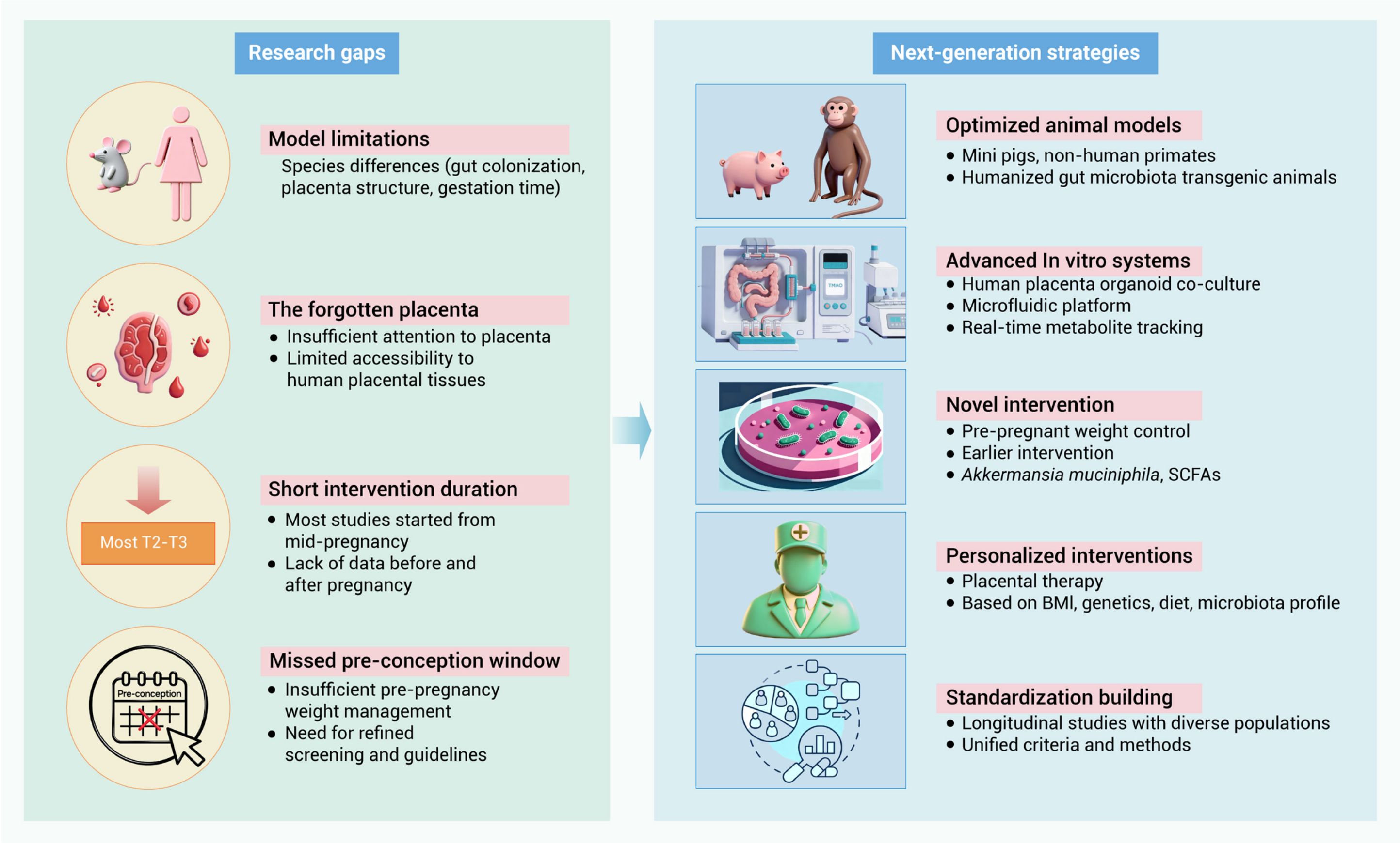

Figure 6. Problems with current research on gut microbiota interventions and the way forward Major research gaps include species-specific limitations of animal models, insufficient focus on the placenta, short intervention duration, and lack of pre-intervention management. Future directions emphasize: (1) optimized experimental models including placenta organoid co-cultures, microfluidic platforms for real-time metabolite tracking, and animal models (mini pigs, non-human primates, and humanized microbiota mice); (2) next-generation interventions such as placental therapy, early probiotic or postbiotic treatment (*Akkermansia muciniphila*, SCFAs); (4) personalized interventions integrating BMI, diet, genetics, and microbiome profiles; and (5) standardization building, including large-scale, multi-ethnic longitudinal studies with unified evaluation criteria.

Realistic translational: Targeted and personalized microbiota therapies

Targeting maternal gut dysbiosis with next-generation probiotics represents a promising avenue for preventing obesity-related gestational complications. Clinical studies have shown that *Akkermansia muciniphila* supplementation improved metabolic syndrome in obese individuals, yet its efficacy in pregnant women with obesity and gestational complications remains untested.[247] Beyond bacteria, advances in metagenomics and culturomics may help identify novel microbial candidates for future therapeutic development.[94,248,249] Postbiotic approaches, SCFAs represent a functional bridge between maternal obesity and gestational disorders, primarily via impaired gut barrier integrity, systemic inflammation, and placental vascular dysfunction, which highlight the therapeutic potential of SCFAs. No clinical evidence currently supports the efficacy of SCFAs in maternal obesity or gestational disorders, likely due to their short biological half-life.[150] However, there is also circumstantial evidence. For instance, one study suggested that butyrate supplementation reduces plasma zonulin and LPS in women, alleviating gut leak, which is one of the most factors for systemic inflammation.[250] Dietary modulation that enhanced butyrate production, particularly high-fiber or Mediterranean diets, has shown benefits in improving GWG and GDM risk,[251-253] though results remain population-dependent.[222] In addition, metformin therapy similarly improved glucose control partially through restoration of propionate metabolism.[254]

To improve safety and efficacy, targeted and personalized gut microbiota interventions are increasingly advocated.[255] Placenta-targeted therapies are emerging as direct and potentially effective interventions. Placental therapy, such as VEGF mRNA delivery, has shown promising efficacy in the PE model, while *Akkermansia muciniphila*-derived extracellular vesicles have also entered and improved placental vascularization in animal studies.[35,70] Such approaches could complement microbiota-based therapies by directly restoring common placental pathology at the junction between mother and fetus. Personalized treatment strategies that consider the choice of microbial strains, dosage, timing, and duration, based on individual host factors (genetics, BMI, diet, and microbiome composition), may help mitigate adverse effects and optimize outcomes.[256,257] A standardized clinical database that integrates these parameters would greatly enhance intervention design. The ultimate challenge is not only to correct dysbiosis but to reshape the metabolic-inflammatory placental interface that constitutes the common soil for PE, GDM, and FGR.

CONCLUSIONS

Maternal obesity is a significant risk factor leading to gestational complications and adverse pregnancy outcomes. Obesity-induced dysbiosis exhibits distinctive features and acts as the mechanistic bridge linking maternal metabolic stress to placental pathology. It constitutes a common soil, characterized by microbial translocation, inflammation at the maternal-fetal interface, and impaired placental vascularization, from which gestational complications such as GDM, PE, and FGR emerge. Recognizing these conditions as interconnected disruption reframes pregnancy complications from isolated syndromes to a unified systems disorder. This framework would transform obesity-related complications and adverse pregnancy outcomes from inevitable consequences into preventable conditions. In the coming decades, refined diagnostics and personalized, targeted interventions may finally shift the field from association to prevention of pregnancy complications.

REFERENCES

1. Johansson K., Bodnar L. M., Stephansson O., et al. (2024). Safety of low weight gain or weight loss in pregnancies with class 1, 2, and 3 obesity: A population-based cohort study. *Lancet.* **403**:1472–1481. DOI:10.1016/S0140-6736(24)00255-1
2. Collaborators G. A. B. (2025). Global, regional, and national prevalence of adult overweight and obesity, 1990-2021, with forecasts to 2050: A forecasting study for the global burden of disease study 2021. *Lancet.* **405**:813–838. DOI:10.1016/S0140-

6736(25)00355-1

3. Shirvanifar M., Ahlqvist V. H., Lundberg M., et al. (2024). Adverse pregnancy outcomes attributable to overweight and obesity across maternal birth regions: A Swedish population-based cohort study. *Lancet Public Health* **9**:e776–e786. DOI:10.1016/s2468-2667(24)00188-9
4. Voerman E., Santos S., Inskip H., et al. (2019). Association of gestational weight gain with adverse maternal and infant outcomes. *JAMA* **321**:1702–1715. DOI:10.1001/jama.2019.3820
5. Weir T. L., Majumder M. and Glastras S. J. (2024). A systematic review of the effects of maternal obesity on neonatal outcomes in women with gestational diabetes. *Obes. Rev.* **25**:e13747. DOI:10.1111/obr.13747
6. Atta N., Ezeoke A., Petry C. J., et al. (2024). Associations of high bmi and excessive gestational weight gain with pregnancy outcomes in women with type 1 diabetes: A systematic review and meta-analysis. *Diabetes Care* **47**:1855–1868. DOI:10.2337/dc24-0725
7. Brombach C., Tong W. and Giussani D. A. (2022). Maternal obesity: New placental paradigms unfolded. *Trends Mol. Med.* **28**:823–835. DOI:10.1016/j.molmed.2022.05.013
8. Catalano P. M. and Shankar K. (2017). Obesity and pregnancy: Mechanisms of short term and long term adverse consequences for mother and child. *BMJ* **356**:j1. DOI:10.1136/bmj.j1
9. Hampton T. (2020). Do gut bacteria play a role in preeclampsia. *JAMA* **323**:2120–2121. DOI:10.1001/jama.2020.4755
10. Pronovost G. N., Yu K. B., Coley-O'Rourke E. J. L., et al. (2023). The maternal microbiome promotes placental development in mice. *Sci. Adv.* **9**:eadk1887. DOI:10.1126/sciadv.adk1887
11. Wu J., Zheng X., Wu C., et al. (2025). Melatonin alleviates high temperature exposure induced fetal growth restriction via the gut-placenta-fetus axis in pregnant mice. *J. Adv. Res.* **68**:131–146. DOI:10.1016/j.jare.2024.02.014
12. Fisman E. Z., Westermeier F. and Santulli G. (2025). A new kid in town: Cardiovascular diabetology-endocrinology reports. *Cardiovasc. Diabetol.* **24**:30. DOI:10.1186/s12933-025-02602-1
13. Hibler E. A. and Lloyd-Jones D. M. (2021). Addressing the "common soil" of risk factors for cardiovascular disease and cancer. *JACC CardioOncol.* **3**:59–61. DOI:10.1016/j.jaccao.2021.02.003
14. Tian Z., Zhang X., Yao G., et al. (2024). Intestinal flora and pregnancy complications: Current insights and future prospects. *Imeta* **3**:e167. DOI:10.1002/imt2.167
15. Miller J. K. and Burns J. (1970). Histopathology of Listeria monocytogenes after oral feeding to mice. *Appl. Microbiol.* **19**:772–775. DOI:10.1128/am.19.5.772-775.1970
16. Wetli C. V., Roldan E. O. and Fojaco R. M. (1983). Listeriosis as a cause of maternal death: An obstetric complication of the acquired immunodeficiency syndrome (AIDS). *Am. J. Obstet. Gynecol.* **147**:7–9. DOI:10.1016/0002-9378(83)90074-1
17. Anderson G. D. (1975). Listeria monocytogenes septicemia in pregnancy. *Obstet. Gynecol.* **46**:102–104. DOI:10.1097/00006250-197507000-00021
18. Li Y., Shibata Y., Zhang L., et al. (2011). Periodontal pathogen Aggregatibacter actinomycetemcomitans LPS induces mitochondria-dependent-apoptosis in human placental trophoblasts. *Placenta* **32**:11–19. DOI:10.1016/j.placenta.2010.10.007
19. Equils O., Uh A., Blue C., et al. (2007). 100: Lipopolysaccharide (LPS) stimulation induces corticotropin releasing hormone (CRH) expression through MyD88 in trophoblast cells. *Am. J. Obstet. Gynecol.* **197**:S42. DOI:10.1016/j.ajog.2007.10.111
20. Aagaard K., Ma J., Antony K. M., et al. (2014). The placenta harbors a unique microbiome. *Sci. Transl. Med.* **6**:237ra265. DOI:10.1126/scitranslmed.3008599
21. Kennedy K. M., de Goffau M. C., Perez-Muñoz M. E., et al. (2023). Questioning the fetal microbiome illustrates pitfalls of low-biomass microbial studies. *Nature* **613**:639–649. DOI:10.1038/s41586-022-05546-8
22. Morffy Smith C. D., Gong M., Andrew A. K., et al. (2019). Composition of the gut microbiota transcends genetic determinants of malaria infection severity and influences pregnancy outcome. *EBioMedicine* **44**:639–655. DOI:10.1016/j.ebiom.2019.05.052
23. Chen X., Li P., Liu M., et al. (2020). Gut dysbiosis induces the development of pre-eclampsia through bacterial translocation. *Gut* **69**:513–522. DOI:10.1136/gutjnl-2019-319101
24. Jin J., Gao L., Zou X., et al. (2022). Gut dysbiosis promotes preeclampsia by regulating macrophages and trophoblasts. *Circ. Res.* **131**:492–506. DOI:10.1161/CIRCRESAHA.122.320771
25. Huang S., Chen J., Cui Z., et al. (2023). Lachnospiraceae-derived butyrate mediates protection of high fermentable fiber against placental inflammation in gestational diabetes mellitus. *Sci. Adv.* **9**:eadi7337. DOI:10.1126/sciadv.adi7337
26. Argaw-Denboba A., Schmidt T. S. B., Di Giacomo M., et al. (2024). Paternal microbiome perturbations impact offspring fitness. *Nature* **629**:652–659. DOI:10.1038/s41586-024-07336-w
27. Gray T. K., Lowe W. and Lester G. E. (1981). Vitamin D and pregnancy: The maternal-fetal metabolism of vitamin D. *Endocr. Rev.* **2**:264–274. DOI:10.1210/edrv-2-3-264
28. Yaron Y., Lessing J. B. and Peyser M. R. (1992). Abruptio placentae associated with perforated appendicitis and generalized peritonitis. *Am. J. Obstet. Gynecol.* **166**:14–15. DOI:10.1016/0002-9378(92)91818-u
29. Disson O., Grayo S., Huillet E., et al. (2008). Conjugated action of two species-specific invasion proteins for fetoplacental listeriosis. *Nature* **455**:1114–1118. DOI:10.1038/nature07303
30. Lecuit M., Nelson D. M., Smith S. D., et al. (2004). Targeting and crossing of the human maternofetal barrier by Listeria monocytogenes: Role of internalin interaction with trophoblast E-cadherin. *Proc. Natl. Acad. Sci. USA* **101**:6152–6157. DOI:10.1073/pnas.0401434101
31. Yeganegi M., Watson C. S., Martins A., et al. (2009). Effect of Lactobacillus rhamnosus GR-1 supernatant and fetal sex on lipopolysaccharide-induced cytokine and prostaglandin-regulating enzymes in human placental trophoblast cells: Implications for treatment of bacterial vaginosis and prevention of preterm labor. *Am. J. Obstet. Gynecol.* **200**:532.e531–532.e538. DOI:10.1016/j.ajog.2008.12.032
32. Yang S., Li W., Challis J. R. G., et al. (2014). Probiotic Lactobacillus rhamnosus GR-1 supernatant prevents lipopolysaccharide-induced preterm birth and reduces inflammation in pregnant CD-1 mice. *Am. J. Obstet. Gynecol.* **211**:44.e41–44.e12. DOI:10.1016/j.ajog.2014.01.029
33. Gomez-Arango L. F., Barrett H. L., McIntyre H. D., et al. (2017). Contributions of the maternal oral and gut microbiome to placental microbial colonization in overweight and obese pregnant women. *Sci. Rep.* **7**:2860. DOI:10.1038/s41598-017-03066-4
34. Gil A., Rueda R., Ozanne S. E., et al. (2020). Is there evidence for bacterial transfer via the placenta and any role in the colonization of the infant gut. *- A systematic review. Crit. Rev. Microbiol.* **46**:493–507. DOI:10.1080/1040841x.2020.1800587
35. Chen Y., Ou Z., Pang M., et al. (2023). Extracellular vesicles derived from Akkermansia muciniphila promote placentation and mitigate preeclampsia in a mouse model. *J. Extracell. Vesicles* **12**:e12328. DOI:10.1002/jev2.12328
36. Xie Y., Zhao F., Wang Y., et al. (2024). Fetal growth restriction induced by maternal gal-3 deficiency is associated with altered gut-placenta axis. *Cell Death Dis.* **15**:575. DOI:10.1038/s41419-024-06962-6
37. Zhang H., Zha X., Zhang B., et al. (2024). Gut microbiota contributes to bisphenol A-induced maternal intestinal and placental apoptosis, oxidative stress, and fetal growth restriction in pregnant ewe model by regulating gut-placental axis. *Microbiome* **12**:28. DOI:10.1186/s40168-024-01749-5
38. Wang J., Gao Y., Ren S., et al. (2024). Gut microbiota-derived trimethylamine N-Oxide: A novel target for the treatment of preeclampsia. *Gut Microbes* **16**:2311888. DOI:10.1080/19490976.2024.2311888
39. Feng C., Wu Y., Zhang X., et al. (2025). Maternal milk fat globule membrane enriched gut *L. murinus* and circulating SCFAs to improve placental efficiency and fetal development in intrauterine growth restricted mice model. *Gut Microbes* **17**:2449095. DOI:10.1080/19490976.2024.2449095
40. Karvas R. M., Zemke J. E., Ali S. S., et al. (2023). 3D-cultured blastoids model human embryogenesis from pre-implantation to early gastrulation stages. *Cell Stem Cell* **30**:1148–1165.e1147. DOI:10.1016/j.stem.2023.08.005
41. Deng Z., Dai F., Wang R., et al. (2024). Organ-on-a-chip: Future of female reproductive pathophysiological models. *J. Nanobiotechnology.* **22**:455. DOI:10.1186/s12951-024-02651-w
42. Mao Q., Ye Q., Xu Y., et al. (2023). Murine trophoblast organoids as a model for trophoblast development and CRISPR-Cas9 screening. *Dev. Cell.* **58**:2992–3008.e2997. DOI:10.1016/j.devcel.2023.11.007
43. Hori T., Okae H., Shibata S., et al. (2024). Trophoblast stem cell-based organoid models of the human placental barrier. *Nat. Commun.* **15**:962. DOI:10.1038/s41467-024-45279-y
44. Wollert T., Pasche B., Rochon M., et al. (2007). Extending the host range of Listeria monocytogenes by rational protein design. *Cell* **129**:891–902. DOI:10.1016/j.cell.2007.03.049
45. Arutyunyan A., Roberts K., Troulé K., et al. (2023). Spatial multiomics map of trophoblast development in early pregnancy. *Nature* **616**:143–151. DOI:10.1038/s41586-023-05869-0
46. Abbas Y., Turco M. Y., Burton G. J., et al. (2020). Investigation of human trophoblast invasion in vitro. *Hum. Reprod. Update* **26**:501–513. DOI:10.1093/humupd/dmaa017
47. Ma T., Yang S. T. and Kniss D. A. (1999). Development of an in vitro human placenta model by the cultivation of human trophoblasts in a fiber-based bioreactor system. *Tissue Eng.* **5**:91–102. DOI:10.1089/ten.1999.5.91
48. Vento-Tormo R., Efremova M., Botting R. A., et al. (2018). Single-cell reconstruction of the early maternal-fetal interface in humans. *Nature* **563**:347–353. DOI:10.1038/s41586-018-0698-6
49. Turco M. Y., Gardner L., Kay R. G., et al. (2018). Trophoblast organoids as a model for maternal-fetal interactions during human placentation. *Nature* **564**:263–267. DOI:10.1038/s41586-018-0753-3
50. Sheridan M. A., Fernando R. C., Gardner L., et al. (2020). Establishment and differentiation of long-term trophoblast organoid cultures from the human placenta. *Nat. Protoc.* **15**:3441–3463. DOI:10.1038/s41596-020-0381-x
51. Greenbaum S., Averbukh I., Soon E., et al. (2023). A spatially resolved timeline of the human maternal-fetal interface. *Nature* **619**:595–605. DOI:10.1038/s41586-023-06298-9
52. Wang S., Liu Y., Qin S., et al. (2022). Composition of maternal circulating short-chain fatty acids in gestational diabetes mellitus and their associations with placental metabolism. *Nutrients* **14**:3727. DOI:10.3390/nu14183727
53. Tao Z., Chen Y., He F., et al. (2023). Alterations in the gut microbiome and metabolisms in pregnancies with fetal growth restriction. *Microbiol. Spectr.*

11:e0007623. DOI:10.1128/spectrum.00076-23

54. Xiong L., Azad M. A. K., Liu Y., et al. (2024). Intrauterine growth restriction affects colonic barrier function via regulating the Nrf2/Keap1 and TLR4-NF-κB/ERK pathways and altering colonic microbiome and metabolome homeostasis in growing-finishing pigs. *Antioxidants* **13**:283. DOI:10.3390/antiox13030283
55. Liu B., Zhu X., Cui Y., et al. (2021). Consumption of dietary fiber from different sources during pregnancy alters sow gut microbiota and improves performance and reduces inflammation in sows and piglets. *mSystems* **6**:e00591–00520. DOI:10.1128/mSystems.00591-20
56. Brantsaeter A. L., Myhre R., Haugen M., et al. (2011). Intake of probiotic food and risk of preeclampsia in primiparous women: The Norwegian mother and child cohort study. *Am. J. Epidemiol.* **174**:807–815. DOI:10.1093/aje/kwr168
57. Nordqvist M., Jacobsson B., Brantsæter A., et al. (2018). Timing of probiotic milk consumption during pregnancy and effects on the incidence of preeclampsia and preterm delivery: A prospective observational cohort study in Norway. *BMJ Open* **8**:e018021. DOI:10.1136/bmjopen-2017-018021
58. Davidson S. J., Barrett H. L., Price S. A., et al. (2021). Probiotics for preventing gestational diabetes. *Cochrane Database. Syst. Rev.* **4**:CD009951. DOI:10.1002/14651858.CD009951.pub3
59. Nachum Z., Perlitz Y., Shavit L. Y., et al. (2024). The effect of oral probiotics on glycemic control of women with gestational diabetes mellitus-a multicenter, randomized, double-blind, placebo-controlled trial. *Am. J. Obstet. Gynecol. MFM* **6**:101224. DOI:10.1016/j.ajogmf.2023.101224
60. Pellonperä O., Mokkala K., Houttu N., et al. (2019). Efficacy of fish oil and/or probiotic intervention on the incidence of gestational diabetes mellitus in an at-risk group of overweight and obese women: A randomized, placebo-controlled, double-blind clinical trial. *Diabetes Care* **42**:1009–1017. DOI:10.2337/dc18-2591
61. Rautava S., Collado M. C., Salminen S., et al. (2012). Probiotics modulate host-microbe interaction in the placenta and fetal gut: A randomized, double-blind, placebo-controlled trial. *Neonatology* **102**:178–184. DOI:10.1159/000339182
62. Callaway L. K., McIntyre H. D., Barrett H. L., et al. (2019). Probiotics for the prevention of gestational diabetes mellitus in overweight and obese women: Findings from the SPRING double-blind randomized controlled trial. *Diabetes Care* **42**:364–371. DOI:10.2337/dc18-2248
63. Mokkala K., Paulin N., Houttu N., et al. (2021). Metagenomics analysis of gut microbiota in response to diet intervention and gestational diabetes in overweight and obese women: A randomised, double-blind, placebo-controlled clinical trial. *Gut* **70**:309–318. DOI:10.1136/gutjnl-2020-321643
64. Cui Z., Wang S., Niu J., et al. (2024). Bifidobacterium species serve as key gut microbiome regulators after intervention in gestational diabetes mellitus. *BMC Microbiol.* **24**:520. DOI:10.1186/s12866-024-03680-z
65. Vanda R., Dastani T., Taghavi S. A., et al. (2024). Pregnancy outcomes in pregnant women taking oral probiotic undergoing cerclage compared to placebo: Two blinded randomized controlled trial. *BMC Pregnancy and Childb.* **24**:311. DOI:10.1186/s12884-024-06496-x
66. Movaghar R., Abbasalizadeh S., Vazifekhah S., et al. (2024). The effects of synbiotic supplementation on blood pressure and other maternal outcomes in pregnant mothers with mild preeclampsia: A triple-blinded randomized controlled trial. *BMC Womens Health* **24**:80. DOI:10.1186/s12905-024-02922-6
67. Wan J., An L., Ren Z., et al. (2023). Effects of galactooligosaccharides on maternal gut microbiota, glucose metabolism, lipid metabolism and inflammation in pregnancy: A randomized controlled pilot study. *Front. Endocrinol.* **14**:1034266. DOI:10.3389/fendo.2023.1034266
68. Phipps E. A., Thadhani R., Benzing T., et al. (2019). Pre-eclampsia: Pathogenesis, novel diagnostics and therapies. *Nat. Rev. Nephrol.* **15**:275–289. DOI:10.1038/s41581-019-0119-6
69. Qin X., Zhang M., Chen S., et al. (2024). Short-chain fatty acids in fetal development and metabolism. *Trends Mol. Med.* **31**:625–639. DOI:10.1016/j.molmed.2024.11.014
70. Swingle K. L., Hamilton A. G., Safford H. C., et al. (2025). Placenta-tropic VEGF mRNA lipid nanoparticles ameliorate murine pre-eclampsia. *Nature* **637**:412–421. DOI:10.1038/s41586-024-08291-2
71. Guo P., Wang W., Xiang Q., et al. (2024). Engineered probiotic ameliorates ulcerative colitis by restoring gut microbiota and redox homeostasis. *Cell Host Microbe* **32**:1502. DOI:10.1016/j.chom.2024.07.028
72. Wang L., Liu Q., Chen Y., et al. (2022). Antioxidant potential of Pediococcus pentosaceus strains from the sow milk bacterial collection in weaned piglets. *Microbiome* **10**:83. DOI:10.1186/s40168-022-01278-z
73. Stringer J. S. A., Pokaprakarn T., Prieto J. C., et al. (2024). Diagnostic accuracy of an integrated ai tool to estimate gestational age from blind ultrasound sweeps. *JAMA* **332**:649–657. DOI:10.1001/jama.2024.10770
74. Bolatai A., He Y. and Wu N. (2022). Vascular endothelial growth factor and its receptors regulation in gestational diabetes mellitus and eclampsia. *J. Transl. Med.* **20**:400. DOI:10.1186/s12967-022-03603-4
75. Zhang C. X. W., Candia A. A. and Sferruzzi-Perri A. N. (2024). Placental inflammation, oxidative stress, and fetal outcomes in maternal obesity. *Trends Endocrin. Met.* **35**:638–647. DOI:10.1016/j.tem.2024.02.002
76. Sweeting A., Hannah W., Backman H., et al. (2024). Epidemiology and management of gestational diabetes. *Lancet.* **404**:175–192. DOI:10.1016/S0140-6736(24)00825-0
77. Olmos-Ortiz A., Flores-Espinosa P., Díaz L., et al. (2021). Immunoendocrine dysregulation during gestational diabetes mellitus: The central role of the placenta. *Int. J. Mol. Sci.* **22**:8087. DOI:10.3390/ijms22158087
78. Wang S., Cui Z. and Yang H. (2024). Interactions between host and gut microbiota in gestational diabetes mellitus and their impacts on offspring. *BMC Microbiol.* **24**:161. DOI:10.1186/s12866-024-03255-y
79. Sun Z., Pan X.-F., Li X., et al. (2023). The gut microbiome dynamically associates with host glucose metabolism throughout pregnancy: Longitudinal findings from a matched case-control study of gestational diabetes mellitus. *Adv. Sci.* **10**:e2205289. DOI:10.1002/advs.202205289
80. Wang S., Liu Y., Tam W. H., et al. (2024). Maternal gestational diabetes mellitus associates with altered gut microbiome composition and head circumference abnormalities in male offspring. *Cell Host Microbe* **32**:1192–1206.e1195. DOI:10.1016/j.chom.2024.06.005
81. Crusell M. K. W., Hansen T. H., Nielsen T., et al. (2018). Gestational diabetes is associated with change in the gut microbiota composition in third trimester of pregnancy and postpartum. *Microbiome* **6**:89. DOI:10.1186/s40168-018-0472-x
82. Hu P., Chen X., Chu X., et al. (2021). Association of gut microbiota during early pregnancy with risk of incident gestational diabetes mellitus. *J. Clin. Endocrin. Metab.* **106**:e4128–e4141. DOI:10.1210/clinem/dgab346
83. Pinto Y., Frishman S., Turjeman S., et al. (2023). Gestational diabetes is driven by microbiota-induced inflammation months before diagnosis. *Gut* **72**:918–928. DOI:10.1136/gutjnl-2022-328406
84. Frishman S., Nuriel-Ohayon M., Turjeman S., et al. (2024). Positive effects of diet-induced microbiome modification on GDM in mice following human faecal transfer. *Gut* **73**:e17. DOI:10.1136/gutjnl-2023-331456
85. Ye D., Huang J., Wu J., et al. (2023). Integrative metagenomic and metabolomic analyses reveal gut microbiota-derived multiple hits connected to development of gestational diabetes mellitus in humans. *Gut Microbes* **15**:2154552. DOI:10.1080/19490976.2022.2154552
86. Dimitriadis E., Rolnik D. L., Zhou W., et al. (2023). Pre-eclampsia. *Nat. Rev. Dis. Primers* **9**:8. DOI:10.1038/s41572-023-00417-6
87. Paquin A., Werlang A. and Coutinho T. (2022). Arterial health abnormalities in women with pre-eclampsia: Contributing role of central obesity. *Eur. Heart J.* **43**:ehac544.2502. DOI:10.1093/eurheartj/ehac544.2502
88. Ray J. G., Abdulaziz K. E., Berger H., et al. (2022). Aspirin use for preeclampsia prevention among women with prepregnancy diabetes, obesity, and hypertension. *JAMA* **327**:388–390. DOI:10.1001/jama.2021.22749
89. Venkatesh S. S., Ferreira T., Benonisdottir S., et al. (2022). Obesity and risk of female reproductive conditions: A Mendelian randomisation study. *PLoS Med* **19**:e1003679. DOI:10.1371/journal.pmed.1003679
90. Tyrmi J. S., Kaartokallio T., Lokki A. I., et al. (2023). Genetic risk factors associated with preeclampsia and hypertensive sisorders of pregnancy. *JAMA Cardiol.* **8**:674–683. DOI:10.1001/jamacardio.2023.1312
91. Ahmadian E., Rahbar Saadat Y., Hosseiniyan Khatibi S. M., et al. (2020). Pre-eclampsia: Microbiota possibly playing a role. *Pharmacol. Res.* **155**:104692. DOI:10.1016/j.phrs.2020.104692
92. Colonetti T., Limas Carmo Teixeira D., Grande A. J., et al. (2023). The role of intestinal microbiota on pre-eclampsia: Systematic review and meta-analysis. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **291**:49–58. DOI:10.1016/j.ejogrb.2023.10.003
93. Liu X., Zeng X., Li X., et al. (2024). Landscapes of gut bacterial and fecal metabolic signatures and their relationship in severe preeclampsia. *J. Transl. Med.* **22**:360. DOI:10.1186/s12967-024-05143-5
94. Chang Y., Chen Y., Zhou Q., et al. (2020). Short-chain fatty acids accompanying changes in the gut microbiome contribute to the development of hypertension in patients with preeclampsia. *Clin. Sci.* **134**:289–302. DOI:10.1042/CS20191253
95. Hemberger M., Hanna C. W. and Dean W. (2020). Mechanisms of early placental development in mouse and humans. *Nat. Rev. Gene* **21**:27–43. DOI:10.1038/s41576-019-0169-4
96. Meijer S., Pasquinelli E., Renzi S., et al. (2023). Gut micro- and mycobiota in preeclampsia: Bacterial composition differences suggest role in pathophysiology. *Biomolecules* **13**:346. DOI:10.3390/biom13020346
97. Spencer R., Maksym K., Hecher K., et al. (2023). Maternal PlGF and umbilical Dopplers predict pregnancy outcomes at diagnosis of early-onset fetal growth restriction. *J. Clin. Invest.* **133**:e169199. DOI:10.1172/JCI169199
98. Martins J. G., Biggio J. R. and Abuhamad A. (2020). Society for maternal-fetal medicine consult series #52: Diagnosis and management of fetal growth restriction: (replaces clinical guideline number 3, April 2012). *Am. J. Obstet. Gynecol.* **223**:B2–B17. DOI:10.1016/j.ajog.2020.05.010
99. Lawn J. E., Ohuma E. O., Bradley E., et al. (2023). Small babies, big risks: Global estimates of prevalence and mortality for vulnerable newborns to accelerate change and improve counting. *Lancet.* **401**:1707–1719. DOI:10.1016/S0140-6736(23)00522-6
100. Conde-Agudelo A., Villar J., Risso M., et al. (2024). Metabolomic signatures associated with fetal growth restriction and small for gestational age: A systematic review. *Nat. Commun.* **15**:9752. DOI:10.1038/s41467-024-53597-4
101. Garcia-Manau P., Bonacina E., Martin-Alonso R., et al. (2025). Angiogenic factors versus fetomaternal Doppler for fetal growth restriction at term: An open-label, randomized controlled trial. *Nat. Med.* **31**:1008–1015. DOI:10.1038/s41591-024-

03421-9

102. Arenas G. A. and Lorca R. A. (2024). Effects of hypoxia on uteroplacental and fetoplacental vascular function during pregnancy. *Front. Physiol.* **15**:1490154. DOI:10.3389/fphys.2024.1490154
103. Hurtado I., Bonacina E., Garcia-Manau P., et al. (2023). Usefulness of angiogenic factors in prenatal counseling of late-onset fetal growth-restricted and small-for-gestational-age gestations: A prospective observational study. *Arch. Gynecol. Obstet.* **308**:1485−1495. DOI:10.1007/s00404-022-06833-5
104. Carbillon L. (2024). Fetal growth decline may reflect placental dysfunction and high stillbirth risk in mothers with obesity. *Am. J. Obstet. Gynecol.* **230**:101−102. DOI:10.1016/j.ajog.2023.09.010
105. Gardosi J. and Hugh O. (2023). Stillbirth risk and smallness for gestational age according to Hadlock, INTERGROWTH-21st, WHO, and grow fetal weight standards: Analysis by maternal ethnicity and body mass index. *Am. J. Obstet. Gynecol. MFM* **229**:547.e541−547.e513. DOI:10.1016/j.ajog.2023.05.026
106. Pritchard N. L., Hiscock R., Walker S. P., et al. (2023). Defining poor growth and stillbirth risk in pregnancy for infants of mothers with overweight and obesity. *Am. J. Obstet. Gynecol.* **229**:59.e51−59.e12. DOI:10.1016/j.ajog.2022.12.322
107. Cömert T. K., Akpinar F., Erkaya S., et al. (2022). The effect of pre-pregnancy obesity on gut and meconium microbiome and relationship with fetal growth. *J. Matern. Fetal Neona.* **35**:10629−10637. DOI:10.1080/14767058.2022.2148098
108. Tu X., Duan C., Lin B., et al. (2022). Characteristics of the gut microbiota in pregnant women with fetal growth restriction. *BMC Pregnancy and Childb.* **22**:297. DOI:10.1186/s12884-022-04635-w
109. Kosińska-Kaczyńska K., Krawczyk D., Bednorz M., et al. (2025). Maternal and placental microbiome and immune crosstalk in pregnancies with small-for-gestational-age fetuses-a pilot case-control study. *Front. Cell Infect. Microbiol.* **15**:1596588. DOI:10.3389/fcimb.2025.1596588
110. He X., Li Z., Li X., et al. (2023). The fecal microbiota of gravidas with fetal growth restriction newborns characterized by metagenomic sequencing. *Curr. Res. Transl. Med.* **71**:103354. DOI:10.1016/j.retram.2022.103354
111. Coskun R., Chang Z. L., Marcial Rodríguez A., et al. (2025). Effects of the gut microbiota on placental angiogenesis and intrauterine growth in gnotobiotic mice. *Proc. Natl. Acad. Sci. USA* **122**:e2426341122. DOI. DOI:10.1073/pnas.2426341122
112. Ruebel M. L., Gilley S. P., Yeruva L., et al. (2024). Associations between maternal microbiome, metabolome and incidence of low-birth weight in Guatemalan participants from the Women First Trial. *Front. Microbiol.* **15**:1456087. DOI:10.3389/fmicb.2024.1456087
113. Ziętek M., Celewicz Z. and Szczuko M. (2021). Short-chain fatty acids, maternal microbiota and metabolism in pregnancy. *Nutrients* **13**:1244. DOI:10.3390/nu13041244
114. Wallace J. G., Bellissimo C. J., Yeo E., et al. (2019). Obesity during pregnancy results in maternal intestinal inflammation, placental hypoxia, and alters fetal glucose metabolism at mid-gestation. *Sci. Rep.* **9**:17621. DOI:10.1038/s41598-019-54098-x
115. Koren O., Konnikova L., Brodin P., et al. (2024). The maternal gut microbiome in pregnancy: Implications for the developing immune system. *Nat. Rev. Gastroenterol. Hepatol.* **21**:35−45. DOI:10.1038/s41575-023-00864-2
116. Enache R.-M., Profir M., Roşu O. A., et al. (2024). The role of gut microbiota in the onset and progression of obesity and associated comorbidities. *Int. J. Mol. Sci.* **25**:12321. DOI:10.3390/ijms252212321
117. Stanislawski M. A., Dabelea D., Wagner B. D., et al. (2017). Pre-pregnancy weight, gestational weight gain, and the gut microbiota of mothers and their infants. *Microbiome* **5**:113. DOI:10.1186/s40168-017-0332-0
118. Yang X., Zhang M., Zhang Y., et al. (2023). Ecological change of the gut microbiota during pregnancy and progression to dyslipidemia. *npj Biofilms and Microbiomes* **9**:14. DOI:10.1038/s41522-023-00383-7
119. Sugino K. Y., Paneth N. and Comstock S. S. (2019). Michigan cohorts to determine associations of maternal pre-pregnancy body mass index with pregnancy and infant gastrointestinal microbial communities: Late pregnancy and early infancy. *PLoS One* **14**:e0213733. DOI:10.1371/journal.pone.0213733
120. Abdullah B., Daud S., Aazmi M. S., et al. (2022). Gut microbiota in pregnant Malaysian women: A comparison between trimesters, body mass index and gestational diabetes status. *BMC Pregnancy and Childb.* **22**:152. DOI:10.1186/s12884-022-04472-x
121. Zacarías M. F., Collado M. C., Gómez-Gallego C., et al. (2018). Pregestational overweight and obesity are associated with differences in gut microbiota composition and systemic inflammation in the third trimester. *PLoS One* **13**:e0200305. DOI:10.1371/journal.pone.0200305
122. Santacruz A., Collado M. C., García-Valdés L., et al. (2010). Gut microbiota composition is associated with body weight, weight gain and biochemical parameters in pregnant women. *Br. J. Nutr.* **104**:83−92. DOI:10.1017/S0007114510000176
123. Yi D., Li T., Xiao Y., et al. (2025). Hydroxytyrosol improved insulin resistance in male offspring born to high-fat diet dams by remodeling gut microbiota. *J. Nutr. Biochem.* **146**:110041. DOI:10.1016/j.jnutbio.2025.110041
124. Marousez L., Verce M., Dubernat L., et al. (2025). Maternal high-fat diet during lactation reduces sialylated milk oligosaccharides and shapes early-life microbiota in rat offspring. *Food Funct.* **16**:5123−5132. DOI:10.1039/d5fo00559k
125. Gohir W., Kennedy K. M., Wallace J. G., et al. (2019). High-fat diet intake modulates maternal intestinal adaptations to pregnancy and results in placental hypoxia, as well as altered fetal gut barrier proteins and immune markers. *J. Physiol.* **597**:3029−3051. DOI:10.1113/JP277353
126. Guo Y., Wang Z., Chen L., et al. (2018). Diet induced maternal obesity affects offspring gut microbiota and persists into young adulthood. *Food Funct.* **9**:4317−4327. DOI:10.1039/c8fo00444g
127. Gomez-Arango L. F., Barrett H. L., McIntyre H. D., et al. (2016). Connections between the gut microbiome and metabolic hormones in early pregnancy in overweight and obese women. *Diabetes* **65**:2214−2223. DOI:10.2337/db16-0278
128. Gomez-Arango L. F., Barrett H. L., McIntyre H. D., et al. (2016). Increased systolic and diastolic blood pressure is associated with altered gut microbiota composition and butyrate production in early pregnancy. *Hypertension* **68**:974−981. DOI:10.1161/HYPERTENSIONAHA.116.07910
129. Han H., Yi B., Zhong R., et al. (2021). From gut microbiota to host appetite: Gut microbiota-derived metabolites as key regulators. *Microbiome* **9**:162. DOI:10.1186/s40168-021-01093-y
130. Wu W., Lo Y., Chiu J., et al. (2024). Gut microbes with the GBU genes determine TMAO production from L-carnitine intake and serve as a biomarker for precision nutrition. *Gut Microbes* **17**:2446374. DOI:10.1080/19490976.2024.2446374
131. York A. (2021). A muciniphila boosts metabolic health. *Nat. Rev. Micro.* **19**:343−343. DOI:10.1038/s41579-021-00556-1
132. Yoon H. S., Cho C. H., Yun M. S., et al. (2021). Akkermansia muciniphila secretes a glucagon-like peptide-1-inducing protein that improves glucose homeostasis and ameliorates metabolic disease in mice. *Nat. Microbiol.* **6**:563−573. DOI:10.1038/s41564-021-00880-5
133. Chanda D. and De D. (2024). Meta-analysis reveals obesity associated gut microbial alteration patterns and reproducible contributors of functional shift. *Gut Microbes* **16**:2304900. DOI:10.1080/19490976.2024.2304900
134. Ziętek M., Celewicz Z., Kikut J., et al. (2021). Implications of SCFAs on the parameters of the lipid and hepatic profile in pregnant women. *Nutrients* **13**:1749. DOI:10.3390/nu13061749
135. Molan K., Ambrožič Avguštin J., Likar M., et al. (2025). Fecal short-chain fatty acids are associated with obesity in gestational diabetes. *Biomedicines* **13**:387. DOI:10.3390/biomedicines13020387
136. Kim K. N., Yao Y. and Ju S. Y. (2019). Short chain fatty acids and fecal microbiota abundance in humans with obesity: A systematic review and meta-analysis. *Nutrients* **11**:2512. DOI:10.3390/nu11102512
137. Mokkala K., Pellonperä O., Röytiö H., et al. (2017). Increased intestinal permeability, measured by serum zonulin, is associated with metabolic risk markers in overweight pregnant women. *Metabolism* **69**:43−50. DOI:10.1016/j.metabol.2016.12.015
138. Mishra S. P., Wang B., Jain S., et al. (2023). A mechanism by which gut microbiota elevates permeability and inflammation in obese/diabetic mice and human gut. *Gut* **72**:1848−1865. DOI:10.1136/gutjnl-2022-327365
139. Tang R., Xiao G., Jian Y., et al. (2022). The gut microbiota dysbiosis in preeclampsia contributed to trophoblast cell proliferation, invasion, and migration via lncRNA BC030099/NF-κB pathway. *Mediators Inflamm.* **2022**:6367264. DOI:10.1155/2022/6367264
140. Feng H., Su R., Song Y., et al. (2016). Positive correlation between enhanced expression of TLR4/MyD88/NF-κB with insulin resistance in placentae of gestational diabetes mellitus. *PLoS One* **11**:e0157185. DOI:10.1371/journal.pone.0157185
141. Cheng S.-B., Nakashima A., Huber W. J., et al. (2019). Pyroptosis is a critical inflammatory pathway in the placenta from early onset preeclampsia and in human trophoblasts exposed to hypoxia and endoplasmic reticulum stressors. *Cell Death Dis.* **10**:927. DOI:10.1038/s41419-019-2162-4
142. Fan M., Li X., Gao X., et al. (2019). LPS induces preeclampsia-like phenotype in rats and htr8/svneo cells dysfunction through TLR4/p38 MAPK pathway. *Front. Physiol.* **10**:1030. DOI:10.3389/fphys.2019.01030
143. Wang J., Gu X., Yang J., et al. (2019). Gut microbiota dysbiosis and increased plasma LPS and TMAO levels in patients with preeclampsia. *Front. Cell. Infect. Microbiol.* **9**:409. DOI:10.3389/fcimb.2019.00409
144. Li H., Liu S., Chen H., et al. (2024). Gut dysbiosis contributes to SCFAs reduction-associated adipose tissue macrophage polarization in gestational diabetes mellitus. *Life Sci.* **350**:122744. DOI:10.1016/j.lfs.2024.122744
145. Tang H., Li H., Li D., et al. (2023). The gut microbiota of pregnant rats alleviates fetal growth restriction by inhibiting the TLR9/MyD88 pathway. *J. Microbiol. Biotechnol.* **33**:1213−1227. DOI:10.4014/jmb.2304.04020
146. Yong W., Zhao Y., Jiang X., et al. (2022). Sodium butyrate alleviates pre-eclampsia in pregnant rats by improving the gut microbiota and short-chain fatty acid metabolites production. *J. Appl. Microbiol.* **132**:1370−1383. DOI:10.1111/jam.15279
147. Tilves C., Yeh H., Maruthur N., et al. (2022). Increases in circulating and fecal butyrate are associated with reduced blood pressure and hypertension: Results from the SPIRIT trial. *J. Am. Heart. Assoc.* **11**:e024763. DOI:10.1161/JAHA.121.024763
148. Cui J., Wang J. and Wang Y. (2023). The role of short-chain fatty acids produced by gut microbiota in the regulation of pre-eclampsia onset. *Front. Cell Infect. Microbiol.*

13:1177768. DOI:10.3389/fcimb.2023.1177768

149. Kimura I., Miyamoto J., Ohue-Kitano R., et al. (2020). Maternal gut microbiota in pregnancy influences offspring metabolic phenotype in mice. *Science* **367**:eaaw8429. DOI:10.1126/science.aaw8429
150. Han W., Wang J., Yan X., et al. (2024). Butyrate and iso-butyrate: A new perspective on nutrition prevention of gestational diabetes mellitus. *Nutrition & Diabetes* **14**:24. DOI:10.1038/s41387-024-00276-4
151. Grzeszczak K., Łanocha-Arendarczyk N., Malinowski W., et al. (2023). Oxidative stress in pregnancy. *Biomolecules* **13**:1768. DOI:10.3390/biom13121768
152. Haidery F., Lambertini L., Tse I., et al. (2025). NRF2 deficiency leads to inadequate beta cell adaptation during pregnancy and gestational diabetes. *Redox Biol.* **81**:103566. DOI:10.1016/j.redox.2025.103566
153. Shi L., Wang Z., Xiao J., et al. (2025). Folic acid alleviates hydrogen peroxide-induced oxidative stress in bovine placental trophoblast cells by regulating the NRF2/mTOR signaling pathway. *Int. J. Mol. Sci.* **26**:2818. DOI:10.3390/ijms26062818
154. Xie G., Zhang Q., Dong J., et al. (2024). Maternal vitamin D3 supplementation in an oxidized-oil diet protects fetus from developmental impairment and ameliorates oxidative stress in mouse placenta and fetus. *J. Nutr.* **154**:2920–2931. DOI:10.1016/j.tjnut.2024.07.025
155. Zakeri S., Rahimi Z., Rezvani N., et al. (2024). The influence of Nrf2 gene promoter methylation on gene expression and oxidative stress parameters in preeclampsia. *BMC Med. Genomics* **17**:64. DOI:10.1186/s12920-023-01791-6
156. Yanagisawa M., Nagamatsu T., Kurano M., et al. (2023). Upregulation of autotaxin by oxidative stress via Nrf2 activation: A novel insight into the compensation mechanism in preeclamptic placenta. *J. Reprod. Immunol.* **160**:104153. DOI:10.1016/j.jri.2023.104153
157. Duan Y., Sun F., Que S., et al. (2018). Prepregnancy maternal diabetes combined with obesity impairs placental mitochondrial function involving Nrf2/ARE pathway and detrimentally alters metabolism of offspring. *Obes. Res. Clin. Pract.* **12**:90–100. DOI:10.1016/j.orcp.2017.01.002
158. Shandilya S., Kumar S., Kumar Jha N., et al. (2022). Interplay of gut microbiota and oxidative stress: Perspective on neurodegeneration and neuroprotection. *J. Adv. Res.* **38**:223–244. DOI:10.1016/j.jare.2021.09.005
159. Kim S. Y., Chae C. W., Lee H. J., et al. (2020). Sodium butyrate inhibits high cholesterol-induced neuronal amyloidogenesis by modulating NRF2 stabilization-mediated ROS levels: Involvement of NOX2 and SOD1. *Cell Death Dis.* **11**:469. DOI:10.1038/s41419-020-2663-1
160. Zhang Y., Cheng Y., Liu J., et al. (2022). Tauroursodeoxycholic acid functions as a critical effector mediating insulin sensitization of metformin in obese mice. *Redox Biol.* **57**:102481. DOI:10.1016/j.redox.2022.102481
161. Zhang D. D. (2025). Thirty years of NRF2: Advances and therapeutic challenges. *Nat. Rev. Drug. Discov.* **24**:421–444. DOI:10.1038/s41573-025-01145-0
162. Pérez-Gutiérrez L. and Ferrara N. (2023). Biology and therapeutic targeting of vascular endothelial growth factor A. *Nat. Rev. Mol. Cell Biol.* **24**:816–834. DOI:10.1038/s41580-023-00631-w
163. Liu J., Quan L., Wang J., et al. (2025). Knockdown of VEGF-B improves HFD-induced insulin resistance by enhancing glucose uptake in vascular endothelial cells via the PI3K/Akt pathway. *Int. J. Biol. Macromol.* **285**:138279. DOI:10.1016/j.ijbiomac.2024.138279
164. Umapathy A., Chamley L. W. and James J. L. (2020). Reconciling the distinct roles of angiogenic/anti-angiogenic factors in the placenta and maternal circulation of normal and pathological pregnancies. *Angiogenesis* **23**:105–117. DOI:10.1007/s10456-019-09694-w
165. Biwer L. A., Lu Q., Ibarrola J., et al. (2023). Smooth muscle mineralocorticoid receptor promotes hypertension after preeclampsia. *Circ. Res.* **132**:674–689. DOI:10.1161/CIRCRESAHA.122.321228
166. Di Martino D. D., Soldavini C. M., Rossi G., et al. (2023). The sFlt-1/PlGF ratio in patients affected by gestational diabetes and SARS-CoV-2 Infection. *Metabolites* **13**:54. DOI:10.3390/metabo13010054
167. Kinugawa M., Kumasawa K., Nemoto K., et al. (2025). Impact of parity and pre-pregnancy BMI on second-trimester sFlt-1 and PlGF levels in normotensive pregnancies. *Hypertens Pregnancy* **44**:2534022. DOI:10.1080/10641955.2025.2534022
168. Lim J. H., Kim Y., Kim M. Y., et al. (2024). Placental growth factor deficiency initiates obesity- and aging-associated metabolic syndrome. *Metabolism* **161**:156002. DOI:10.1016/j.metabol.2024.156002
169. Lin X., Zhang Y., He X., et al. (2021). The choline metabolite TMAO inhibits netosis and promotes placental development in GDM of humans and mice. *Diabetes* **70**:2250–2263. DOI:10.2337/db21-0188
170. Wen Y., Peng L., Xu R., et al. (2019). Maternal serum trimethylamine-N-oxide is significantly increased in cases with established preeclampsia. *Pregnancy Hypertens* **15**:114–117. DOI:10.1016/j.preghy.2018.12.001
171. Zhou T., Heianza Y., Chen Y., et al. (2019). Circulating gut microbiota metabolite Trimethylamine N-Oxide (TMAO) and changes in bone density in response to weight loss diets: The POUNDS lost trial. *Diabetes Care* **42**:1365–1371. DOI:10.2337/dc19-0134
172. Chang Q.-X., Chen X., Ming-Xin Y., et al. (2021). Trimethylamine N-oxide increases soluble fms-like tyrosine Kinase-1 in human placenta via NADPH oxidase dependent ROS accumulation. *Placenta* **103**:134–140. DOI:10.1016/j.placenta.2020.10.021
173. Zhou S., Xue J., Shan J., et al. (2022). Gut-flora-dependent metabolite trimethylamine-n-oxide promotes atherosclerosis-associated inflammation responses by indirect ros stimulation and signaling involving AMPK and SIRT1. *Nutrients* **14**:3338. DOI:10.3390/nu14163338
174. Ma Y., Yang Y., Lv M., et al. (2022). 1,25(OH)2D3 alleviates LPS-induced preeclampsia-like rats impairment in the protective effect by TLR4/NF-kB pathway. *Placenta* **130**:34–41. DOI:10.1016/j.placenta.2022.10.012
175. Albers R. E., Kaufman M. R., Natale B. V., et al. (2019). Trophoblast-specific expression of Hif-1α results in preeclampsia-Like symptoms and fetal growth restriction. *Sci. Rep.* **9**:2742. DOI:10.1038/s41598-019-39426-5
176. Desoye G. and Carter A. M. (2022). Fetoplacental oxygen homeostasis in pregnancies with maternal diabetes mellitus and obesity. *Nat. Rev. Endocrinol.* **18**:593–607. DOI:10.1038/s41574-022-00717-z
177. Bellissimo C. J., Ribeiro T. A., Yeo E., et al. (2025). Maternal high-fat, high-sucrose diet-induced excess adiposity is linked to placental hypoxia and disruption of fetoplacental immune homeostasis in late gestation. *Biol. Reprod.* **7**:ioaf143. DOI:10.1093/biolre/ioaf143
178. Adams D., Beckers K., Gomes V., et al. (2021). Abstract P224: Obesity is associated with hypoxia at the maternal-fetal interface in a mouse model of superimposed preeclampsia, BPH/5. *Hypertension* **78**:AP224–AP224. DOI:10.1161/hyp.78.suppl_1.P224
179. Yuan X., Ruan W., Bobrow B., et al. (2023). Targeting hypoxia-inducible factors: Therapeutic opportunities and challenges. *Nat. Rev. Drug Discov.* **23**:175–200. DOI:10.1038/s41573-023-00848-6
180. Deng F., Yin C., Luo C., et al. (2025). Lactobacillus reuteri-mediated dietary xylooligosaccharides enhance jejunal cell survival via suppression of oxygen-dependent apoptotic processes in a pig model. *Imeta* **4**:e70080. DOI:10.1002/imt2.70080
181. Xu J., Yang Y., Li X., et al. (2023). Pleiotropic activities of succinate: The interplay between gut microbiota and cardiovascular diseases. *Imeta* **2**:e124. DOI:10.1002/imt2.124
182. Wang X., Xu S., Zhou X., et al. (2021). Low chorionic villous succinate accumulation associates with recurrent spontaneous abortion risk. *Nat. Commun.* **12**:3428. DOI:10.1038/s41467-021-23827-0
183. Huber-Ruano I., Calvo E., Mayneris-Perxachs J., et al. (2022). Orally administered Odoribacter laneus improves glucose control and inflammatory profile in obese mice by depleting circulating succinate. *Microbiome* **10**:135. DOI:10.1186/s40168-022-01306-y
184. Serena C., Ceperuelo-Mallafré V., Keiran N., et al. (2018). Elevated circulating levels of succinate in human obesity are linked to specific gut microbiota. *ISME J.* **12**:1642–1657. DOI:10.1038/s41396-018-0068-2
185. de Goffau, M.C., Lager, S., Sovio, U., et al. (2019). Human placenta has no microbiome but can contain potential pathogens. *Nature* **572**:329–334. DOI:10.1038/s41586-019-1451-5
186. Gaccioli F., Stephens K., Sovio U., et al. (2023). Placental Streptococcus agalactiae DNA is associated with neonatal unit admission and foetal pro-inflammatory cytokines in term infants. *Nat. Microbiol.* **8**:2338–2348. DOI:10.1038/s41564-023-01528-2
187. Benny P. A., Al-Akwaa F. M., Dirkx C., et al. (2021). Placentas delivered by pre-pregnant obese women have reduced abundance and diversity in the microbiome. *FASEB J.* **35**:e21524. DOI:10.1096/fj.202002184RR
188. Tanz L. J., Stuart J. J., Rimm E. B., et al. (2017). Abstract P314: Higher c-reactive protein levels among women with a history of hypertensive disorders of pregnancy. *Circulation* **135**:AP314–AP314. DOI:10.1161/circ.135.suppl_1.p314
189. Ye C., Katagiri S., Miyasaka N., et al. (2020). The periodontopathic bacteria in placenta, saliva and subgingival plaque of threatened preterm labor and preterm low birth weight cases: A longitudinal study in Japanese pregnant women. *Clin. Oral Investig.* **24**:4261–4270. DOI:10.1007/s00784-020-03287-4
190. Parhi L., Abed J., Shhadeh A., et al. (2022). Placental colonization by Fusobacterium nucleatum is mediated by binding of the Fap2 lectin to placentally displayed Gal-GalNAc. *Cell Rep.* **38**:110537. DOI:10.1016/j.celrep.2022.110537
191. Stockham S., Stamford J. E., Roberts C. T., et al. (2015). Abnormal pregnancy outcomes in mice using an induced periodontitis model and the haematogenous migration of Fusobacterium nucleatum sub-species to the murine placenta. *PLoS One* **10**:e0120050. DOI:10.1371/journal.pone.0120050
192. Wu C., Chen Y., Scheible M., et al. (2021). Genetic and molecular determinants of polymicrobial interactions in Fusobacterium nucleatum. *Proc. Natl. Acad. Sci. USA* **118**:e2006482118. DOI:10.1073/pnas.2006482118
193. Kotzur R., Kahlon S., Isaacson B., et al. (2024). Pregnancy trained decidual NK cells protect pregnancies from harmful Fusobacterium nucleatum infection. *PLoS Pathog.* **20**:e1011923. DOI:10.1371/journal.ppat.1011923
194. Einenkel R., Ehrhardt J., Zygmunt M., et al. (2024). Less is more! Low amount of Fusobacterium nucleatum supports macrophage-mediated trophoblast functions in vitro. *Front. Immunol.* **15**:1447190. DOI:10.3389/fimmu.2024.1447190
195. Zakis D. R., Paulissen E., Kornete L., et al. (2022). The evidence for placental microbiome and its composition in healthy pregnancies: A systematic review. *J.*

Reprod. Immunol. **149**:103455. DOI:10.1016/j.jri.2021.103455

196. Socha M. W., Malinowski B., Puk O., et al. (2021). The role of NF-κB in uterine spiral arteries remodeling, insight into the cornerstone of preeclampsia. *Int. J. Mol. Sci.* **22**:704. DOI:10.3390/ijms22020704
197. Chen C., Yang Z. and Qiu Z. (2023). Bioinformatics prediction and experimental validation of the role of macrophage polarization and ferroptosis in gestational diabetes mellitus. *J. Inflamm. Res.* **16**:6087–6105. DOI:10.2147/jir.S440826
198. Zheng X., Ma W., Wang Y., et al. (2023). Heat stress-induced fetal intrauterine growth restriction is associated with elevated LPS levels along the maternal intestine-placenta-fetus axis in pregnant mice. *J. Agric. Food. Chem.* **71**:19592–19609. DOI:10.1021/acs.jafc.3c07058
199. Zhang H., Liu X., Zheng Y., et al. (2022). Effects of the maternal gut microbiome and gut-placental axis on melatonin efficacy in alleviating cadmium-induced fetal growth restriction. *Ecotoxicol. Environ. Saf.* **237**:113550. DOI:10.1016/j.ecoenv.2022.113550
200. Cotechini T., Komisarenko M., Sperou A., et al. (2014). Inflammation in rat pregnancy inhibits spiral artery remodeling leading to fetal growth restriction and features of preeclampsia. *J. Exp. Med.* **211**:165–179. DOI:10.1084/jem.20130295
201. Jahan F., Vasam G., Cariaco Y., et al. (2023). A comparison of rat models that best mimic immune-driven preeclampsia in humans. *Front. Endocr.* **14**:1219205. DOI:10.3389/fendo.2023.1219205
202. Fricke E. M., Elgin T. G., Gong H., et al. (2018). Lipopolysaccharide-induced maternal inflammation induces direct placental injury without alteration in placental blood flow and induces a secondary fetal intestinal injury that persists into adulthood. *Am. J. Reprod. Immunol.* **79**:e12816. DOI:10.1111/aji.12816
203. Deer E., Herrock O., Campbell N., et al. (2023). The role of immune cells and mediators in preeclampsia. *Nat. Rev. Nephrol.* **19**:257–270. DOI:10.1038/s41581-022-00670-0
204. Joshi N. P., Madiwale S. D., Sundrani D. P., et al. (2023). Fatty acids, inflammation and angiogenesis in women with gestational diabetes mellitus. *Biochimie* **212**:31–40. DOI:10.1016/j.biochi.2023.04.005
205. Al-Ofi E., Alrafiah A., Maidi S., et al. (2021). Altered expression of angiogenic biomarkers in pregnancy associated with gestational diabetes. *Int. J. Gen. Med.* **14**:3367–3375. DOI:10.2147/IJGM.S316670
206. Villota S. D., Toledo-Rodriguez M. and Leach L. (2021). Compromised barrier integrity of human feto-placental vessels from gestational diabetic pregnancies is related to downregulation of occludin expression. *Diabetologia* **64**:195–210. DOI:10.1007/s00125-020-05290-6
207. Musa E., Salazar-Petres E., Arowolo A., et al. (2023). Obesity and gestational diabetes independently and collectively induce specific effects on placental structure, inflammation and endocrine function in a cohort of South African women. *J. Physiol.* **601**:1287–1306. DOI:10.1113/JP284139
208. Chen D., Wang Y., Li S., et al. (2022). Maternal propionate supplementation ameliorates glucose and lipid metabolic disturbance in hypoxia-induced fetal growth restriction. *Food Funct.* **13**:10724–10736. DOI:10.1039/d2fo01481e
209. Guo H., Yang Y., Qiao Y., et al. (2021). Heat stress affects fetal brain and intestinal function associated with the alterations of placental barrier in late pregnant mouse. *Ecotoxicol. Environ. Saf.* **227**:112916. DOI:10.1016/j.ecoenv.2021.112916
210. Sun P., Wang M., Chai X., et al. (2025). Disruption of tryptophan metabolism by high-fat diet-triggered maternal immune activation promotes social behavioral deficits in male mice. *Nat. Commun.* **16**:2105. DOI:10.1038/s41467-025-57414-4
211. Sun P., Wang M., Liu Y., et al. (2023). High-fat diet-disturbed gut microbiota-colonocyte interactions contribute to dysregulating peripheral tryptophan-kynurenine metabolism. *Microbiome* **11**:154. DOI:10.1186/s40168-023-01606-x
212. Pessa-Morikawa T., Husso A., Kärkkäinen O., et al. (2022). Maternal microbiota-derived metabolic profile in fetal murine intestine, brain and placenta. *BMC Microbiol.* **22**:46. DOI:10.1186/s12866-022-02457-6
213. Peng X., Huang Y., Wang G., et al. (2022). Maternal long-term intake of inulin improves fetal development through gut microbiota and related metabolites in a rat model. *J. Agric. Food Chem.* **70**:1840–1851. DOI:10.1021/acs.jafc.1c07284
214. Perry A., Stephanou A. and Rayman M. P. (2022). Dietary factors that affect the risk of pre-eclampsia. *BMJ Nutr. Prev. Health.* **5**:118–133. DOI:10.1136/bmjnph-2021-000399
215. Hart T. L., Petersen K. S. and Kris-Etherton P. M. (2022). Nutrition recommendations for a healthy pregnancy and lactation in women with overweight and obesity – strategies for weight loss before and after pregnancy. *Fertil. and Steril.* **118**:434–446. DOI:10.1016/j.fertnstert.2022.07.027
216. Yu E. W., Gao L., Stastka P., et al. (2020). Fecal microbiota transplantation for the improvement of metabolism in obesity: The FMT-TRIM double-blind placebo-controlled pilot trial. *PLoS Med.* **17**:e1003051. DOI:10.1371/journal.pmed.1003051
217. Tao Y., Gu Y., Mao X., et al. (2020). Effects of probiotics on type II diabetes mellitus: A meta-analysis. *J. Transl. Med.* **18**:30. DOI:10.1186/s12967-020-02213-2
218. Halkjær S. I., Refslund Danielsen M., de Knegt V. E., et al. (2024). Multi-strain probiotics during pregnancy in women with obesity influence infant gut microbiome development: Results from a randomized, double-blind placebo-controlled study. *Gut Microbes* **16**:2337968. DOI:10.1080/19490976.2024.2337968
219. Jones J. M., Reinke S. N., Mousavi-Derazmahalleh M., et al. (2024). Maternal prebiotic supplementation during pregnancy and lactation modifies the microbiome and short chain fatty acid profile of both mother and infant. *Clin. Nutr.* **43**:969–980. DOI:10.1016/j.clnu.2024.02.030
220. Halkjær S. I., de Knegt V. E., Kallemose T., et al. (2023). No effect of multi-strain probiotic supplementation on metabolic and inflammatory markers and newborn body composition in pregnant women with obesity: Results from a randomized, double-blind placebo-controlled study. *Nutr. Metab. Cardiovasc. Dis.* **33**:2444–2454. DOI:10.1016/j.numecd.2023.07.030
221. Halkjær S. I., de Knegt V. E., Lo B., et al. (2020). Multistrain probiotic increases the gut microbiota diversity in obese pregnant women: Results from a randomized, double-blind placebo-controlled study. *Curr. Dev. Nutr.* **4**:nzaa095. DOI:10.1093/cdn/nzaa095
222. Okesene-Gafa K. A. M., Li M., McKinlay C. J. D., et al. (2019). Effect of antenatal dietary interventions in maternal obesity on pregnancy weight-gain and birthweight: Healthy mums and babies (HUMBA) randomized trial. *Am. J. Obstet. Gynecol.* **221**:152.e151–152.e113. DOI:10.1016/j.ajog.2019.03.003
223. Lindsay K. L., Kennelly M., Culliton M., et al. (2014). Probiotics in obese pregnancy do not reduce maternal fasting glucose: A double-blind, placebo-controlled, randomized trial (Probiotics in Pregnancy Study). *Am. J. Clin. Nutr.* **99**:1432–1439. DOI:10.3945/ajcn.113.079723
224. Saros L., Vahlberg T., Koivuniemi E., et al. (2022). Fish oil and/or probiotics intervention in overweight/obese pregnant women and overweight risk in 24-month-old children. *J. Pediatr. Gastroenterol. Nutr.* **76**:218–226. DOI:10.1097/MPG.0000000000003659
225. Fu Y., Gou W., Wu P., et al. (2024). Landscape of the gut mycobiome dynamics during pregnancy and its relationship with host metabolism and pregnancy health. *Gut* **73**:1302–1312. DOI:10.1136/gutjnl-2024-332260
226. Hasain Z., Raja Ali R. A., Ahmad H. F., et al. (2022). The roles of probiotics in the gut microbiota composition and metabolic outcomes in asymptomatic post-gestational diabetes women: A randomized controlled trial. *Nutrients* **14**:3878. DOI:10.3390/nu14183878
227. Chatzakis C., Goulis D. G., Mareti E., et al. (2019). Prevention of gestational diabetes mellitus in overweight or obese pregnant women: A network meta-analysis. *Diabetes Res. Clin. Pract.* **158**:107924. DOI:10.1016/j.diabres.2019.107924
228. Wang C., Tung Y., Chang H., et al. (2020). Effect of probiotic supplementation on newborn birth weight for mother with gestational diabetes mellitus or overweight/obesity: A systematic review and meta-analysis. *Nutrients* **12**:3477. DOI:10.3390/nu12113477
229. Grev J., Berg M. and Soll R. (2018). Maternal probiotic supplementation for prevention of morbidity and mortality in preterm infants. *Cochrane Database Syst. Rev.* **12**:CD012519. DOI:10.1002/14651858.CD012519.pub2
230. Mantaring J., Benyacoub J., Destura R., et al. (2018). Effect of maternal supplement beverage with and without probiotics during pregnancy and lactation on maternal and infant health: A randomized controlled trial in the Philippines. *BMC Pregnancy and Childb.* **18**:193. DOI:10.1186/s12884-018-1828-8
231. Hemberger M. and Dean W. (2023). The placenta: Epigenetic insights into trophoblast developmental models of a generation-bridging organ with long-lasting impact on lifelong health. *Physiol. Rev.* **103**:2523–2560. DOI:10.1152/physrev.00001.2023
232. Han X., Cai C., Deng W., et al. (2024). Landscape of human organoids: Ideal model in clinics and research. *The Innovation* **5**:100620. DOI:10.1016/j.xinn.2024.100620
233. Itsuma N., Nakazawa M. and Yoko M. A. (2024). 3D morphogenesis and bacterial co-culture in a canine gut-on-a-chip using biopsy-derived intestinal organoids from healthy and ibd patients. *Gastroenterology* **30**:S85. DOI:10.1053/j.gastro.2023.11.271
234. Montgomery-Csobán T., Kavanagh K., Murray P., et al. (2024). Machine learning-enabled maternal risk assessment for women with pre-eclampsia (the PIERS-ML model): A modelling study. *Lancet Digit. Health* **6**:e238–e250. DOI:10.1016/S2589-7500(23)00267-4
235. Wang L., Jia Z., Xu K., et al. (2024). When will dual-purpose pigs fly. *The Innovation* **5**:100702. DOI:10.1016/j.xinn.2024.100702
236. Wild R. A., Zhao D., McPhaul M. J., et al. (2025). Weight loss before conception: Effects on atherogenic apolipoprotein lipid particles and endothelial function during pregnancy. *F&S Reports* **6**:185–192. DOI:10.1016/j.xfre.2025.02.009
237. Hinkle S. N., Mumford S. L., Grantz K. L., et al. (2023). Gestational weight change in a diverse pregnancy cohort and mortality over 50 years: A prospective observational cohort study. *Lancet.* **402**:1857–1865. DOI:10.1016/s0140-6736(23)01517-9
238. Perumal N., Wang D., Darling A. M., et al. (2023). Suboptimal gestational weight gain and neonatal outcomes in low and middle income countries: Individual participant data meta-analysis. *BMJ* **382**:e072249. DOI:10.1136/bmj-2022-072249
239. Kasahara K., Ichikawa Y., Hironaka J., et al. (2025). Time for a change? Threshold for obesity in contemporary Japanese population. *Metabolism* **171**:156352. DOI:10.1016/j.metabol.2025.156352
240. Sun X., Sun Z., Peng W., et al. (2024). Expert consensus and call on actions for weight management in China: Advancing healthy China initiative through strategic actions. *China CDC Weekly* **6**:1347–1353. DOI:10.46234/ccdcw2024.268
241. Hillesund E. R., Seland S., Bere E., et al. (2018). Preeclampsia and gestational weight gain in the Norwegian Fit for Delivery trial. *BMC Res. Notes* **11**:282. DOI:10.1186/s13104-018-3396-4

242. Catalano P. M. (2019). Reassessing strategies to improve pregnancy outcomes in overweight and obese women. *Lancet Diabetes Endocrinol.* **7**:2–3. DOI:10.1016/S2213-8587(18)30337-1
243. Houttu N., Vahlberg T., Miles E. A., et al. (2023). The impact of fish oil and/or probiotics on serum fatty acids and the interaction with low-grade inflammation in pregnant women with overweight and obesity: Secondary analysis of a randomised controlled trial. *Br. J. Nutr.* **131**:1–16. DOI:10.1017/S0007114523001915
244. Chen Y., Li Z., Tye K. D., et al. (2019). Probiotic supplementation during human pregnancy affects the gut microbiota and immune status. *Front. Cell Infect. Microbiol.* **9**:254. DOI:10.3389/fcimb.2019.00254
245. Obuchowska A., Gorczyca K., Standyło A., et al. (2022). Effects of probiotic supplementation during pregnancy on the future maternal risk of metabolic syndrome. *Int. J. Mol. Sci.* **23**:8253. DOI:10.3390/ijms23158253
246. Gao S. and Wang J. (2023). Maternal and infant microbiome: Next-generation indicators and targets for intergenerational health and nutrition care. *Protein Cell* **14**:807–823. DOI:10.1093/procel/pwad029
247. Cani P. D., Depommier C., Derrien M., et al. (2022). Akkermansia muciniphila: Paradigm for next-generation beneficial microorganisms. *Nat. Rev. Gastroenterol Hepatol.* **19**:625–637. DOI:10.1038/s41575-022-00631-9
248. Altemani F., Barrett H. L., Gomez-Arango L., et al. (2021). Pregnant women who develop preeclampsia have lower abundance of the butyrate-producer Coprococcus in their gut microbiota. *Pregnancy Hypertens* **23**:211–219. DOI:10.1016/j.preghy.2021.01.002
249. Rasmussen T. S., Mentzel C. M. J., Danielsen M. R., et al. (2023). Fecal virome transfer improves proliferation of commensal gut Akkermansia muciniphila and unexpectedly enhances the fertility rate in laboratory mice. *Gut Microbes* **15**:2208504. DOI:10.1080/19490976.2023.2208504
250. Qaisar R., Zuhra H., Karim A., et al. (2025). Butyrate improves handgrip strength and physical performance by reducing intestinal leak in post-menopausal women, a randomized controlled trial. *Euro. J. Nutr.* **64**:141. DOI:10.1007/s00394-025-03656-3
251. H. Al Wattar B., Dodds J., Placzek A., et al. (2019). Mediterranean-style diet in pregnant women with metabolic risk factors (ESTEEM): A pragmatic multicentre randomised trial. *PLoS Med.* **16**:e1002857. DOI:10.1371/journal.pmed.1002857
252. Zhang D., Cheng D., Cao Y., et al. (2022). The effect of dietary fiber supplement on prevention of gestational diabetes mellitus in women with pre-pregnancy overweight/obesity: A randomized controlled trial. *Front. Pharm.* **13**:922015. DOI:10.3389/fphar.2022.922015
253. Harreiter J., Simmons D., Desoye G., et al. (2019). Nutritional lifestyle intervention in obese pregnant women, including lower carbohydrate intake, is associated with increased maternal free fatty acids, 3-β-hydroxybutyrate, and fasting glucose concentrations: A secondary factorial analysis of the european multicenter, randomized controlled DALI lifestyle intervention trial. *Diabetes Care* **42**:1380–1389. DOI:10.2337/dc19-0418
254. Molina-Vega M., Picón-César M. J., Gutiérrez-Repiso C., et al. (2021). Metformin action over gut microbiota is related to weight and glycemic control in gestational diabetes mellitus: A randomized trial. *Biomed. Pharmacother.* **145**:112465. DOI:10.1016/j.biopha.2021.112465
255. Wu K., Zhang Y., Wang T., et al. (2025). Advancing disease-modifying therapies for Parkinson's disease: Current strategies and future directions. *The Innovation* 101112. DOI:10.1016/j.xinn.2025.101112
256. Ratiner K., Ciocan D., Abdeen S. K., et al. (2024). Utilization of the microbiome in personalized medicine. *Nat. Rev. Microbiol.* **22**:291–308. DOI:10.1038/s41579-023-00998-9
257. Carneiro P. V., Montenegro N. d. A., Lana A., et al. (2022). Lipids from gut microbiota: Pursuing a personalized treatment. *Trends Mol Med* **28**:631–643. DOI:10.1016/j.molmed.2022.06.001

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AUTHOR CONTRIBUTIONS

Y.W., R.Z., and L.W. were responsible for writing - original draft. J.H., M.S., and S.O. contributed to writing - review and editing. L.C. and H.Z. contributed to supervision and funding acquisition. All authors contributed to and approved the final version of the manuscript.

DECLARATION OF INTERESTS

The authors declare no conflicts of interest. L.W. is an Editorial Board member of The Innovation Life and was blinded from reviewing or making final decisions on the manuscript.

DATA AND CODE AVAILABILITY

This manuscript does not generate any code or data.