Gut microbiota-immune crosstalk in recurrent pregnancy loss: Mechanisms and therapeutic perspectives (Review)

NANJIAN LUO, HAN HU, XIAOTING ZENG, YI HUAN ZHANG, QI DENG, EN NI TANG and YU HU

Department of Reproductive Medicine, Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou 563000, P.R. China

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Abstract. Recent studies have indicated the relationships between the human reproductive system, gut microbiota and immune crosstalk. These interactions can influence pregnancy outcomes, which occasionally result in adverse consequences for the mother and fetus. However, key questions remain unresolved, such as identifying the microbiota capable of modulating immune cells during pregnancy. The present review aimed to investigate the relationship between microbiota and T cell types and to clarify the mechanism through which these interactions occur. In pregnancy-related disease models, it is still unclear whether T helper cell (Th17)/regulatory T cells (Treg cells) are generated *in situ* or migrate into inflamed tissues. The present review explored the association of gastrointestinal dysbiosis with the female reproductive system and the role of the maternal-fetal interface. In particular, the effect of gut microbiota-derived short-chain fatty acids, bile acids, indoles and their derivatives on immune signaling networks is discussed. Furthermore, the effects of these networks on infectious, metabolic and female pregnancy periods are summarized. Finally, the translational potential of modulating gut microbiota through probiotics and dietary interventions to restore immune homeostasis and improve pregnancy outcomes in Recurrent pregnancy loss (RPL) is also evaluated. The present review aimed to assist patients in developing a more profound comprehension of the underlying causes of unexplained RPL and broaden the spectrum of potential therapeutic strategies for infertility.

Contents

Correspondence to: Professor Yu Hu, Department of Reproductive Medicine, Affiliated Hospital of Zunyi Medical University, 149 Dalian Road, Zunyi, Guizhou 563000, P.R. China
E-mail: YH_Vicky@zmu.edu

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1. Introduction

Spontaneous abortion is a frequent pregnancy problem, accounting for around 30% of miscarriages. When a miscarriage occurs frequently, it is referred to as recurrent miscarriage (RPL), and it affects roughly 3-5% of pregnant couples. RPL often implies the existence of probable pathogenic issues, necessitating a full medical evaluation to determine the reason and implement specific treatment options. It is one of the most challenging medical issues due to its unknown etiology and limited treatment options (1). Even after excluding the chromosomal, endocrine, infectious, anatomical and autoimmune factors, a significant proportion of miscarriages (>50%) remains unexplained despite thorough investigation (2). Numerous study have reported the role of immune cells in the pathogenesis of RPL, attributed to the complex immunological environment present in early pregnancy (3,4). A normal pregnancy must be accompanied by a healthy immune microenvironment at the maternal-fetal interface. This interface can be affected by imbalances in cytokines, growth factors and regulatory T cells (Tregs), which can lead to implantation and pregnancy failure. Furthermore, numerous studies have demonstrated that the interactions between gut microbiota and immune cells can markedly affect the cytokine network imbalances associated with poor female reproductive performance (5,6). Indeed, the human gut microbiota can affect every stage and level of female reproduction, including follicle maturation and oocyte migration, fertilization and embryo migration, implantation and the entire duration of pregnancy, up to and including delivery (7). The dysbiosis of gut microbiota, caused by the disruption of commensal microbiota, has been identified as a risk factor in the development of inflammation and autoimmune diseases (8). Numerous studies have demonstrated that gut microbiota and immune cells communicate pivotally, a process that is indispensable for the induction, development, training and function of the host's immune system (9-11). However, further research is required to explore the effect of gut microbial metabolites on host immunity. Emerging

evidence suggests that the dysbiosis of gut microbiota and subsequent immune dysregulation play a pivotal role in RPL pathogenesis. The gut microbiota produces key metabolites, including short-chain fatty acids (SCFAs), bile acids (BAs) and indoles, which modulate immune responses and influence pregnancy outcomes. The present review explored the intricate crosstalk between gut microbiota-derived metabolites and maternal immune adaptations, with particular focus on their regulatory effects on CD4+T cells, inflammasome-NF-κB inhibitor α (NF-κB)-Th17 balance and aryl hydrocarbon receptor (AHR)-mediated pathways (12,13). A deeper understanding of these mechanisms may pave the way for novel therapeutic strategies targeting gut microbiota to improve pregnancy maintenance. The present study reviewed the key mechanisms through which the gut microbiota might affect cellular immunity in RPL.

2. Gut microbial metabolites and their effects on pregnancy

The gastrointestinal tract is home to a diverse community of microorganisms, with an estimated >500 distinct species (9). Gut microbiota' is a collective term, denoting various bacterial, archaeal, viral and fungal organisms. These organisms are further classified into four distinct phyla, namely Firmicutes, Bacteroidetes, Proteobacteria and Actinobacteria (14). Table I summarizes the class and function of the gut microbiota (15-23). The gut microbiota can generate numerous small-molecule metabolites, including fatty acids, BA, indoles and derivatives of indoles. Throughout a woman's lifetime, gut microbiota interacts with estrogens androgens, insulin and other hormones, playing a major role in the reproductive endocrine system. Studies have indicated that numerous diseases and conditions can be attributed to an imbalance in the composition of gut microbiota (24). These include pregnancy complications, adverse pregnancy outcomes, polycystic ovary syndrome, endometriosis and cancer (25). Therefore, it is imperative to explore the origins and destinations of the gut microbiota-derived metabolites.

3. Immune dysregulation and pregnancy complications

Immune dysregulation at the maternal-fetal interface has been implicated in the development of pregnancy complications, such as RPL, preeclampsia and preterm birth. RPL is often accompanied by an imbalance in the Th1/Th2 cytokine profile, characterized by an increase in Th1-type cytokines and a decrease in Th2-type cytokines. This imbalance can lead to an enhanced immune response against the fetus and consequently an increased risk of miscarriage (26,27). Preeclampsia is associated with an abnormal activation of the immune system, including increased production of pro-inflammatory cytokines and activation of immune cells, which contributes to the development of hypertension and other symptoms. In preterm birth, inflammation at the maternal-fetal interface, often triggered by infection or other factors, can lead to premature activation of the immune system and consequently to preterm labor (28). Pregnancy represents a significant challenge to the maternal immune system, as it must tolerate significant alterations in metabolism and hormone levels. The maternal-fetal interface is a complex microenvironment where immune cells of the mother and fetus interact. Trophoblast cells, which form the outer layer of the placenta, express unique molecules that help evade immune recognition and rejection. At the maternal-fetal interface, the immune cells, such as decidual natural killer (dNK) cells, macrophages and T cells, play important roles in regulating trophoblast invasion, angiogenesis and immune tolerance (29,30). dNK cells are the most abundant immune cells in the decidua and secrete cytokines and chemokines that promote trophoblast invasion and spiral artery remodeling (31,32). Macrophages in the decidua also contribute to immune regulation and tissue remodeling. T cells at the maternal-fetal interface are mainly composed of Treg cells, which help suppress immune responses against the fetus. In fact, the maternal-fetal interface is not an absolute barrier and fetal cells can migrate into the maternal circulation (33). For successful embryo implantation and to ensure the survival of the allogeneic fetus, the fetus and placenta must mount an effective defense against attacks by maternal immune system cells. The maternal immune system needs to tolerate the semi-allogeneic fetus while also protecting against infections. This balance is achieved by regulating various immune cell subsets, including T helper (Th) cells, Tregs and macrophages. Th17 cells, which secrete interleukin (IL)17A, IL-17F, IL-22 and IL-26, play an important role in inflammatory immune responses and autoimmune diseases. It has been demonstrated that during pregnancy, Th17 cell differentiation might be induced due to the presence of local allogeneic fetal antigens, systemic inflammation and increased pro-inflammatory cytokines (34). Th17 cells secrete inflammatory factors that are involved in autoimmune diseases, rejection of allografts and inflammation. Tregs can transition between a Th17-like phenotype when stimulated by antigen-presenting cells, particularly monocytes, in the presence of specific cytokines, such as IL-2 and IL-15. Moreover, exogenous IL-1β, IL-23 and IL-21 further enhance this process, underscoring the remarkable plasticity of immune responses and immune cell phenotypes (35). Studies have demonstrated a correlation between elevated levels of inflammatory cytokines, including IL-6 and IL-1β and an increase in Th17 cells in RPL (36,37). Furthermore, an alteration in the immune system towards Th2-type cytokine responses is observed, which inhibits the deleterious effects of the cell-mediated (Th1-type) immune system. The aberrant shift in Th1/Th2 cytokines during the early stages of pregnancy initiates and amplifies the sequence of proinflammatory cytokines that are implicated in RPL. It has been demonstrated that CD4+ and CD8+ T cells may contribute to the pathophysiology of RPL (38). CD4 is a glycoprotein that is found on the surface of immune cells, particularly on the surface of Th cells, monocytes, macrophages and dendritic cells (DCs) (39,40). CD8 is a co-receptor transmembrane glycoprotein found on cytotoxic T cells (CD8+ T cells). Differences in lymphocyte phenotypes between women experiencing unexplained pregnancy losses and healthy women. The authors' findings indicated that the women who experienced RPL exhibited a markedly higher proportion of CD4+ and CD8+ T cells compared with healthy women (41). Human CD4+/CD25+ Treg cells could inhibit IL-17 secretion via cell-to-cell interactions in healthy controls and this regulation was disturbed in cases of unexplained

Table I. Description of the classes and functions of gut microbiota.

Type of microbiome	Change	Effect
Escherichia and *Shigella* (15)	Reduce the production of short-chain fatty acids	1) Increased intestinal permeability and induce chronic mild inflammation by activating the immune system, resulting in pro-inflammatory cytokines infecting insulin receptors and leading to insulin resistance or hyperinsulinemia. 2) Probiotics enhance immune regulation by promoting Treg maturation and IL-10 production. This action helps suppress the Th2 immune response, which is characterized by the expression of cytokines such as IL-4. 3) A disruption in the gut microbes balance can result in miscarriage, preterm birth, preeclampsia and other complications associated with pregnancy.
Bacteroides vulgatus (16)	Decrease glymodeoxycholic acid and taurosodeoxycholic acid	
Prevotellaceae (17)	Reduce production of anti-inflammatory metabolites	
Lactobacilli and *Bifidobacteria* (17)	Reduce immunity and nutrient absorption	
Acinetobacter (18)	Reduced strong Th1 and anti-inflammatory responses by immune cells	
Cellulomonas (19)	A rare but emerging human pathogen, causing infection in only 4 reported cases in the literature	
Fusobacterium (20)	Influences intestinal immunity by shaping Th17 responses in an FFAR2-dependent manner	
Clostridiales and *Verrucomicrobia* (21)	Positively associated with the regulatory T-cell transcription factor Foxp3	
Enterococci (22)	Production of the factors including cytolysin for eliminating competitive bacteria or the generation of aggregation substances	
Shigella dysenteriae (23)	Invasion of the human colonic epithelium and regulation of proinflammatory cytokines, resulting in severe intestinal inflammatory response and epithelial destruction	

Th17, T-helper cell 17; FFAR2, free fatty acid receptor 2; Foxp3, forkhead box P3; IL-4, interleukin 4.

RPL (42). Murine models demonstrated that AHR activation by indoles could suppress Th17 cells; however, human trials showed inconsistent results, which might be due to fundamental differences in placental architecture (hemochorial vs. endotheliochorial) and immune cell composition (43).

In summary, compared with those of non-pregnant women, the Tregs of pregnant women have markedly increased suppressive activity in the first and second trimesters. However, this suppressive activity is markedly decreased in the third trimester. The balance between Th17 cells and Tregs is crucial for successful embryo implantation and pregnancy establishment. Dysregulation of the immune system during pregnancy can lead to RPL occurrence (44,45).

4. Potential mechanism of gut microbiota-derived metabolites in regulating the immune system and pregnancy outcomes

SCFAs regulate CD4⁺ T cells and affect pregnancy. The major intestinal SCFAs, including acetate, propionate and butyrate, are primarily produced by gut microbiota via fermentation of indigestible carbohydrates. Acetate is generated by Bacteroidetes, *Bifidobacterium* and *Clostridium* through the acetyl-CoA or Wood-Ljungdahl pathways. Propionate is synthesized by Bacteroidetes and *Clostridium spp.* via succinate, acrylate, or propylene glycol pathways. Butyrate is mainly derived from Firmicutes through acetyl-CoA condensation or acetate coenzyme A-transferase pathways (facilitated by gut fungi, such as *Morchella*) (18,46-51).

SCFAs serve as energy sources for intestinal cells and signaling molecules in systemic circulation and modulate tissues, such as the liver and adipose tissues (52). They exert anti-inflammatory effects by regulating cytokines and immune cell activity. The maternal gut and blood have elevated levels of SCFAs during pregnancy, which cross the placenta to influence fetal immunity (53). Notably, acetic acid administration induces abortion in 24 h (54) and a higher propionate/acetate ratio in early pregnancy is associated with increased inflammation and relapse in women with multiple sclerosis (55). This highlights the critical role of SCFAs in maintaining healthy pregnancies.

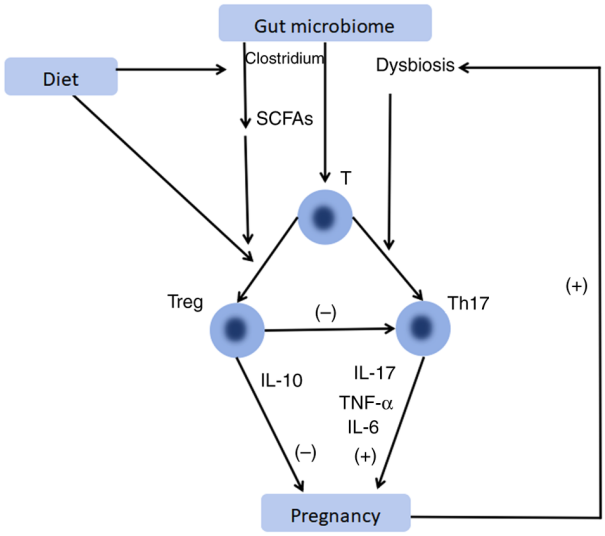

Figure 1. SCFAs regulate CD4+ T cells, affecting RPL. SCFAs, short-chain fatty acids; IL-10, interleukin 10; Th17, T helper cell 17; TNF-α, tumor necrosis factor α; Treg, regulatory T cell.

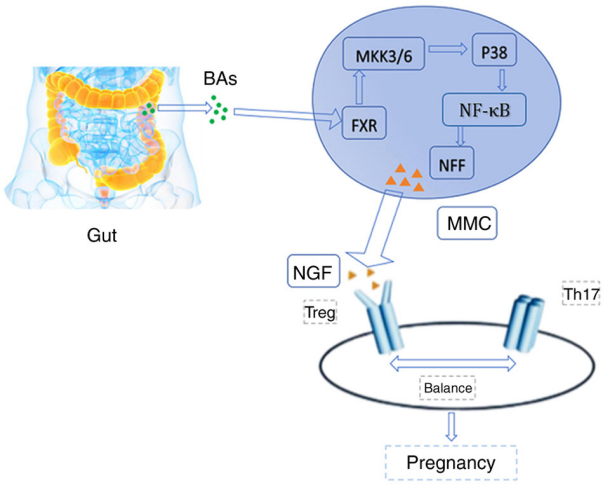

Figure 2. BAs inhibit the NF-κB pathway, affecting the balance between inflammasome and Th17 during RPL. BAs, bile acids; FXR, farnesoid X receptor; MKK3/6, mitogen-activated protein kinase kinase 3 and 6; P38, p38 mitogen-activated protein kinase; NF-κB, nuclear factor κB; NFF, non-filterable factor; MMC, mucosal mast cell; Treg, T-regulatory cell; NGF, nerve growth factor.

As shown in Fig. 1, SCFAs promote $CD8^+$ memory T cell formation and regulate Th1, Th17 and Treg differentiation to maintain intestinal homeostasis. They enhance tolerogenic DCs in the gut, inducing Treg differentiation (56) and modulating immune cells via humoral/glycolipid pathways. Pathogen-induced Th17 cells rely on anaerobic glycolysis and oxidative phosphorylation (OXPHOS), while commensal microbiota-induced Th17 cells depend only on OXPHOS (52). SCFAs act through G protein-coupled receptors (*GPR43/FFAR2*, *GPR41/FFAR3*, *GPR109A/HCAR2*) to trigger signaling cascades such as *ERK* and *STAT3*. This leads to upregulation of *IL-10* and *Foxp3* gene expression, promoting Treg differentiation (57-59). They also inhibit HDACs (such as class I), increasing histone acetylation at *Foxp3* loci to stabilize Tregs and suppress pro-inflammatory genes in other T-cell subsets (60,61). The reduction in SCFAs caused by the dysbiosis of gut microbiota can weaken these mechanisms, leading to Th17/Treg imbalance and inflammation at the maternal-fetal interface that contribute to RPL (62). SCFAs may prevent pregnancy complications by enhancing anti-inflammatory cytokines (such as IL-10) and Treg differentiation (63).

Bas inhibit the NF-κB pathway and modulate the inflammasome-Th17 balance during pregnancy. BAs are synthesized from cholesterol in the liver mostly via the classical pathway, producing cholic and chenodeoxycholic acids. They are secreted into the intestine, where they play a role in lipid digestion and regulate metabolism, signaling pathways and composition of gut microbiota (64,65). Gut microbiota metabolize primary BAs into secondary BAs via deconjugation, hydroxylation, dehydration, or epimerization, involving species, such as *Bacteroides* and *Bifidobacterium* (66,67). BAs activate thyroid hormone-activating enzyme D2, influencing energy expenditure. Their serum levels fluctuate with thyroid function, which is critical for fetal brain development (68).

Elevated maternal serum BA levels during pregnancy increase risks of adverse outcomes such as stillbirth (69). BAs regulate immune function by modulating the expression of immune genes and cell activity. They bind to farnesoid X receptor (*FXR*) and G protein-coupled receptor for bile acids 1 (*GPBAR1*) to inhibit NF-κB activation, thereby suppressing pro-inflammatory cytokine transcription; they also modulate NOD-like receptor thermal protein domain associated protein 3 inflammasome activity and Th17/Treg balance (70). Conversely, BA-induced GPBAR1 activation triggers NF-κB in trophoblasts, promoting placental inflammation and abnormal leukocyte infiltration (Fig. 2), which could return to affect pregnancy (24). Murine models showed placental inflammation at serum BAs >40 μmol/l, while human intrahepatic cholestasis of pregnancy (ICP) exhibited variable thresholds (10-100 μmol/l), indicating species-specific vulnerability (71,72).

BAs also regulate bile acid homeostasis via enterocyte L-cell receptors, activating FXR-Retinoid X Receptor (*RXR*) dimerization to induce ileal bile acid-binding protein, Oxysterols and hormones, which inhibit apical sodium-dependent bile acid transporter (73,74). This modulates entero-hepatic innate immunity, maintaining tolerogenic phenotypes (52). BAs were traditionally thought to promote inflammation due to their accumulation in the livers of patients with liver diseases and disrupt cellular membranes. However, they have anti-inflammatory properties, particularly in the innate immune system. Two life cycle assessment metabolites, 3-oxoLCA and isoalloLCA, can directly affect CD4+ T cells, suppressing Th17 differentiation and enhancing Treg differentiation (75,76).

Indoles drive AHR to regulate Th17 differentiation and pregnancy. Indoles, microbial metabolites of tryptophan (Trp), are produced by >85 bacterial species (such as Fusobacterium, Escherichia coli and Bacteroides) via tryptophanase-mediated conversion) (77). Clostridium further metabolizes Trp into derivatives such as tryptamine, indole-3-lactate and indole-3-acetate (I3A);

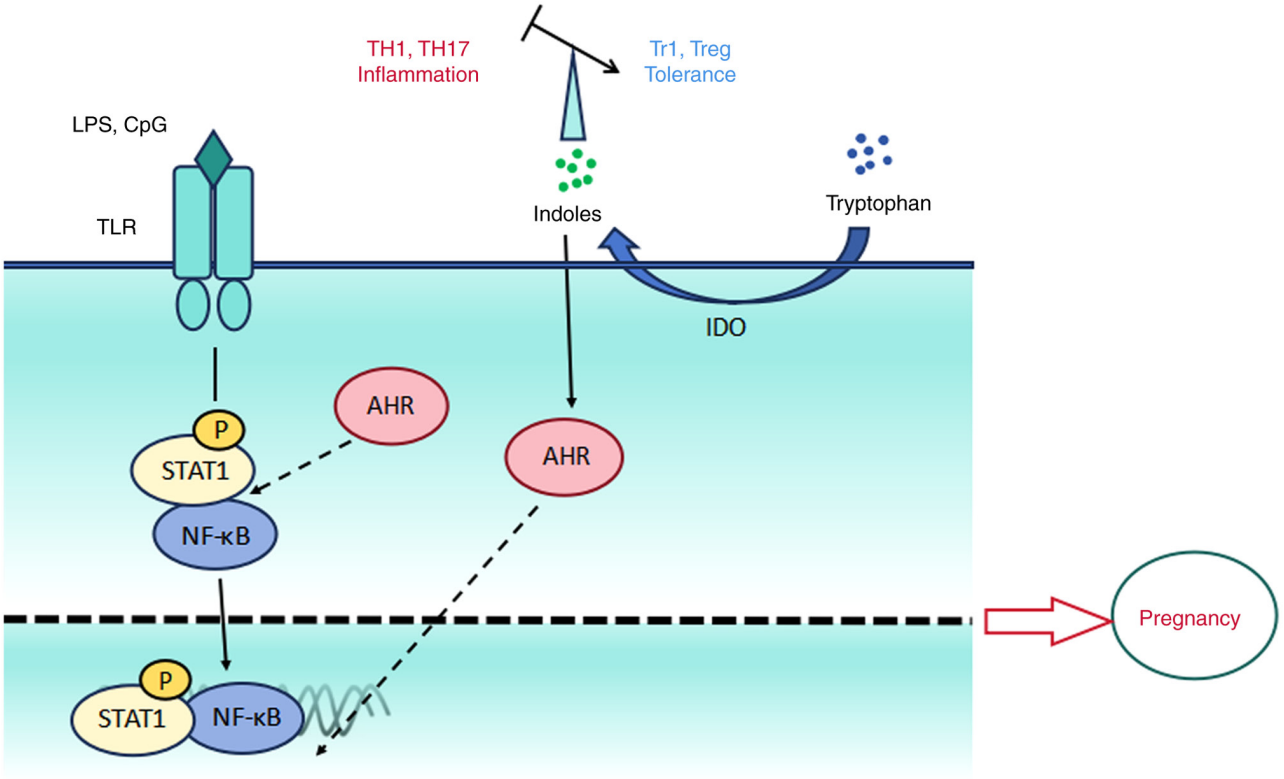

Figure 3. Indoles drive AHR, affecting the early differentiation of Th17 cells to regulate RPL. TH1, T helper cell 1; Treg, T-regulatory cell; Tr1, T regulatory type 1; IDO, indoleamine 2;3-dioxygenase; ARH, aryl hydrocarbon receptor; LPS, lipopolysaccharides; CpG, cytosine-phosphate-guanine; TLR, Toll-like receptors; P, properdin; STAT1, signal transducer and activator of transduction 1; NF-κB, nuclear factor κB.

deficiencies in tryptamine and I3A accelerate inflammation. Indole-3-propionate and other derivatives, such as indole-3-aldehyde, act via AHR to modulate immune responses (78).

As shown in Fig. 3, plasma Trp levels decrease during pregnancy, which might be linked to immune activation (79). Indoles activate *AHR*, critical for gut epithelial barrier maintenance, and regulate T-cell subsets (Th17, *FOXP3*$^{+}$ Tregs and Tr1) (43). *AHR* activation by indoles balances immunity by promoting Tr1 conversion and influencing early Th17 differentiation; Th17 cells are associated with adverse pregnancy outcomes. Additionally, microbial Trp metabolites regulate placental vascular development via *AHR* (78). However, indole-based compounds (such as I3C) may induce fetal mortality. Moreover, I3A exposure during rat gestation days 12-14 could cause microencephaly, highlighting context-dependent effects.

Indoleamine 2,3-dioxygenase (IDO), expressed in placental syncytiotrophoblasts and blastocyst membranes, catalyzes Trp degradation and may contribute to pregnancy immunosuppression. High-fat diets upregulate IDO, shifting Trp metabolism from indole to kynurenine production, thereby reducing insulin sensitivity. *Lactobacillus reuteri* produces an indole derivative of Trp, which activates AHR in CD4+ T cells and downregulates T-helper-inducing POZ/Krüppel-like factor (ThpoK), enabling the differentiation of CD4+ T cells into double positive intraepithelial lymphocytes with immunomodulatory function. Mammalian fetuses can survive an immune attack of the maternal T cells by preventing the release of L-Trp via IDO (80,81). IDO may induce potent anti-inflammatory and antioxidant effects in pregnant women. This highlights the crosstalk between gut microbiota and immune cells in reproductive organs.

Mechanism of crosstalk between gut microbiota and immune cells in RPL. In summary, pregnant women exhibit increased inflammatory processes in the placenta, characterized by hypoxia, elevated vascular density and reduced placental maturity. Meanwhile, alterations in dietary habits, sleep patterns and hormonal profiles during pregnancy might affect the composition of gut microbiota (75). SCFAs production is associated with genes, such as free fatty acid receptors 1-4, and plays a role in regulating immune cells (such as Tregs, Th17 cells and effector T cells) (82,83). They affect pregnancy outcomes by altering the composition of gut microbiota and fetal metabolic programming. BAs, encoded by genes, including *IBABP* and *FXR*, aid in fat digestion in the intestine. They also regulate immune cells, such as T cells, B cells and DCs (84). In pregnancy, elevated levels of BAs can induce inflammation, cause respiratory distress in newborns and lead to meconium-stained amniotic fluid. Indoles, as tryptophan metabolites, encompass various derivatives. Encoded by genes such as *NRF2* and *AHR*, they regulate immune cells expressing cytokines, such as IL-6 and TNF-α and are critical for key pregnancy processes, including placentation. Specifically, indoles can activate the pregnane X receptor (*PXR*) to exert anti-inflammatory effects. Furthermore, excessive production of certain

Table II. Characteristics and functions of gut microbiota-derived metabolites.

Production name	Type	Encoded genes	Immune cells	Pregnancy-related effects
Short chain fatty acids (48,67)	Acetic acid (C2: 0), Propionic acid (C3: 0), Butyric acid (C4: 0), Valeric acid (C5: 0), Caproic acid (C6: 0)	FFAR1 (GPR40), FFAR3 (GPR41), FFAR2 (GPR43), GPR84, FFAR4 (GPR120)	Th17/Treg cells, IL6, Il1β and TNF-α, CD4+ effector T cells, CD8+ effector T cells	1) During pregnancy, the gut microbiota undergoes profound changes in both quantity and composition. In the first and third trimesters, the number of Bifidobacteria, Proteobacteria and lactic acid-producing bacteria increases, while the number of butyrate-producing bacteria decreases. 2) By synthesising lipids and glucose, pionic acid can be used as a source of energy. SCFAs may influence fetal metabolic programming via their interactions with the uteroplacental GPR41 and GPR43 receptors and their role in inflammatory processes during pregnancy.
BAs (67)	Primary BAs, Secondary BAs	IBABP/FABP6, ASBT, FXR/NR1H4, BSEP, RXRα, LRH1, LXR	T cells, B cells, DCs, NK cells, Th1/17 cells, Treg cells	1) Increased levels of BAs induce the production of proinflammatory mediators in hepatocytes, which attract immune cells and trigger inflammation during pregnancy. 2) Increased levels of BAs result in an enhanced efficiency of ATP-independent transport mechanisms, which disrupts pulmonary surfactants, resulting in respiratory distress in newborns and can cause amniotic fluid to become meconium-stained.
Indoles and derivatives (85)	Idole-3-pyruvic acid, Indole-3-lactate, Indole-3-acrylate, Indole-3-acetate, Indole-3-propionate, Indole-3-aldehyde, Indoxyl-3-sulfate	NRF2, AhR, PXR,	IL-6, TNF-α, Th1/17 cell,CD103, CD11b+, CD4+ effector T cells	1) During pregnancy, tryptophan catabolism is necessary for early placentation, fetal vasodilation and rejection prevention. 2) Indoles could activate PXR and induce anti-inflammatory responses.

BAs, bile acids; Th, T helper; Treg, regulatory T; FFAR1, free fatty acid receptor 1; GPR84, G protein-coupled receptor 84; FFAR4, free fatty acid receptor 4; IBABP/FABP6, Ileal BA binding protein; ASBT, apical sodium-dependent BA transporter; FXR/NR1H4, farnesoid X receptor; BSEP, bile salt export pump; RXRα, retinoid X receptor α; LRH1, LRH1 liver receptor homolog 1; LXR, liver X receptor; NRF2, nuclear factor erythroid 2-related factor 2; AhR, aryl hydrogen receptor; PXR, pregnane X receptor.

microbial by-products, such as fatty acids, BAs, indoles and their derivatives, is a hallmark of leaky gut syndrome. Gut-derived lipopolysaccharides drive macrophages toward the pro-inflammatory M1 phenotype, impairing trophoblast invasion. This is followed by the activation of inflammatory response-related cytokines, such as Th17 cells, Tregs, NK T cells, CD4+/CD8+ T cells and various ILs. Consequently, these cascading events may exert detrimental effects on fetal development and nutrient supply. The underlying mechanism of crosstalk between gut microbiota and immune cells in RPL (48,67,85) is summarized in Table II and Fig. 4.

5. Clinical translation and therapeutic perspectives

The crosstalk between reproductive immunology and the gut is still in its infancy, with numerous exciting and promising research outcomes. Critically, probiotics (particularly *Lactobacillus* and butyrate-producing bacteria), dietary modifications (high-fiber

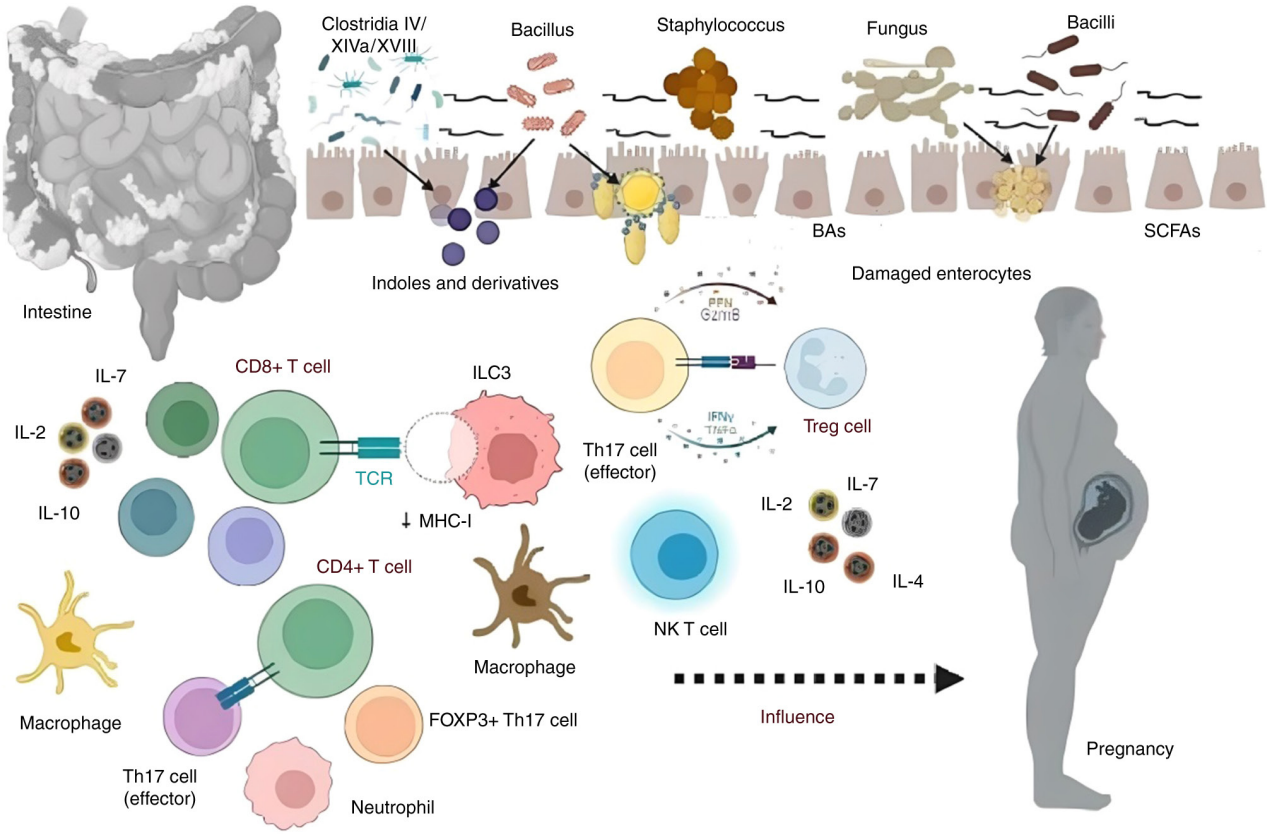

Figure 4. Mechanism of crosstalk between gut microbiota and immune cells in RPL. BAs, bile acids; SCFAs, short-chain fatty acids; TCR, T-cell receptor; ILC3, group 3 innate lymphoid cell; MHC-1, major histocompatibility complex class I; IL-2, interleukin 2; Th17 cell, T helper cell 17; NK T cell, natural killer T cell; FOXP3, forkhead box P3.

or Mediterranean diets) and metabolite supplementation (butyrate and AHR ligands) represent promising strategies to correct dysbiosis and reestablish fetal tolerance. Personalized approaches leveraging multi-omics profiling will be key to advancing RPL therapeutics, offering hope for patients with previously unexplained pregnancy losses. Immune imbalances in RPL patients are modifiable. Future studies must prioritize translational validation, such as large randomized controlled trials of microbiota-targeting therapies to assess the function of *Lactobacillus crispatus* in RPL with standardized outcomes, including live birth rate and immune biomarkers. The treatment methods and examples are discussed below.

Probiotics and live biotherapeutics. Emerging clinical evidence supports the use of specific probiotic strains to correct dysbiosis of gut microbiota and immune imbalances in RPL (86). *Lactobacillus*-dominated interventions, such as the vaginal or oral administration of *L. crispatus* and *L. rhamnosus*, have been shown to increase the endometrial abundance of *Lactobacillus* (>90%), which was associated with improved implantation rates (OR=3.7; P<0.01) and reduced miscarriage risk in randomized controlled trials patients. This is attributed to enhanced IL-10 production, Treg induction and the suppression of pathogenic biofilm formation by *Gardnerella* and *Streptococcus*. The bacterial strains, such as *Clostridium butyricum* and *Faecalibacterium prausnitzi* (administered orally), markedly elevate fecal butyrate levels (>40-60%) and increase peripheral blood Treg frequencies (>2.1-fold) in RPL patients, concomitant with reduced Th17-mediated inflammation. A recent randomized controlled trial (n=850) reported a non-significant increase in clinical pregnancy rates and a slight reduction in miscarriage risk with probiotics treatment (87). Taken together, these findings underscore that the probiotic interventions, whether *Lactobacillus*-dominated or SCFA-producing, act through complementary pathways to correct the microbial and immune dysregulation underlying RPL. By restoring *Lactobacillus* dominance in the endometrium or enhancing SCFA-mediated immune modulation, these strains offer targeted, microbiota-based strategies to improve reproductive outcomes in women with RPL.

Fecal microbiota transplantation (FMT). Some studies suggest that FMT may offer a potential therapeutic approach for RPL by restoring a healthy gut microbiota, which plays a crucial role in immune regulation and pregnancy maintenance. FMT from healthy donors has demonstrated efficacy in reducing pregnancy loss. FMT from normal pregnant women to abortion-prone dams restored gut microbial diversity, the Chao1 index was negatively associated with the changes in IL-17A and IFN-γ and the Shannon index was negatively associated with changes in IL-17A levels (88). Pilot human studies are underway (NCT04817969), evaluating FMT for unexplained RPL (11,89), with preliminary data showing normalization of BA and SCFA profiles in 70% of recipients. Together, these findings bridge preclinical promise with early

clinical progress, suggesting that FMT might one day address a significant unmet need in RPL treatment, particularly for cases where traditional approaches have failed (90,91). With the advances in research, further exploration of the precise mechanisms linking gut microbial balance to pregnancy success, along with large-scale clinical trials, will be crucial to validating the efficacy and safety of FMT in reproductive care.

Dietary and metabolite supplementation. Increased dietary fiber intake (≥30 g/day) during pregnancy, a key modulator of reproductive health, has been linked to improved pregnancy outcomes. The consumption of such fiber can elevate fecal SCFA levels, specifically butyrate, by 3-4-fold. Cohort studies have further associated high fiber intake with a lower risk of miscarriage (92). This beneficial effect is rooted in fiber's role as a critical substrate for beneficial gut bacteria, including *Bifidobacterium* and *Roseburia*, which metabolize it to produce immune-modulating metabolites that help maintain a pregnancy-supporting environment. In addition to general dietary fiber intake, targeted dietary patterns rich in complementary nutrients have also shown promise. For instance, Mediterranean diet interventions, characterized by high levels of polyphenols and fiber, have been found to markedly reduce inflammatory cytokines, with >40% reductions in IL-6 and >30% reductions in TNF-α in women with RPL who are attempting new pregnancies. Concurrently, these interventions improve the function of Tregs, which play a pivotal role in suppressing harmful immune responses against the fetus (93,94). Notably, the metabolic byproducts of fiber fermentation, such as butyrate, have been directly investigated for their therapeutic potential. Butyrate supplementation effectively reverses dysbiosis in female mice, markedly increases Treg cell populations and decreases preterm birth rates, highlighting the metabolite's direct role in supporting implantation and fetal retention (95). Similarly, interventions targeting other inflammatory pathways in high-risk pregnancies have yielded positive results. For women with ICP, cholestyramine therapy has proven effective. A review demonstrated that in women with unexplained recurrent spontaneous abortion (URSA), the butyrate supplementation could reduced uterine NK cell cytotoxicity and impact Treg cell level (95). It also normalized TNF-α/IL-10 ratio, which has been linked to endometriosis and pregnancy failure (37,96). Notably, butyrate-producing bacteria play an important role in pregnancy maintenance. It reduces the risk of preterm birth (OR=0.3) and stillbirth (OR=0.2) by lowering serum BA levels and inhibiting placental inflammation, thereby addressing a condition where BA accumulation triggers harmful inflammatory cascades. Additionally, bioactive compounds derived from dietary sources have shown promise in preclinical models. I3C, a compound found in cruciferous vegetables, activates AHR signaling in murine RPL models. This activation suppresses aberrant Th17 cell responses, which drive inflammation and fetal loss and ultimately prevents pregnancy failure (43). Collectively, these findings highlight a consistent theme: Dietary components, their microbial metabolites and targeted supplements can exert profound effects on pregnancy outcomes by modulating immune function, reducing inflammation and restoring balance to the pathways critical for fetal survival. From fiber's role in nurturing beneficial gut bacteria to specific metabolites and compounds that directly regulate immune cell activity, these interventions offer promising avenues for improving reproductive health in at-risk populations.

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Availability of data and materials

Not applicable.

Authors' contributions

YH conceived the project and prepared the manuscript. HH and XZT made substantial contributions to conception and design. QD contributed to the acquisition and interpretation of data. YHZ and ENT drafted the manuscript and revised it critically for important intellectual content. NL revised the manuscript for important intellectual content. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Authors' information

Dr Yu Hu ORCID:0000-0002-5041-9104.

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