

Review

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Review

The Inflammatory Landscape of Pregnancy: Maternal–Fetal Immunity, Basis for Disease, and Targeted Treatments

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Abstract

Inflammation is a normal and essential feature of pregnancy, supporting implantation, placental development, and parturition. When dysregulated, however, inflammatory pathways contribute to major obstetric complications such as preeclampsia, fetal growth restriction (FGR), and preterm birth, which account for substantial maternal and perinatal morbidity and mortality. This review synthesizes current understanding of the maternal–fetal immune interface, examines how inflammation contributes to pregnancy disorders, and explores therapeutic strategies that link pathogenic mechanisms to targeted interventions. The placenta functions as an active immunological hub, coordinating innate and adaptive immune responses to maintain tolerance while protecting against infection. In preeclampsia and FGR, excessive activation—driven by inflammasome signaling, Th1/Th17 polarization, and altered natural killer and macrophage function—impairs placental perfusion, promotes antiangiogenic pathways, and induces systemic endothelial dysfunction. Established therapies, including low-dose aspirin, low-molecular-weight heparin, and antenatal corticosteroids, aim to mitigate inflammation and optimize fetal outcomes, while adjunctive strategies target oxidative stress, nutritional deficits, and the maternal microbiome. Emerging approaches such as cytokine-targeted biologics, inflammasome inhibitors, and mesenchymal stem cell therapies show promise but require rigorous evaluation of safety and efficacy. A deeper understanding of placental immunology and inflammatory signaling is essential to develop precision therapies. Future research should prioritize biomarker validation, pathway-specific interventions, and equitable implementation to reduce inflammation-driven pregnancy complications.

Keywords: preeclampsia; fetal growth restriction; placenta; maternal–fetal interface; inflammation; pregnancy complications; targeted therapy

1. Introduction

Inflammation is a fundamental physiological process in pregnancy, supporting implantation, placental development, and the onset of labor [1–4]. Through immune modulation, the maternal

immune system maintains a paradoxical balance: tolerating a semi-allogeneic fetus while maintaining intact immune defense. The success of this process hinges on precise regulation of immune activity: an early proinflammatory environment supports implantation and trophoblast invasion; an anti-inflammatory state during mid-gestation promotes fetal growth; and a resurgence of inflammation late in pregnancy triggers labor [4,5].

Evidence suggests that placental inflammation isn't just a secondary effect but a driving force behind obstetric diseases, linking preeclampsia, fetal growth restriction (FGR), and preterm birth within a shared immunopathogenic spectrum [6,7]. Hypertensive disorders of pregnancy (HDP), particularly preeclampsia, remain among the top causes of maternal mortality worldwide [8,9]. According to the World Health Organization, preeclampsia affects around 3–5% of pregnancies and is responsible for roughly 42,000 maternal deaths and over 500,000 perinatal deaths annually, including close to 200,000 stillbirths [10,11]. The burden disproportionately hits low- and middle-income countries—due to late diagnoses, limited prenatal care, and structural inequalities—widening global disparities in maternal and neonatal outcomes [9,12]. Beyond the immediate complications, preeclampsia frequently co-occurs with preterm birth, contributing to long-term cardiovascular, metabolic, and neurodevelopmental issues for both mother and child [13,14]. Together, these conditions form a continuum of immune-mediated placental dysfunction, marked by endothelial activation, antiangiogenic signaling, and systemic inflammation [13,15–17].

The placenta is increasingly recognized as an immunologically dynamic organ where trophoblasts, decidual stromal cells, and immune subsets—including uterine natural killer (uNK) cells, macrophages, and regulatory T cells—coordinate tolerance and defense [3,18]. This balance is maintained by molecules such as HLA-G, PD-L1, and Galectin-1, which modulate maternal cytotoxic responses and maintain fetomaternal harmony [19]. However, placental hypoxia, oxidative stress, infection, or sterile danger signals can reprogram this immune environment, tipping it toward pathological inflammation [5,19–21]. The result is poor vascular remodeling, increased secretion of soluble fms-like tyrosine kinase-1 (sFlt-1), and widespread endothelial dysfunction, all of which contribute to preeclampsia and FGR [22–26]. Recent findings demonstrate that activation of the NLRP3 inflammasome (an intracellular protein complex) acts as a central mediator linking trophoblast stress to maternal inflammation [21,27]. NLRP3-dependent maturation of interleukins (IL)-1 β and IL-18 amplifies Th1/Th17 polarization, disrupts uNK cell cytotoxicity, and perpetuates oxidative damage [28–30]. Cytokines such as tumor necrosis factor- α (TNF- α), IL-6, and IL-17 further boost endothelial activation by increasing vascular permeability, suppressing nitric oxide bioavailability, and promoting oxidative stress [31–33]. Spatial and single-cell transcriptomic studies reveal how these inflammatory circuits are organized within the placenta, shedding light on fetomaternal immune communication [18,34].

Scientific advances have begun to translate into preventive and therapeutic strategies. Aspirin, started before 16 weeks' gestation, lowers the incidence of early preeclampsia by inhibiting cyclooxygenase-1 and modulating inflammatory signaling [35]. Complementary approaches—such as optimizing maternal nutrition, managing metabolic inflammation, and modulating the microbiome—are gaining support as regulators of immune homeostasis during pregnancy [36–39]. Meanwhile, emerging therapies—such as inflammasome inhibitors (e.g., MCC950), cytokine-targeted biologics, and mesenchymal stem cell treatments—represent the cutting edge of therapeutics [40]. Still, their clinical application demands thorough evaluation of maternal-fetal safety, dose optimization, and long-term developmental effects.

Despite years of research, immune communication between the placenta and maternal endothelium remains incompletely understood. This review aims to synthesize current evidence on how dysregulated inflammation at the maternal-fetal interface drives placental dysfunction, with particular emphasis on preeclampsia and FGR as models of inflammation-mediated obstetric disease. We integrate biomarkers, mechanisms, and therapeutic prospects to pinpoint new intervention targets that can improve pregnancy outcomes and reduce global maternal health disparities.

Ultimately, our goal is to provide a practical framework that links pathogenic pathways to targeted interventions that enhance maternal and neonatal health.

2. Immune Development in the Placenta

The placenta plays a central role in pregnancy, mediating the delicate balance between maternal immune tolerance toward the fetus—a semi-allograft genetically distinct from the mother—and protection against infection [41,42]. The maternal–fetal interface, formed by the decidua and fetal trophoblast-derived tissues, constitutes a highly specialized immunological environment in which the maternal immune system adapts to sustain fetal growth while maintaining antimicrobial defense [43,44]. Successful pregnancy, therefore, requires down-regulation of cytotoxic adaptive responses and preservation of robust innate immunity to protect against pathogens [41,42,45] (Figure 1).

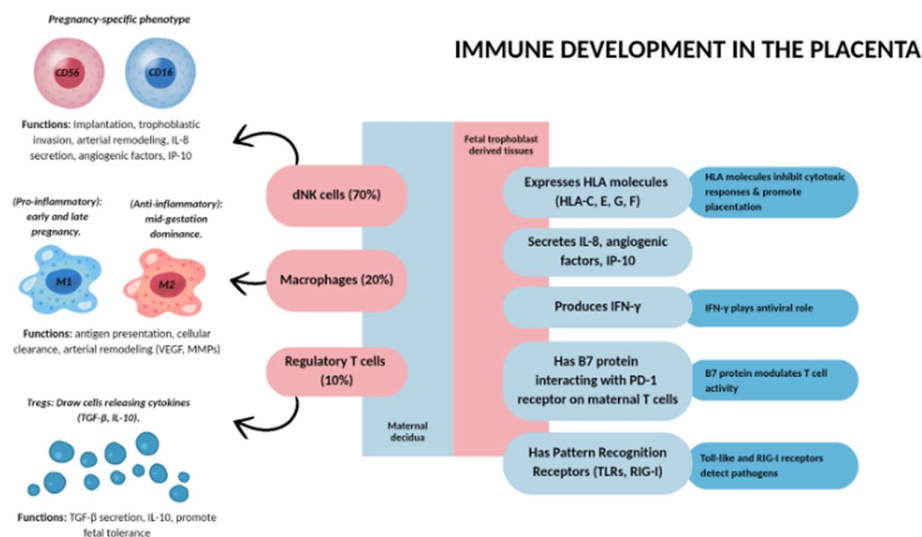


Figure 1. Immune development of the placenta. Left panel: Within the maternal decidua, pregnancy-specific immune remodeling is illustrated by the distribution of decidual NK (dNK) cells, macrophages, and regulatory T cells (Tregs). dNK cells adopt a tolerant phenotype that promotes spiral artery remodeling; decidual macrophages show M1 (pro-inflammatory) and M2 (pro-repair/tolerogenic) states that dynamically shift across gestation; and Tregs suppress excessive maternal immune activation through IL-10/TGF- β , fostering vascular adaptation and placental growth. Right panel: Fetal trophoblast-derived tissues express a restricted repertoire of HLA molecules (e.g., HLA-G, HLA-C, HLA-E) that interact with inhibitory and activating receptors on maternal NK and T cells, modulating immune tolerance. Co-stimulatory and checkpoint pathways (including B7 family proteins) fine-tune maternal T-cell responses, together establishing a balanced immune environment that supports placental development while preserving maternal defense.

2.1. Immune Cells at the Maternal–Fetal Interface

Immune cell populations at this interface are recruited and regulated by cytokines secreted by trophoblasts and decidual stromal cells [46,47]. In early gestation, decidual natural killer (dNK) cells account for approximately 70% of immune cells, macrophages for 20%, and regulatory T cells (Tregs) for 10% [3,4,18,48]. Smaller populations include B lymphocytes, mast cells, and dendritic cells [3,4].

2.1.1. Natural Killer Cells

dNK cells, located around invading extravillous trophoblasts, display a pregnancy-specific phenotype (CD56^{bright}CD16⁻) shaped by interleukin-15 (IL-15) and transforming growth factor- β (TGF- β) [3,49,50]. They facilitate implantation, trophoblast invasion, and spiral artery remodeling by secreting IL-8, angiogenic mediators, and interferon-inducible protein-10 (IP-10) [49]. Their numbers decline during gestation, with Tregs assuming a more prominent immunoregulatory role [21,42,50]. Ultimately, this finely tuned balance of immune activation and tolerance at the maternal-fetal interface is fundamental to successful gestation.

2.1.2. Decidual Macrophages

Macrophages in the decidua exhibit marked plasticity, responding dynamically to local microenvironmental cues [49]. They serve as primary antigen-presenting cells, recruited through trophoblast-derived IL-10 and macrophage colony-stimulating factor [51]. Two functional phenotypes predominate: pro-inflammatory M1 macrophages—most abundant during implantation and near term—and anti-inflammatory M2 macrophages, which dominate during established placentation [51]. Both subsets contribute to spiral artery remodeling, clearance of apoptotic cells, and antimicrobial defense through secretion of vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs) [51,52]. Through this coordinated functional versatility, decidual macrophages play an essential role in sustaining tissue homeostasis and supporting a successful pregnancy.

2.1.3. Regulatory T Cells

Regulatory T cells (Tregs) play a central role in maintaining immune tolerance during pregnancy, helping the mother's immune system accept the semi-allogeneic fetus while still protecting against infection. Tregs secrete anti-inflammatory cytokines, including TGF- β and IL-10, promoting tolerance to fetal antigens, supporting implantation, and limiting excessive inflammation [53]. At the maternal-fetal interface, Tregs suppress excessive inflammatory responses, promote vascular remodeling, and support healthy placental development through cytokines such as IL-10 and TGF- β . When Treg number or function is reduced—or pro-inflammatory T-cell subsets dominate—immune imbalance can drive endothelial dysfunction, placental malperfusion, and tissue injury. This dysregulation has been implicated in complications including preeclampsia, fetal growth restriction, recurrent pregnancy loss, and preterm birth [41,42]. Their population expands throughout gestation, and direct interactions between trophoblasts and Tregs appear critical for their differentiation and function [53,54]. Although therapeutic strategies that boost Treg activity (e.g., targeted immunomodulation, microbiome-influenced metabolites, or cell-based approaches) are under investigation, clinical translation remains early; restoring immune tolerance without compromising host defense is the key challenge.

2.2. Mechanisms of Immune Adaptation and Tolerance

Several molecular pathways sustain maternal tolerance while preserving host defense:

- Human Leukocyte Antigen (HLA): Extravillous trophoblasts express non-classical HLA molecules (HLA-C, HLA-E, HLA-G, HLA-F) that inhibit cytotoxic immune responses and facilitate placentation. HLA-G promotes NK-cell secretion of fetal growth factors [55].
- B7 Protein Family: High expression of costimulatory molecules such as B7-H1 on trophoblasts interacts with PD-1 receptors on maternal T cells, suppressing Th17 responses and enhancing Treg activity [56].
- TNF Superfamily Members: Placental Fas ligand (FasL) and TNF-related apoptosis-inducing ligand (TRAIL) induce apoptosis in activated maternal T cells [55], preventing immune-mediated rejection.

- Pattern Recognition Receptors: Toll-like receptors (TLRs) and RIG-I like receptors on trophoblasts detect pathogen-associated molecular patterns, initiating controlled inflammatory cascades that preserve defense without disrupting tolerance [57].
- Maternal–Fetal IgG Transfer: Immunoglobulin G is actively transported across the placenta during the second and third trimesters, conferring passive immunity to the neonate and infant [58].
- Interferon- γ (IFN- γ): Produced by syncytiotrophoblast, IFN- γ plays a crucial role in antiviral protection and local immune signaling [59].
- Other Immunomodulators: Galectin-1, sex hormones such as progesterone and estrogen, and complement regulatory proteins (CD46, CD55, CD59) collectively maintain immune equilibrium and protect the fetus from complement-mediated injury [19].

Collectively, these molecular pathways orchestrate a finely tuned immunological state in which tolerance toward fetal antigens is actively maintained while essential antimicrobial defenses are preserved. This dynamic equilibrium ensures proper placental development, protects the fetus from immune-mediated damage, and supports a successful pregnancy despite the unique immunological challenges of gestation. Beyond these classical immunoregulatory pathways, emerging evidence highlights an additional layer of immune modulation involving the placental and maternal microbiomes, which may influence both immune development and susceptibility to inflammation-driven obstetric disorders.

3. The Maternal Microbiome: A Hidden Regulator of Pregnancy

Throughout pregnancy, the maternal microbiome undergoes profound physiological shifts driven by hormonal, metabolic, and immunological changes. These alterations influence maternal health and fetal development, shaping susceptibility to conditions such as gestational diabetes mellitus and other noncommunicable diseases [60–63]. In preeclampsia, studies have demonstrated consistent alterations in gut microbiota composition, including increased abundance of Proteobacteria and Actinobacteria, accompanied by reduced levels of genera such as Prevotella, Varibaculum, Lactobacillus, and Porphyromonas [64]. These changes reflect a shift toward a proinflammatory microbial profile, supporting the hypothesis that maternal gut dysbiosis may contribute to systemic inflammation, endothelial dysfunction, and ultimately placental disease. *Together, these findings underscore the maternal microbiome as a dynamic regulator of immune and metabolic homeostasis during pregnancy. Understanding how microbial dysbiosis contributes to disorders such as preeclampsia offers a promising avenue for early risk stratification and targeted interventions to improve maternal and neonatal outcomes.*

3.1. Placental Microbiome

For decades, the placenta was considered a sterile environment. However, recent advances in sequencing technologies have challenged this assumption, suggesting the presence of a unique placental microbiome [65]. Despite these findings, essential gaps remain regarding its origin – whether derived from the maternal oral cavity, genital tract, or hematogenous spread – and its relationship to pregnancy outcomes, both physiological and pathological [66–68].

Recent research by Saadaoui et al. using molecular biology and 16S rRNA sequencing, discovered different placental microbiomes according to the various outcomes, showing differences between the oral microbiome, with information about specific bacteria (*Treponema maltophilum*) and the outcome observed in these pregnancies in specific moments (potential biomarker), and reporting information about some bacteria as *Ureaplasma urealyticum* more abundant in PTB placenta [67,69]. Some studies have identified four major phyla in the placental microbiome (*Firmicutes*, *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria*), and changes in the placental microbiome may be associated with adverse pregnancy outcomes and comorbidities, including preterm birth (PTB), gestational diabetes

mellitus, and severe chorioamnionitis. In some cases, contamination from ascending vaginal bacteria might influence the changes in the placental microbiome [70].

Based on the information to date, the placental microbiome is unique but resembles that of an oral origin [65,71]. It's well established that the placenta contributes to early immune development, and maternal antigens may be associated with the initial formation of immune cell populations and clinical outcomes. If antibiotics are administered to the mother during the prenatal period, dysbiosis occurs, resulting in altered infant immune development and increased susceptibility to viral infections [72]. Although many questions remain open, it is well established that numerous adjustments occur in women during pregnancy (hormonal, immunological, physiological), which increase the risk of other clinical conditions, such as infections distant from the placenta (vaginal, oral), and are associated with PTB and LBW (low birth weight) [54,73].

4. Evidence of Altered Inflammation in Preeclampsia

Normal pregnancy is characterized by a controlled, low-grade systemic inflammatory state that is essential for implantation, placental development, and preparation for parturition [74,75]. Compared with the non-pregnant state, pregnancy is associated with leukocytosis [74], increased complement activation, and dynamic shifts in peripheral leukocyte populations [74]. Distinct immunological phases have been described, reflecting changes in both innate and adaptive immunity [4,42,73,74]. This physiological inflammatory environment represents a balance between proinflammatory mediators—such as TNF- α , IL-2, IL-4, IL-6, IL-8, IL-10, interferon- γ (IFN- γ), and monocyte chemoattractant protein-1 (MCP-1) [4,41,42]—and anti-inflammatory/regulatory mechanisms (Figure 2).

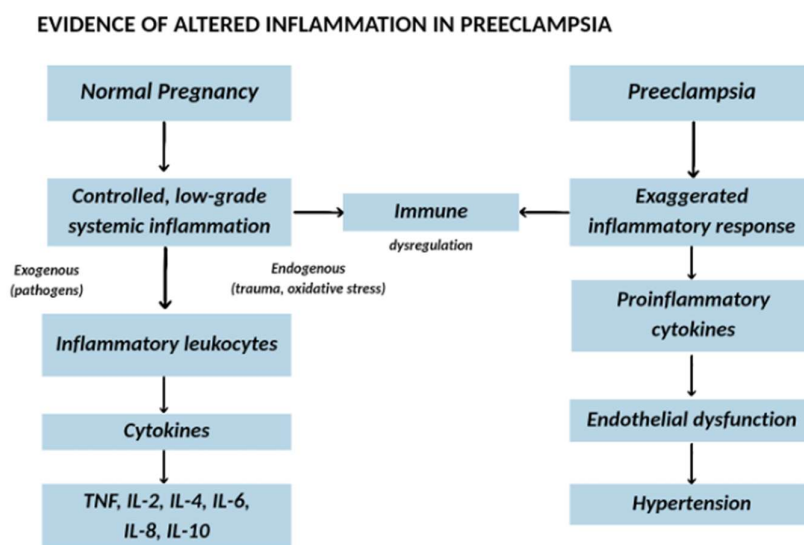


Figure 2. Schematic overview of altered inflammation in preeclampsia. This diagram contrasts immune balance in normal pregnancy with the exaggerated inflammatory state characteristic of preeclampsia. Under physiologic conditions, a controlled, low-grade inflammatory milieu supports placental development and vascular adaptation. In preeclampsia, this equilibrium is disrupted: pro-inflammatory cytokines are elevated, anti-angiogenic factors (e.g., sFlt-1, sEng) increase, and maternal immune profiles shift toward heightened activation. These changes converge to drive endothelial dysfunction, oxidative stress, and impaired placental perfusion, culminating clinically in hypertension and multi-organ involvement.

Preeclampsia shares some features with the inflammatory state of normal pregnancy, but the intensity of the response is markedly increased [13,76,77]. This exaggerated inflammation is thought to originate from syncytiotrophoblast stress due to hypoxia, oxidative stress, or both [5,75,76,78], leading to the release of proinflammatory cytokines and antiangiogenic factors [5,16,75]. The inflammatory response may be triggered by both exogenous danger signals (e.g., pathogens) and endogenous signals (products of trauma, ischemia, necrosis, or oxidative stress) [79–81]. It involves inflammatory leukocytes (granulocytes, macrophages, and NK cells) in concert with endothelial cells, platelets, and soluble mediators, such as complement [42,77].

Preeclampsia is conceptualized as a two-stage disorder [13,76]:

1. Pre-clinical Stage – Abnormal placentation and inadequate spiral artery remodeling, leading to placental hypoperfusion [20,82].
2. Clinical Stage – Systemic maternal endothelial dysfunction and hypertension [24,75,83].

Placental-derived antiangiogenic factors—such as increased sFlt-1 and soluble endoglin (sEng) and decreased placental growth factor (PlGF)—are distinctive features of preeclampsia and contribute to widespread endothelial injury [83,84]. In summary, preeclampsia represents the convergence of dysregulated inflammation, imbalanced angiogenic signaling, and heightened long-term cardiovascular vulnerability [77,78,84]. Excess maternal inflammatory activation injures the endothelium and amplifies oxidative stress, whereas anti-angiogenic factors, such as sFlt-1 and sEng, disrupt placental perfusion and propagate systemic vascular dysfunction. These acute pathophysiologic pathways not only drive the clinical syndrome of hypertension, proteinuria, and multi-organ involvement but also leave a persistent imprint on maternal cardiovascular health, explaining the markedly increased risk of later hypertension, ischemic heart disease, and stroke [22,29,85]. Understanding how immune, vascular, and metabolic networks intersect in preeclampsia is essential for developing therapies that protect both immediate pregnancy outcomes and lifelong cardiovascular health.

4.1. Immune Dysregulation and Cytokine Imbalance

Since Medawar's 1953 hypothesis that the fetus is an "allograft" [44,86], early theories posited that maternal immune privilege at the maternal–fetal interface was necessary to maintain pregnancy [55,74]. These models emphasized maternal immune suppression, reduced expression of major histocompatibility complex (MHC) antigens in fetal tissue, and a shift from Th1 to Th2 cytokine dominance [57,81,86,87]. Contemporary evidence, however, indicates that a balanced interplay between pro- and anti-inflammatory responses is essential for successful pregnancy [81,86]. In early gestation, implantation and placental development are inherently proinflammatory but are tightly regulated by anti-inflammatory mediators, such as IL-10 and Tregs [1,54].

In preeclampsia, this balance is disrupted [77,88]. There is an overactivation of Th1 and Th17 responses, reduced Treg activity, and increased activation of cytotoxic NK cells and autoreactive B cells [77,87]. This leads to increased innate immune activation in both the maternal circulation and the uteroplacental unit [75,76,81]. The result is superficial trophoblast invasion, poor spiral artery remodeling, and worsening placental ischemia with escalating oxidative stress [21,87,89,90].

4.2. Cytokines and Endothelial Dysfunction in Preeclampsia

Chronic immune activation in preeclampsia is characterized by elevated levels of proinflammatory cytokines, particularly TNF- α , IL-6, and IL-17 [31,32,77,87,91]. These act locally and systemically, perpetuating oxidative stress, vascular inflammation, and endothelial damage.

- TNF- α and IL-6: Promote endothelial adhesion molecule expression, increase vascular permeability, and impair endothelial nitric oxide synthase (eNOS) activity, reducing nitric oxide (NO) bioavailability and vasodilation [91,92]. Experimental models show that a two-fold increase in TNF- α elevates mean arterial pressure (MAP) and reduces renal plasma flow and

glomerular filtration rate (GFR) [92,93]. IL-6 exerts similar effects and has been linked to increased plasma renin activity [92,94].

- IL-17: In animal models, IL-17 increases MAP, induces placental oxidative stress, and stimulates B cells to produce angiotensin II type 1 receptor autoantibodies (AT1-AA), exacerbating hypertension and vascular injury [95].

Together, these inflammatory and immunological disturbances integrate placental dysfunction with maternal endothelial injury, forming the central pathogenic axis that underlies the clinical manifestations of preeclampsia (Figure 3).

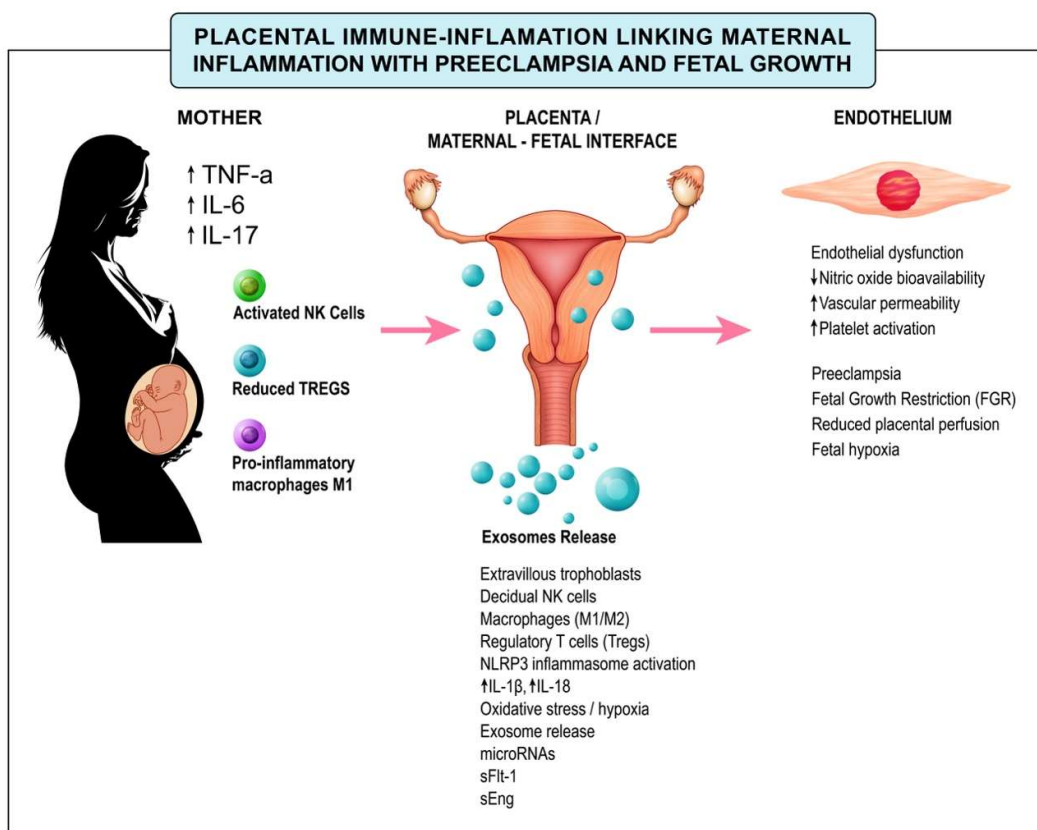


Figure 3. Placental immune inflammation linking maternal inflammation with preeclampsia and fetal growth. This schematic illustrates how maternal immune activation shapes the maternal–fetal interface and influences placental and fetal outcomes. Maternal macrophages, regulatory T cells, and circulating cytokines modulate the decidual milieu, whereas trophoblast-derived exosomes that carry microRNAs act as key effectors coordinating crosstalk between inflammatory and angiogenic pathways. The resulting balance—or imbalance—between pro-inflammatory signals and pro-angiogenic support determines endothelial health and uteroplacental perfusion. When maternal susceptibility and heightened inflammation prevail, endothelial dysfunction and impaired placental vascularization ensue, contributing to preeclampsia and restricted fetal growth.

5. Inflammation and Fetal Growth Restriction

FGR is a complex clinical condition associated with increased perinatal morbidity and mortality [96,97]. It is primarily a consequence of placental insufficiency and alterations in the intrauterine inflammatory environment, both of which can have lasting effects on perinatal and long-term health [98–100]. FGR is defined as the failure of a fetus to achieve its genetically determined growth potential [97]. Clinically, the most widely accepted criterion is an estimated fetal weight below the 10th percentile for gestational age, as defined by standardized growth charts [101]. Multiple etiological

factors contribute to FGR, with inflammation playing a pivotal role in its pathogenesis [102]. Excessive placental inflammation can be triggered by maternal stress, hypoxia, and endogenous danger signals such as uric acid crystals [6,28,79]. These stimuli activate placental inflammasomes—, particularly NLRP3, through IL-1-dependent pathways, impairing trophoblast function and contributing to placental insufficiency [27–29] (Figure 4).

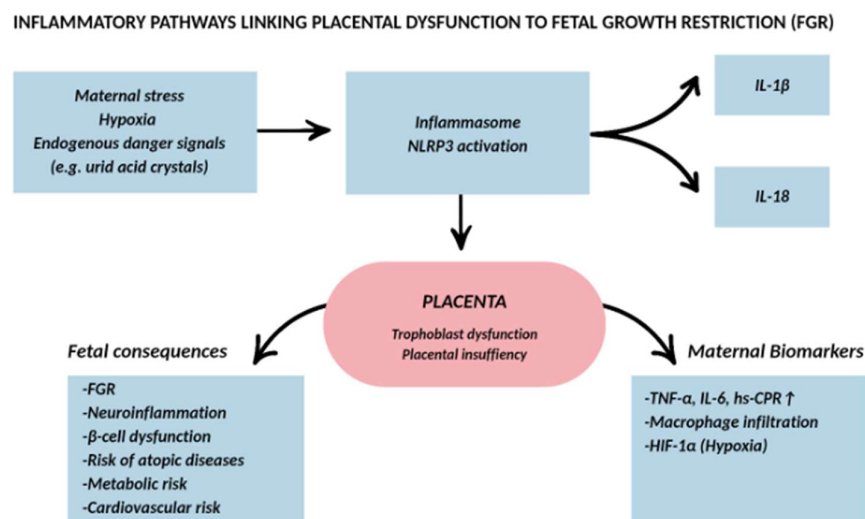


Figure 4. Inflammatory pathways linking placental dysfunction to fetal growth restriction. Maternal hypoxia and endogenous danger signals activate the NLRP3 inflammasome, increasing IL-1 β and IL-18 production and leading to trophoblast dysfunction, placental insufficiency, and maternal inflammatory biomarkers. These processes contribute to adverse fetal outcomes, including FGR, neuroinflammation, metabolic dysregulation, and long-term cardiovascular risk.

The NLRP3 inflammasome, a multiprotein complex, mediates the maturation of proinflammatory cytokines such as IL-1 β and IL-18, which are critical in amplifying inflammatory responses [28,32]. Experimental models demonstrate that sustained maternal inflammation can disrupt fetal metabolic programming, affecting skeletal muscle glucose metabolism and β -cell function, with potential implications for future metabolic disease risk [103]. Placental inflammation is also associated with increased macrophage infiltration and a proinflammatory cytokine profile in both placental tissue and maternal serum [6,72,88]. Furthermore, inflammation in FGR may extend beyond the placenta, affecting other systems such as the central nervous system—where neuroinflammation can impair brain development [104–106]—and the skin, where inflammatory changes may predispose to childhood atopic diseases [62].

Assessment of inflammatory involvement in FGR includes evaluation of both systemic and local biomarkers. Elevated maternal serum levels of TNF- α , IL-6, and high-sensitivity C-reactive protein (hs-CRP) have been reported in pregnancies complicated by FGR, with correlations to adverse neonatal outcomes such as low birth weight and reduced Apgar scores [79,103,107]. Histological and immunohistochemical analyses of placental tissue reveal increased macrophage density and a predominance of proinflammatory markers [108,109]. Additionally, hypoxia-induced factors such as hypoxia-inducible factor 1-alpha (HIF-1 α) accumulate in placentas of pregnancies complicated with FGR, linking placental hypoxia to sterile inflammation and dysfunction [110]. The inflammatory milieu associated with FGR may have lasting effects on both the fetus and the mother. Children with a history of poor postnatal growth demonstrate elevated circulating inflammatory markers—such as C-reactive protein, hepatocyte growth factor, IL-8, and TNF- α —compared with age-matched controls

[111]. This low-grade inflammation may increase the risk of future metabolic and cardiovascular disease. Animal studies indicate that FGR can blunt the neonatal proinflammatory response to infectious stimuli, mediated by reduced nuclear factor kappa B (NF- κ B) activation [112]. This suggests impaired innate immunity and increased susceptibility to infection. On the maternal side, pregnancies complicated by FGR often show elevated proinflammatory cytokines, reinforcing the concept of a shared maternal–fetal inflammatory environment [6].

6. Immune Dysregulation in Placental Insufficiency: Clinical Implications and Translational Perspectives

There is consistent evidence that preeclampsia and FGR are associated with increased circulating inflammatory markers, including TNF- α , IL-6, and IL-17 [33,77,81,95]. These cytokines amplify oxidative stress in placental tissue, aggravating endothelial dysfunction and contributing to the most acute and clinically severe stages of the disease. However, interpreting these biomarkers in clinical practice remains challenging, as inflammation can also be influenced by maternal characteristics such as advanced age, prolonged interpregnancy interval, obesity, and comorbidities, including chronic hypertension, diabetes, renal disease, and autoimmune conditions (Figure 5).

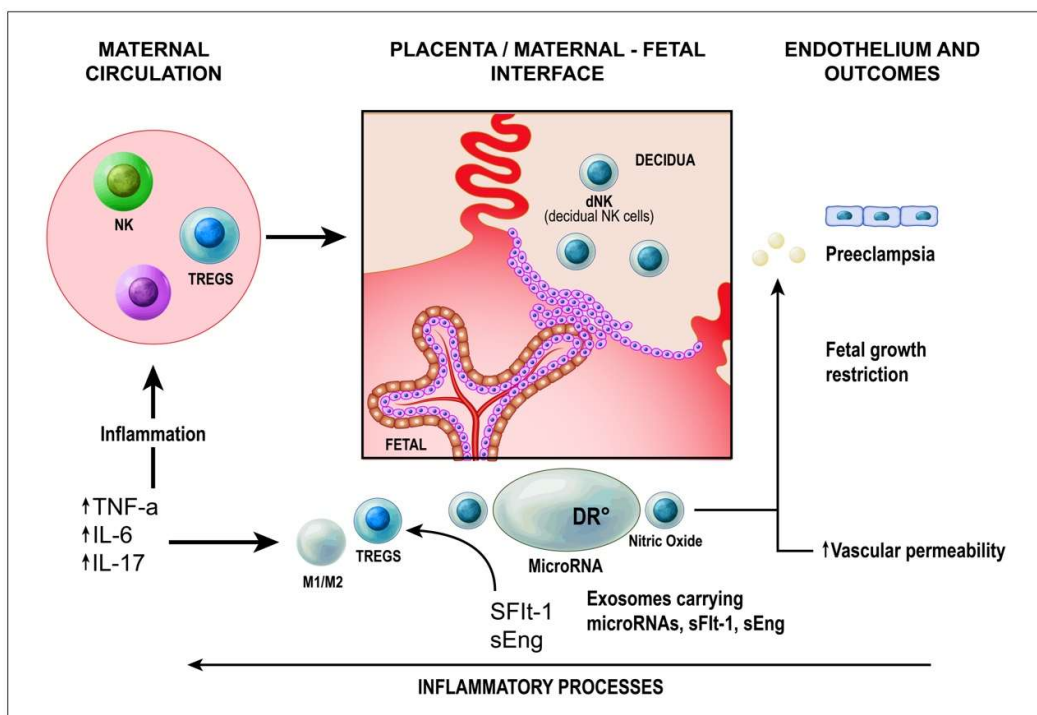


Figure 5. Inflammatory Balance and Vascular Dysfunction as a Unifying Pathway to Preeclampsia and Fetal Growth Restriction. This model depicts pregnancy as a continuum between controlled, physiologic inflammation—necessary for implantation, placental development, and parturition—and dysregulated, exaggerated inflammation that becomes pathogenic. As inflammation intensifies, endothelial injury and angiogenic imbalance increase proportionally, leading to progressive impairment of uteroplacental perfusion. The degree of vascular involvement determines downstream fetal consequences, including altered angiogenesis and growth restriction. At the clinical level, this shared pathway manifests primarily as two outcomes: preeclampsia and fetal growth restriction, which may occur alone or together. The schematic highlights how the interplay between inflammation and vascular dysfunction provides a unified framework to understand these related pregnancy disorders.

Beyond heightened inflammation, preeclampsia is also characterized by impaired anti-inflammatory regulation [77]. A consistent finding across studies is the reduction in Tregs and decreased IL-10 production—both essential for maintaining immunological tolerance at the maternal–fetal interface. Several reports indicate that Treg cell depletion is more pronounced in early-onset, severe preeclampsia compared with late-onset or milder forms [82,86,113]. Reduced Treg function promotes increased trophoblast apoptosis, shallow trophoblast invasion, and inadequate spiral artery remodeling [53,86], highlighting a mechanistic link between immune dysregulation and the placental malperfusion that precedes clinical disease [77].

IL-10 plays a central role in this process. As a key anti-inflammatory cytokine that restrains Th1-driven inflammation and supports Treg differentiation, its reduction in preeclampsia further skews the maternal immune milieu toward a cytotoxic, proinflammatory state. This imbalance contributes to hypertension, endothelial activation, and ultimately impaired fetal growth [5,75]. Together, these findings underscore the importance of immune homeostasis for optimal pregnancy outcomes. Clinically, they highlight potential avenues for intervention: therapies that enhance Treg function, restore IL-10 signaling, or attenuate excessive cytokine activity could help rebalance inflammatory pathways and improve maternal and perinatal outcomes. Although still experimental, strategies such as Treg cell transfer, IL-10–based therapies, and selective immunomodulators hold promise and warrant further investigation in well-designed translational studies [77].

Strengthening the bridge between immunopathology and clinical care is essential. By identifying immune signatures that distinguish pathological inflammation from physiological adaptation, future diagnostic tools and targeted therapies may allow earlier detection, personalized risk stratification, and more effective prevention of the maternal and neonatal complications associated with preeclampsia.

7. Therapy Development

Therapeutic strategies for pregnancy-associated inflammatory disorders must achieve a delicate balance between modulating the maternal immune response and ensuring fetal safety. The primary objective is to attenuate excessive inflammation—implicated in adverse outcomes such as preeclampsia, FGR, and preterm birth—while preserving adequate host defense against infections. Current management combines evidence-based interventions from established clinical guidelines with emerging approaches that target specific inflammatory pathways (Table 1). *Understanding how these interventions modulate the maternal–fetal immune landscape is essential for developing more precise and effective therapies.*

Table 1. Comparative Therapies aimed to modulate inflammation during pregnancy.

Category	Type	Mechanism of Action	Evidence Level
Low-Dose Aspirin	Established	COX-1 inhibition → ↓ platelet aggregation & inflammation	High – Multiple RCTs in PE prevention
Low Molecular Weight Heparin	Established	Anticoagulation + modulation of complement & leukocyte trafficking	Moderate – Observational studies & some RCTs
Antenatal Corticosteroids	Established	Promote fetal lung maturation, transient anti-inflammatory effect	High – Standard of care in threatened preterm birth
Antioxidants & Nutritional Modulation	Adjuvative	Reduce oxidative stress, improve endothelial function	Low to Moderate – Inconsistent RCT results
Lifestyle & Microbiome Modulation	Adjuvative	Improve immune tolerance & reduce systemic inflammation	Low – Ongoing trials
Cytokine-Targeted Biologics	Emerging	Neutralize pro-inflammatory cytokines (e.g., TNF- α , IL-6)	Experimental – Limited pregnancy-specific data
Inflammasome Inhibitors	Emerging	Block NLRP3 inflammasome activation	Preclinical – Animal models

Cell-Based Therapies	Emerging	Promote immune tolerance & tissue repair at maternal–fetal interface	Preclinical – Early-phase studies
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7.1. Established Therapies

7.1.1. Low-Dose Aspirin

Low-dose aspirin (LDA), initiated before 16 weeks of gestation, reduces the incidence of preeclampsia and other placental-mediated complications. Its mechanism involves inhibition of platelet aggregation and modulation of inflammatory responses via selective cyclooxygenase-1 (COX-1) blockade [35,114]. Emerging clinical guidelines increasingly support the use of LDA in women identified as high risk for preeclampsia following first-trimester screening. Evidence from randomized trials and meta-analyses demonstrates that initiating LDA—ideally before 16 weeks—significantly reduces the risk of preeclampsia, particularly early-onset disease, and associated outcomes, including preterm birth and fetal growth restriction [35,114]. Screening-based strategies enable targeted treatment of women most likely to benefit, thereby optimizing the risk–benefit balance. Collectively, these data underpin current recommendations endorsing prophylactic LDA as a cornerstone of prevention in appropriately selected pregnancies.

7.1.2. Anticoagulants

Low molecular weight heparin (LMWH) is indicated in selected high-risk pregnancies, particularly in the context of thrombophilia or recurrent pregnancy loss. Beyond its anticoagulant properties, LMWH exhibits anti-inflammatory effects by modulating complement activation and leukocyte trafficking [85]. A growing body of evidence suggests that adjunctive LMWH may confer benefit in women at high risk of preeclampsia who do not have thrombophilia. In a meta-analysis of 10 randomized trials (1,758 participants), LMWH significantly reduced the incidence of preeclampsia, with risk reduction confined mainly to studies in which low-dose aspirin was the primary intervention. The combination of LMWH and LDA was also associated with fewer preterm births and fewer cases of fetal growth restriction, without affecting placental abruption rates. Overall, these findings support the selective use of LMWH as an adjunct to LDA in carefully defined high-risk populations [115].

7.1.3. Corticosteroids

Antenatal corticosteroids remain a cornerstone when preterm delivery is anticipated in pregnancies complicated by fetal growth restriction or preeclampsia, primarily because they accelerate fetal lung maturation and reduce neonatal respiratory distress, intraventricular hemorrhage, and death [116,117]. Although they do not directly treat placental insufficiency or maternal disease, their use can safely extend the window for optimizing delivery timing and adjunctive care. In these high-risk contexts, clinicians must balance benefits against potential maternal effects—including transient hyperglycemia, fluid retention, and a small increase in infectious risk—particularly in women with diabetes or severe hypertension. Overall, a single standard course before early preterm birth is strongly supported, while repeat dosing requires individualized consideration [116,117].

These established therapies delineate the current therapeutic landscape—effective in specific contexts yet fundamentally constrained by the need to safeguard the maternal–fetal unit. This limitation underscores an urgent scientific priority: to design next-generation immunomodulatory approaches that selectively suppress pathological inflammation while preserving fetal development. As insights into placental immunobiology expand, the development of truly targeted, precision therapies in pregnancy are shifting from possibility to near inevitability.

7.2. Adjunctive and Supportive Interventions

7.2.1. Antioxidants and Nutritional Modulation

Oxidative stress is a key contributor to placental inflammation [118,119]. Although antioxidants such as vitamins C and E have been extensively evaluated, large clinical trials have not demonstrated consistent benefit in preventing preeclampsia [81]. Melatonin, with potent antioxidant and vasoprotective properties, has shown promising results in small-scale studies [120,121], suggesting a potential role for targeted antioxidant therapy. Experimental data demonstrate that melatonin reduces placental oxidative stress and enhances antioxidant defenses without altering key anti-angiogenic mediators, and that it partially protects endothelial function in vitro. In a phase I clinical study involving women with established preeclampsia, melatonin administration was safe for both mother and fetus [120]. It was associated with a meaningful prolongation of pregnancy, along with reduced requirements for escalation of antihypertensive therapy [120]. Although significant biochemical markers of disease severity remained unchanged, these findings suggest that melatonin may attenuate maternal endothelial injury and help stabilize the disease long enough to improve perinatal outcomes, warranting larger confirmatory trials.

Recent high-quality evidence challenges earlier assumptions regarding routine calcium supplementation for the prevention of preeclampsia [122]. Across large, prospectively registered randomized trials, calcium showed little to no effect on preeclampsia, preterm birth, or major maternal and perinatal outcomes, regardless of baseline intake or dose. Overall, current data suggest that dietary calcium alone is unlikely to modify preeclampsia risk meaningfully and should not replace proven preventive strategies in high-risk pregnancies [122].

7.2.3. Lifestyle and Microbiome Modulation

Optimizing maternal diet, engaging in regular moderate physical activity, and using probiotic supplementation are under investigation as strategies to modulate systemic inflammation and enhance immune tolerance during pregnancy [36,123]. Lifestyle and microbiome modulation are emerging areas of interest in strategies to reduce the risk of preeclampsia, although the evidence remains preliminary. Observational and mechanistic studies suggest that healthy dietary patterns, appropriate weight gain, physical activity, and smoking avoidance may attenuate systemic inflammation, improve metabolic function, and support vascular health—pathways central to preeclampsia [124]. Parallel research indicates that alterations in the gut, vaginal, and placental microbiomes may influence immune tolerance, endothelial function, and oxidative stress, raising the possibility that probiotics, prebiotics, or diet-driven microbial shifts could play a preventive role. However, high-quality randomized trials are scarce, and standardized interventions have not yet been defined. For now, lifestyle optimization should be encouraged as part of comprehensive antenatal care, while microbiome-targeted therapies remain promising but investigational.

7.3. Emerging and Experimental Therapies

7.3.1. Cytokine-Targeted Biologics

Monoclonal antibodies that neutralize pro-inflammatory cytokines (e.g., anti-TNF- α , anti-IL-6) have been successful in treating autoimmune diseases and are now under consideration for the treatment of pregnancy-related inflammatory disorders [125]. Their capacity to exert highly specific immunomodulatory effects makes them an appealing, although still experimental, therapeutic avenue. Experimental models suggest these cytokines contribute to endothelial dysfunction, placental malperfusion, and systemic oxidative stress, and targeted blockade can partially restore vascular homeostasis. Clinically, experience in pregnant patients largely comes from women treated for autoimmune diseases, where selected agents (e.g., certain anti-TNF drugs) have shown acceptable safety profiles when carefully monitored; however, robust randomized data specific to hypertensive or placental disorders are lacking. At present, cytokine-neutralizing antibodies remain

investigational for pregnancy-specific indications, and their future role will depend on trials that balance maternal benefit with fetal immune and developmental safety.

7.3.2. Inflammasome Inhibitors

Given the pivotal role of NLRP3 inflammasome activation in placental inflammation and FGR, small-molecule inhibitors such as MCC950 are being tested in preclinical models [126]. By targeting upstream inflammatory signaling, these agents may help mitigate placental injury. Inflammasome inhibitors, particularly those targeting NLRP3, offer a novel approach for pregnancy disorders in which excessive IL-1 β and IL-18 signaling drives endothelial and placental injury, such as preeclampsia and fetal growth restriction [127]. Preclinical models suggest that pharmacologic blockade of inflammasome activation can attenuate oxidative stress, vascular dysfunction, and placental inflammation, thereby improving maternal hemodynamics and fetal growth [127]. However, clinical experience in pregnancy is virtually absent, and concerns remain regarding host defense and fetal immune development. At present, inflammasome inhibition is a promising but purely experimental strategy that requires rigorous safety and efficacy trials before translation to obstetric care.

7.3.3. Cell-Based Therapies

Mesenchymal stem cell (MSC) therapy represents a novel approach aimed at promoting immune tolerance and facilitating tissue repair at the maternal–fetal interface [128]. Early data indicate that MSCs possess strong immunomodulatory and regenerative potential, positioning them as a promising frontier in perinatal therapeutics. Cell-based therapies are emerging as an innovative strategy for preeclampsia, aiming to repair rather than merely temporize placental and endothelial injury [128]. Mesenchymal stromal cells, endothelial progenitor cells, and regulatory T-cell–based approaches have been shown in preclinical models to improve uteroplacental perfusion, dampen inflammation, and restore endothelial function, primarily through paracrine and immunomodulatory mechanisms. Early-phase studies outside pregnancy suggest acceptable safety profiles for some platforms, but robust clinical data in pregnant populations are lacking. For now, cell-based therapies remain experimental, offering a compelling future avenue for disease modification in severe or early-onset preeclampsia [128].

7.3.4. Safety Considerations

The administration of anti-inflammatory agents during pregnancy requires rigorous assessment of their teratogenic potential, effects on fetal immune development, and potential long-term effects on offspring. Current guidelines advocate for individualized risk–benefit evaluation and preferential use of therapies with well-established safety profiles [129,130].

7.4. Future Therapies

While current and emerging therapeutic approaches offer promising avenues for managing pregnancy-associated inflammatory disorders, ongoing research is advancing toward even more targeted and biologically precise interventions. Among these, exosome-based strategies are among the most innovative and rapidly evolving frontiers.

8. Exosomal Signaling at the Maternal–Fetal Interface: Orchestrating Immune and Vascular Adaptation

Exosomes are nanoscale extracellular vesicles that transport proteins, DNA, mRNA, and microRNAs (miRNAs) and function as key mediators of intercellular communication across multiple tissues [131]. They are secreted by diverse cell types—including trophoblasts, endothelial cells, and immune cells—and participate actively in both physiological and pathological immune modulation [82,131–133]. Through selective cargo delivery, exosomes influence inflammatory pathways by

transporting miRNAs that regulate interferons (IFN- α/γ), TNF- α , and various interleukins central to immune activation [134].

During pregnancy, placental exosomes contribute significantly to homeostasis, inflammation control, and maternal–fetal tolerance [133,135–137]. Specific miRNAs such as miR-146a and miR-21 play central roles in regulating immune responses, controlling macrophage activity, and modulating hypoxia-driven inflammation [82,138,139]. Placental exosomes also help maintain tolerance to the semi-allogeneic fetus by shaping maternal immune cell phenotypes and restraining cytotoxic responses that might otherwise threaten placental integrity [138].

Alterations in exosomal composition have been closely linked to complications such as preeclampsia. Several studies have demonstrated that preeclamptic placentas release exosomes enriched with inflammatory and antiangiogenic cargo—including dysregulated miRNAs and increased sFlt-1—which antagonizes PlGF and VEGF, contributing to impaired trophoblast invasion and endothelial dysfunction [140]. These findings position exosomes as both mechanistic contributors and potential early biomarkers of disease [141]. Given their profound immunomodulatory properties, exosomes have emerged as promising candidates for next-generation therapies. Preclinical models indicate that mesenchymal stromal cell-derived extracellular vesicles can prevent preeclampsia-like physiology by restoring uterine immune balance, reducing inflammation, and improving placental vascular remodeling [142]. Such evidence suggests that exosome-based interventions may one day enable targeted, noninvasive modulation of the uteroplacental environment to prevent hypertensive disorders and their associated maternal–fetal complications.

Taken together, these insights highlight exosomes as a compelling therapeutic and diagnostic frontier in reproductive immunology. Their dual potential—as biomarkers and as immunomodulatory agents—suggests that they may play a transformative role in the future management of inflammation-mediated pregnancy disorders [139,141]. Collectively, these adjunctive and experimental interventions reflect a rapidly advancing field that seeks to refine immune modulation without compromising fetal development. As understanding of placental immunobiology deepens, the transition from broadly acting therapies to targeted, mechanism-based strategies is becoming increasingly feasible, offering a path toward safer and more effective treatments for pregnancy-associated inflammatory disorders.

9. Future Perspectives

Advances in immunology and molecular biology are rapidly reshaping our understanding of pregnancy-related inflammatory disorders. In the next decade, integration of multi-omics approaches—including transcriptomics, proteomics, and metabolomics—may allow the identification of precise molecular signatures for early risk stratification and targeted intervention. Artificial intelligence-driven predictive models could enable real-time clinical decision support by combining biomarker data with maternal and fetal parameters [102]. Furthermore, global health strategies must address disparities in access to diagnostic tools and therapeutics, ensuring that innovations benefit populations in low- and middle-income countries where the burden of preeclampsia, FGR, and preterm birth remains highest. Collaborative translational research networks will be essential to accelerate the validation of novel therapies, clarify their safety profiles, and implement them within equitable, sustainable healthcare frameworks.

10. Conclusions

Pregnancy-associated inflammatory disorders represent a significant challenge in maternal–fetal medicine due to their complex pathophysiology, heterogeneous clinical presentations, and potential for long-term consequences in both mother and child. Evidence reviewed here highlights the central role of immune and inflammatory mechanisms in conditions such as preeclampsia and FGR and underscores the placenta as a pivotal site for immune regulation. Advances in our understanding of the maternal–fetal immune interface have opened new opportunities for targeted interventions,

ranging from established pharmacologic strategies to emerging biologic and cell-based therapies. Future research should focus on refining diagnostic biomarkers, elucidating precise inflammatory pathways, and ensuring the safety and efficacy of novel interventions, to improve pregnancy outcomes and reduce intergenerational health risks.

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Abbreviations

FGR	Fetal growth restriction
Th1	T-helper 1 cells
Th2	T-helper 2 cells
HDP	Hypertensive disorders of pregnancy
uNK	Uterine natural killer cells
HLA-G	Human Leukocyte Antigen-G
PD-L1	Programmed Death-Ligand 1
sFlt-1	soluble fms-like tyrosine kinase-1
NLRP3	NOD-like receptor family, pyrin domain containing 3
IL	Interleukin
TNF- α	Tumor necrosis factor- α
dNK	Decidual natural killer cells
CD56	Cluster of Differentiation 56
IP-10	Interferon-inducible protein-10
VEGF	Vascular endothelial growth factor
Tregs	Regulatory T cells
TGF- β	Transforming Growth Factor-Beta
FasL	Placental Fas ligand
TLRs	Toll-like receptors
PTB	Preterm birth
LBW	Low birth weight
MCP-1	Monocyte chemotactic protein-1
PlGF	Placental growth factor
sEng	Soluble endoglin
MHC	Histocompatibility complex
eNOS	Endothelial nitric oxide synthase
NO	Nitric oxide
MAP	Mean arterial pressure
HIF-1 α	Hypoxia-inducible factor 1-alpha
NF- κ B	Nuclear factor kappa B
LDA	Low-dose aspirin

COX-1	Cyclooxygenase-1
LMWH	Low molecular weight heparin
MSC	Mesenchymal stem cell
miRNAs	microRNAs

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