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Review

Mechanisms of Complement Activation and NETosis Interplay in Early Pregnancy Loss: From Autoimmunity to Thrombogenesis

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Abstract

Early Pregnancy Loss (EPL) represents a formidable challenge in reproductive medicine. Its complex pathophysiology is primarily characterized by dysregulation of both the immune and coagulation systems. In recent years, abnormal activation of the complement system and neutrophil extracellular trap formation (NETosis) have received increasing scientific attention as key molecular events underlying EPL. This interest is fueled significantly by compelling evidence from non-pregnant models, such as antiphospholipid syndrome (APS) and severe infections (e.g., COVID-19), which demonstrate a pathogenic synergy between complement and NETosis in thrombo-inflammatory pathways. Dysregulation of the complement system can trigger strong inflammatory responses and promote a prothrombotic state. Similarly, excessive NETosis acts as a significant driver of tissue damage and thrombosis. This review aims to systematically delineate the complex crosstalk between complement activation and NETosis in EPL, with particular emphasis on their bidirectional regulatory relationship within autoimmune and thrombo-inflammatory pathways. By thoroughly analyzing the critical pathological role of this "complement-NETosis axis" in disrupting uteroplacental interface homeostasis and ultimately causing pregnancy failure, this review not only presents an integrative conceptual framework for comprehensively understanding the molecular mechanisms of EPL, but, more importantly, proposes a novel hypothesis, based on mechanistic insights derived from non-pregnant models, that this axis may play acentral role in EPL. This perspective provides a framework for future research, encompassing the validation of associated potential biomarkers and the exploration of targeted intervention strategies, thereby holding promise for advancing precise clinical intervention paradigms for specific EPL subtypes.

Keywords: complement activation; NETosis; early pregnancy loss; autoimmunity; thrombosis; immuno-inflammation

1. Introduction

Early Pregnancy Loss (EPL) is among the most common complications in human reproduction, affecting an estimated 12% to 30% of clinically recognized pregnancies. Its recurrent form, known as recurrent pregnancy loss (RPL), imposes substantial physiological and psychological burdens on up to 5% of couples of reproductive age [1,2]. The etiology of EPL is highly heterogeneous, involving a wide range of factors, including genetic anomalies, endocrine dysfunction, anatomical abnormalities, and infectious agents [3,4]. Among these, embryonic chromosomal aberrations such as aneuploidy and structural rearrangements are widely considered the leading cause of sporadic EPL, accounting for approximately 40% to 50% of cases [4,5]. Nevertheless, nearly half of EPL cases remain unexplained after standard clinical evaluation and are classified as idiopathic. This considerable knowledge gap underscores the likely contribution of non-genetic factors to pregnancy failure and has shifted research attention toward immune dysregulation and maladaptive inflammatory responses at the maternal-fetal interface processes increasingly recognized as central mechanisms underlying the inability to sustain a viable pregnancy [6,7].

EPL is multifaceted and interwoven, encompassing genetic abnormalities (such as embryonic aneuploidy), maternal endocrine disorders (e.g., luteal phase deficiency), anatomical anomalies of the uterus, infectious factors, and increasingly recognized imbalances in immune tolerance. Among these, the disruption of immune homeostasis at the maternal-fetal interface, particularly the aberrant activation and dysregulation of the innate immune system, has emerged as a pivotal breakthrough in elucidating numerous cases of unexplained EPL. Among all the mechanisms, the excessive activation and dysregulation of the innate immune system are particularly crucial. The complement system, a central component of innate immunity, plays a dual role in pregnancy maintenance. Under physiological conditions, its tightly regulated activation is crucial for establishing maternal-fetal immune tolerance, facilitating trophoblast invasion, and supporting proper placental development. In contrast, dysregulation or excessive activation of the complement cascade disrupts this delicate balance, triggering pro-inflammatory and pro-thrombotic pathways that can lead to placental dysfunction and adverse pregnancy outcomes (APOs), such as EPL and preeclampsia [8,9]. The need for localized regulation is evident at

the molecular level: effector components of the complement system, together with endogenous regulatory proteins including CD46, CD55, and CD59 are constitutively expressed in decidual and trophoblastic cells at the maternal-fetal interface. Moreover, the expression of these molecules is modulated by cytokines such as interferon-gamma (IFN-γ), highlighting their integration into the local immune regulatory network during gestation [8]. Clinically, the pathogenic role of complement dysregulation is well established, with aberrant activation strongly associated with immune-mediated placental injury, including chronic villitis. The deposition of complement activation products such as C4d in affected placental tissue serves as an important histopathological observation, providing strong correlative evidence that complement-driven inflammation is associated with the pathological mechanisms underlying EPL [10]. However, as C4d deposition can occur in various contexts, definitive proof of a causative role requires interventional studies demonstrating that blocking complement activation improves pregnancy outcomes.

The formation of NETosis, a key innate immune effector process, may also play a dual role in pregnancy, contributing to both host defense and potential pregnancy pathology. The complement system, as an integral component of innate immunity, shares functional parallels with neutrophil extracellular traps (NETs) complex bioactive structures composed of chromatin fibers, histones, and key effector enzymes such as myeloperoxidase (MPO) and neutrophil elastase (NE). The formation of NETs, a process known as NETosis, represents a critical aspect of innate immune defense [11]. Like the complement system, NETs exhibit dual roles in both physiological and pathological contexts during pregnancy. Under homeostatic conditions, NET formation is tightly regulated in a spatiotemporally controlled manner, contributing essential functions to immune equilibrium at the maternal-fetal interface and supporting placental development [12,13]. However, dysregulation of this process characterized by excessive NET formation or impaired clearance can turn NETs into potent mediators of tissue injury. In such settings, NETs act as central platforms for immunothrombosis, a mechanism extensively documented in the pathogenesis of preeclampsia and antiphospholipid syndrome (APS)-associated pregnancy complications [14].

The central thesis of this review is to elucidate the synergistic pathological interplay between NETosis and the complement system. Together, these two pathways form a self-amplifying positive feedback loop: complement activation products serve as potent inducers of NETosis, while NETs, particularly their cationic histones, act as inflammatory scaffolds that strongly activate the complement cascade. This bidirectional interaction sustains a vicious cycle that intensifies inflammatory tissue damage and promotes thrombosis [14]. At the molecular level, complement activation product C5a serves as a canonical and potent signal for inducing NETosis in neutrophils through binding to its receptor C5aR1. Conversely, histones (e.g., H3, H4) and DNA within neutrophil extracellular traps (NETs) not only directly activate the alternative complement pathway but may also impair the function of complement regulatory proteins such as factor H via oxidative modification or proteolytic cleavage mediated by enzymes like myeloperoxidase (MPO), thereby further attenuating inhibition of the complement cascade. Moreover, whether additional mediators, such as specific inflammasome activation products or lipid mediators, play bridging roles in this crosstalk remains an open frontier for investigation. Infectious agents, such as human parvovirus B19 (B19V), can trigger this "complement-NET axis", providing a critical pathophysiological mechanism underlying adverse pregnancy outcomes, including EPL [15].

Current evidence demonstrates a close association between complement activation and NETosis in the pathogenesis of various autoimmune and thrombotic disorders, strongly supporting their pivotal role in the pathophysiology of EPL. For example, in APS, a prototypical autoimmune thrombotic disorder, dysregulated complement activation and excessive NET formation are well-established pathological hallmarks [14]. Since APS is a major contributor to adverse pregnancy outcomes, its underlying disease mechanisms provide a compelling model for exploring analogous complement-NETosis interactions in the context of EPL. In addition, oxidative stress during pregnancy may act as an upstream trigger, promoting aberrant activation of both the complement system and neutrophils, thereby amplifying local inflammatory responses, compromising placental barrier integrity, and ultimately contributing to pregnancy failure [2]. Furthermore, the regulation of the maternal-fetal microenvironment is a complex system. The regulatory effects of steroid hormones (such as progesterone) on the functions of immune cells and inflammatory pathways cannot be ignored. The potential interactive influence between it and the complement-NETosis axis is an important direction that needs to be explored in the future. Progesterone, a pivotal hormone for maintaining gestation, exerts potent anti-inflammatory and immunomodulatory effects through the widespread expression of its receptors on immune cells. Studies indicate that progesterone downregulates the production of pro-inflammatory cytokines and may indirectly influence complement activity and neutrophil reactivity [16]. Investigating whether and how progesterone and its derivatives, such as dydrogesterone, modulate the "complement–NETosis axis" is essential for elucidating the mechanistic basis of hormonal therapy in miscarriage prevention and for developing combined immunomodulatory strategies. This represents a critical research direction bridging endocrine regulation and innate immune dysregulation.

In light of these findings, this review systematically examines the intricate crosstalk between complement acti-

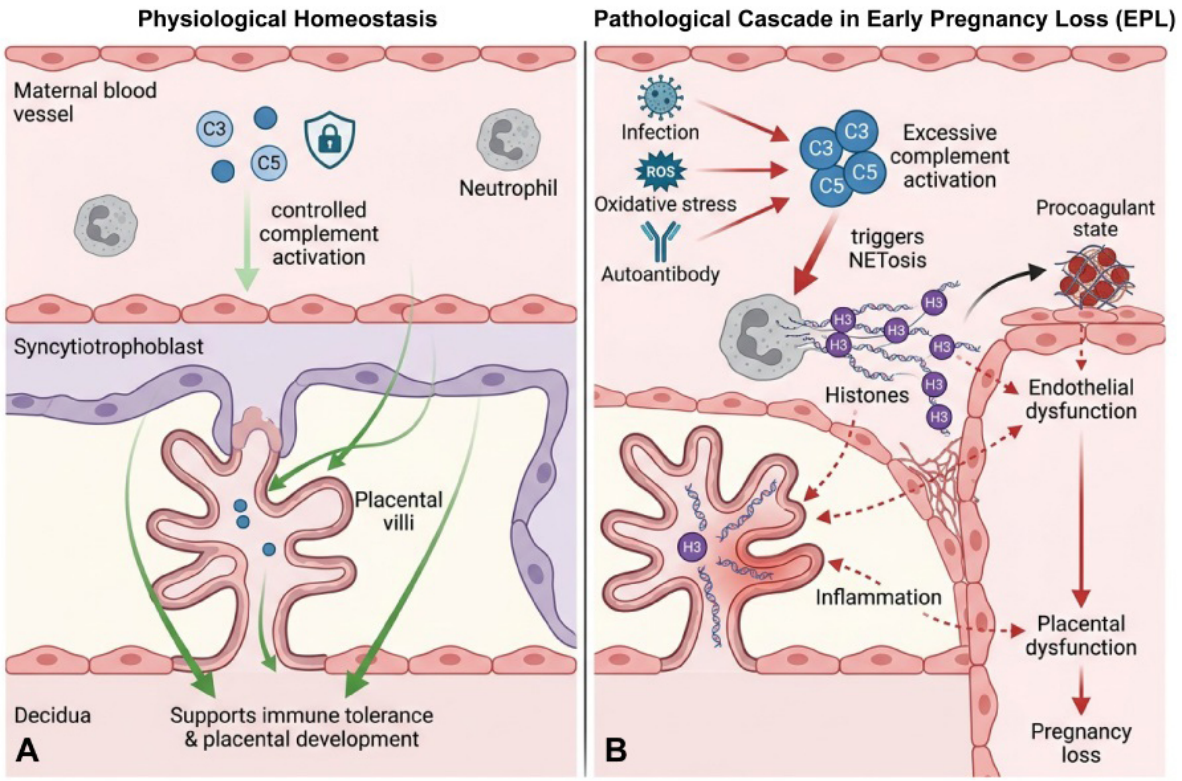

Fig. 1. Proposed schematic model of immune homeostasis and dysregulation at the maternal-fetal interface in early pregnancy. (A) Physiological immune homeostasis (left panel): Under normal conditions, tightly regulated complement activation supports placental development, immune tolerance, and pregnancy viability. (B) Proposed pathological cascade in EPL (right panel): Various triggers (e.g., infection, oxidative stress, autoantibodies) may induce excessive complement activation, which promotes NET formation. NETs can release histones and other components, potentially fueling inflammation, endothelial dysfunction, and a procoagulant state. This cascade is hypothesized to contribute to placental dysfunction and pregnancy loss. This model illustrates the complement-NETosis axis as a central, yet likely context-dependent, pathogenic driver. Its relevance and predominance may vary across the heterogeneous etiologies of EPL, and it may coexist with other pathological mechanisms. EPL, Early Pregnancy Loss; NET, neutrophil extracellular trap; NETosis, neutrophil extracellular trap formation. Created in BioRender. Ma, J. (2026) https://BioRender.com/5zdpgyh.

vation and NETosis in EPL, aiming to clarify their specific roles in autoimmune and thrombotic pathways. This analysis is expected to provide novel theoretical insights for early diagnosis, risk stratification, and the development of innovative therapeutic interventions for EPL.

EPL remains a clinical challenge, characterized by complex etiology and highly interconnected pathogenic mechanisms involving dysregulation across multiple pathways, including genetic, immune, and inflammatory components. The complement system and NETosis, as key elements of innate immunity, play essential roles both in maintaining immune homeostasis during pregnancy and in driving pathological processes. This review emphasizes the reciprocal interaction between complement activation and NETosis, which may represent a critical pathogenic mechanism underlying the onset and progression of EPL, particularly in pregnancies complicated by autoimmune and thrombotic abnormalities. Therefore, a detailed investigation of the specific roles of complement activation and NETosis in EPL not only enhances our understanding of its multifactorial pathogenesis but also holds promise for identifying novel biomarkers and therapeutic targets, thereby facilitating clinical translation and advancing practical innovations in this field. A proposed model integrating this complement-NETosis axis within the maternal-fetal interface is summarized in Fig. 1.

2. Mechanism of Complement Activation in Early Pregnancy Loss

2.1 Complement System at the Maternal-Fetal Interface: A Critical Initiator of Early Pregnancy Loss

The complement system, a central effector mechanism of innate immunity, comprises three primary activation pathways: classical, alternative, and lectin. These pathways converge to generate potent inflammatory mediators (anaphylatoxins C3a and C5a), opsonins (C3b), and the membrane attack complex (MAC, C5b-9), which together enable precise immune surveillance and facilitate tissue remodeling. During early pregnancy, complement activity is tightly regulated in a spatiotemporal manner at

the maternal-fetal interface. Trophoblast cells express high levels of complement regulatory proteins, including CD46, CD55, and CD59, forming a critical protective barrier. This regulatory network ensures that complement activation is restricted to essential physiological functions, such as clearing apoptotic debris and promoting trophoblast invasion, thereby maintaining local immune homeostasis [8].

However, this homeostatic state is highly vulnerable to disruption. When the complement system becomes dysregulated and hyperactivated, its destructive potential is unleashed, triggering intense local inflammatory responses, vascular endothelial injury, and thromboinflammatory pathological processes that directly compromise placental vascularization and function [9]. To date, most direct evidence implicating excessive complement activation in tissue injury derives from studies in non-pregnant populations, particularly in autoimmune diseases (e.g., systemic lupus erythematosus, antiphospholipid syndrome) and thrombotic microangiopathies (e.g., atypical hemolytic uremic syndrome) [14]. Critically, the pathogenic potential of complement dysregulation is not merely theoretical in the context of pregnancy. Compelling evidence from the obstetric complication preeclampsia demonstrates that excessive complement activation, driven by placental stress and systemic inflammation, is a key mediator of endothelial dysfunction, angiogenic imbalance, and the characteristic multi-organ injury [17]. It is important to note that preeclampsia is a multifactorial disorder, also involving mechanisms such as aberrant placental implantation, oxidative stress, and dysregulated adaptive immunity. Nevertheless, the evidence in PE provides a salient example of how complement activation can be a significant pathogenic component within the complex landscape of pregnancy-related diseases.

It is reasonable to extend these mechanisms to the pathological framework of EPL. Clinical evidence has firmly established links between dysregulation of specific complement pathways and EPL. For example, inherited deficiencies in mannose-binding lectin (MBL), a key component of the lectin pathway, have been shown to significantly increase the risk of recurrent pregnancy loss (RPL). The proposed mechanism suggests that MBL insufficiency may impair placental angiogenesis and disrupt maternal-fetal immune tolerance [18,19]. Thus, the complement system functions not merely as a passive immune defense mechanism, but as an active and potent regulator of the maternal-fetal microenvironment. Its dysregulation represents a critical initiating pathological event capable of triggering inflammatory and thrombotic cascades that culminate in early pregnancy loss [20,21].

2.2 Dysregulated Complement Activation and Autoimmune Responses

Abnormal activation of the complement system represents a central pathological mechanism through which circulating autoantibodies mediate localized tissue damage in autoimmune diseases. In prototypical conditions such as systemic lupus erythematosus (SLE), persistent complement activation triggered by circulating immune complexes leads to systemic complement consumption (hypocomplementemia), a well-established gold-standard biomarker for monitoring disease activity [22,23,24]. This pathological damage is primarily mediated by the potent anaphylatoxins C3a and C5a generated during the complement cascade. As key inflammatory mediators, these molecules not only recruit and activate effector cells, such as neutrophils and monocytes, but also induce NETosis, thereby establishing a self-amplifying positive feedback loop that perpetuates inflammation and thrombosis, ultimately exacerbating tissue injury [25,26,27,28].

This destructive mechanism has been directly demonstrated in the pathophysiology of certain forms of EPL [14]. In patients with unexplained EPL, significantly elevated levels of complement activation products have been consistently observed, indicating a strong association between complement dysregulation and pregnancy failure [14]. It is crucial to note that this association does not, by itself, establish causation. APS-associated recurrent miscarriage provides a well-documented clinical proof-of-concept: antiphospholipid antibodies bind to target antigens and activate the complement system, triggering endothelial injury, immunothrombosis, and inflammatory cascades at the maternal-fetal interface, ultimately resulting in pregnancy loss [29,30]. Thus, the complement system serves not only as a biomarker of autoimmunity but also as a central pathological effector in this autoimmune-related subset of EPL. The extent to which this mechanism extends to other, non-autoimmune forms of EPL remains an active area of investigation.

2.3 Complement System: The Central Driver of Immunothrombosis

The crosstalk between the complement and coagulation systems plays a central role in the pathophysiology of thromboinflammation. Complement activation is not merely a downstream consequence of immune activation but serves as a critical upstream trigger for thrombus formation. Its prothrombotic effect is primarily mediated through a “dual-hit” mechanism initiated by the terminal pathway. First, the membrane attack complex (MAC, C5b-9) assembles on vascular endothelial cells, causing sublethal or lethal injury that exposes procoagulant substrates and induces cellular activation [31,32]. Second, the potent anaphylatoxin C5a, upon binding to its receptor, activates platelets and endothelial cells and recruits neutrophils, collectively fostering a highly prothrombotic microenvironment [25,33].

The pathogenic role of this mechanism is well established in two classical disorders: paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic

syndrome (aHUS). In both conditions, dysregulated complement activation serves as the primary driver of life-threatening systemic thrombotic complications [34,35,36]. Applying this "immune thrombosis" paradigm to EPL research is of great significance. In the context of EPL, this systemic pathogenic mechanism manifests locally at the maternal-fetal interface as placental thrombotic microangiopathy, a key pathological feature underlying placental insufficiency [18,37]. Notably, the marked therapeutic efficacy of C5-targeted inhibitors, such as eculizumab, in these diseases has not only significantly reduced the incidence of thrombotic events but also provided compelling pharmacological evidence that the terminal complement pathway plays a central role in thrombogenesis. This evidence strongly supports targeting the complement system as a pivotal therapeutic strategy for preventing EPL-associated thrombotic complications [26,38].

2.4 Complement Activation in EPL: Clinical Evidence and Translational Implications

The bidirectional interplay between the complement system and NETosis plays a central pathological role in autoimmune-associated EPL. Autoimmune disorders, such as SLE, anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV), and APS, are characterized by dysregulated complement activation and enhanced NET formation, also known as NETosis. These immune abnormalities significantly increase the risk of adverse pregnancy outcomes, including EPL [22,39,40]. Evidence suggests that the complement-NETosis axis contributes to vascular inflammation, promotes immunothrombosis, and disrupts placental microcirculation. This leads to impaired embryonic perfusion and ischemic necrosis, representing a key pathogenic mechanism in EPL [18,41].

Clinical studies have reported that serum levels of key complement components, including C3, C5, and the terminal membrane attack complex (C5b-9), are elevated in some patients with EPL. At the same time, markers of NETosis, such as myeloperoxidase-DNA (MPO-DNA) complexes and circulating histone levels, have also been observed to be increased in EPL cohorts [42,43]. It is important to note that references 42 and 43 primarily describe complement and NETosis alterations in conditions such as COVID-19 and IgA vasculitis. Their citation here serves to illustrate the established pathophysiological link between complement activation and NETosis, thereby supporting the biological plausibility of investigating this axis in EPL. These parallel observations indicate that the complement-NETosis axis may represent a promising pathogenic mechanism and biomarker candidate in EPL, particularly in specific subtypes such as those with an autoimmune or hyperinflammatory phenotype. Moreover, studies in other disease contexts have shown that aberrant activation of the complement receptor C5aR1 and its downstream signaling pathways, particularly the MAPK and ERK cascades, is a potent driver of NETosis. This suggests the potential of targeting complement-mediated signaling to regulate NET formation in relevant patient subgroups [44].

3. Pathological Role of NETosis in Early Pregnancy Loss

3.1 Biological Characteristics and Induction Mechanisms of NETosis

NETosis represents a distinct form of immune defense in which neutrophils release web-like structures composed of decondensed chromatin and granular proteins, known as NETs, to capture and eliminate pathogens. This process involves the decondensation and disintegration of nuclear chromatin, along with the coordinated release of granular enzymes such as MPO and elastase. These components act together to immobilize and neutralize pathogens effectively, limiting microbial dissemination [45].

NET formation can be triggered by a wide range of physiological and pathological stimuli, including bacterial toxins, viral components, inflammatory mediators, and complement activation products. For example, complement-derived anaphylatoxins can directly induce NETosis through interactions with specific surface receptors on neutrophils [46,47]. While NETs play a crucial role in host defense against infection, excessive or dysregulated NET formation, as well as impaired clearance, can cause collateral tissue damage and amplify inflammatory responses, illustrating their dual functional nature [48]. Physiological NETosis supports pathogen clearance and the maintenance of immune homeostasis. In contrast, pathological NETosis may promote autoimmune activation by persistent exposure to self-antigens and stimulation of autoreactive immune pathways [46].

A comprehensive understanding of the mechanisms that induce NETosis, its biological characteristics, and its regulatory pathways is therefore critically important under both physiological and pathological conditions. This knowledge is essential for elucidating the immunopathological mechanisms underlying early pregnancy loss and for guiding the development of novel clinical interventions.

3.2 Association Between NETosis and Autoimmunity

By exposing self-antigens, neutrophil extracellular traps (NETs) play a key role in the pathogenesis of autoimmune diseases such as systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) [42]. In APS, NETosis has been identified as a central pathological nexus linking antiphospholipid antibodies, complement activation, and thrombosis [14]. This mechanism is directly relevant to the pathological process of autoimmune early pregnancy loss (EPL). Given that APS is a well-established cause of pregnancy loss, NETosis strongly implicated as a critical effector in the placental inflammation and thrombosis characteristic of APS-related obstetric complications [14]. Furthermore, dysregulation of NETosis is a well-documented

feature of SLE. Given that SLE disease activity is a known risk factor for adverse pregnancy outcomes, it is plausible to hypothesize that aberrant NETosis may serve as a contributing mechanism to pregnancy complications in affected patients, although direct evidence in obstetric cohorts remains to be fully elucidated. Therefore, although research on NETosis in "idiopathic" EPL is still in its early stages, the study of pregnancy-complicated autoimmune diseases such as APS provides compelling indirect evidence and a valuable pathogenic model for understanding how NETosis may contribute to maternal-fetal immune dysregulation and pregnancy failure.

3.3 Mechanisms of NETosis in Promoting Thrombosis

NETs promote thrombosis by providing a unique structural scaffold that facilitates the adhesion and aggregation of platelets, erythrocytes, and coagulation factors. The DNA and histones abundantly present in NETs serve as critical platforms for platelet adhesion and activation, thereby enhancing platelet aggregatory capacity [49]. In addition, histones and proteolytic enzymes within NETs can directly damage vascular endothelial cells, leading to endothelial dysfunction and activation. This process induces a procoagulant phenotype on the endothelial surface, markedly increasing susceptibility to thrombosis [50].

NETosis exhibits a strong synergistic interaction with complement system activation, forming a self-amplifying positive feedback loop between inflammation and coagulation that substantially elevates thrombotic risk. For example, in pathological conditions such as APS and vaccine-induced immune thrombotic thrombocytopenia (VITT), the interplay between NETosis and complement activation has been shown to significantly promote thrombus formation and contribute to severe clinical complications, including adverse pregnancy outcomes [39,51]. Emerging evidence also indicates that interactions between JAK2V617F-mutated platelets and neutrophils enhance NETosis, accelerating thrombogenesis. Notably, antiplatelet agents such as aspirin can partially suppress this process [52], suggesting that modulation of NETosis may represent a viable therapeutic strategy to reduce thrombotic risk.

Moreover, NETs contribute to a prothrombotic microenvironment by inducing localized oxidative stress and inflammatory responses [53]. These prothrombotic and tissue-damaging properties of NETs, which have been well-documented in non-obstetric contexts such as deep vein thrombosis and sepsis, can be extrapolated to the unique physiology of pregnancy. The placental bed is a site of inherent hypercoagulability [54], and it is plausible that NET-driven processes may compromise hemodynamic stability and placental function [55], thereby potentially increasing the risk of early pregnancy loss [53,54,55].

In summary, NETosis drives thrombosis through multifaceted mechanisms involving structural, cellular, and synergistic interactions with the complement system. While these mechanisms are established in systemic thrombotic disorders, their operation within the unique maternal-fetal interface during early pregnancy is of paramount importance. The critical question thus becomes: how does NETosis, particularly in concert with complement activation, translate into the specific pathological endpoint of early pregnancy loss (EPL)? The following section examines the clinical and pathological evidence linking this axis directly to EPL.

3.4 Clinical Evidence and Pathological Correlations of NETosis in EPL

At the maternal-fetal interface, the synergy between NETosis and complement activation potently amplifies the physiological hypercoagulable state of pregnancy. NET-derived components (e.g., DNA, histones, granular enzymes) not only promote platelet aggregation but also activate coagulation factors and the complement cascade, forging an integrated immune-coagulation network [14,33]. Sustained complement activation, in turn, intensifies coagulation, driving fibrin deposition and placental microvascular occlusion. This process of placental immunothrombosis leads to hypoperfusion, tissue hypoxia, and, ultimately, embryonic demise or developmental compromise [14].

Clinical evidence directly supports the relevance of this axis in EPL. Studies report elevated levels of NETosis biomarkers (e.g., MPO-DNA complexes, circulating histones) in the circulation of women experiencing EPL [42,43]. In autoimmune-associated EPL, such as in APS, the complement-NETosis axis is considered a central effector of placental vascular injury and thrombosis [14,39].

Given this mechanistic and clinical foundation, therapeutic strategies targeting the complement-NETosis feedback loop have garnered significant interest. Preclinical and early clinical explorations involve complement inhibitors (e.g., C5aR1 antagonists) combined with NETosis-targeted agents (e.g., PAD4 inhibitors, recombinant DNase I), aiming to break the cycle of inflammation and coagulation to improve pregnancy outcomes [42,43].

In conclusion, NETosis, especially through its interplay with complement, plays a pivotal role in the pathogenesis of EPL, particularly in autoimmune contexts. Its dysregulation drives placental immunothrombosis and dysfunction. Dynamic monitoring of NETosis-related biomarkers holds promise for risk stratification, and targeting this axis offers a novel therapeutic avenue for preventing pregnancy loss [22].

4. Interplay Between Complement Activation and NETosis and Their Combined Impact on Early Pregnancy Loss

The preceding sections have detailed the independent roles of complement activation (Section 2) and NETosis (Section 3) in the pathogenesis of EPL. Critically, these pathways do not operate in isolation but engage in a syner-

Table 1. Evidence linking complement activation and NETosis to early pregnancy loss across different etiologies.

Disease/background	Evidence for complement activation	Evidence of NETosis	Strength of evidence & nature of link	Proposed association with EPL and potential mechanisms
Antiphospholipid Syndrome (APS)	Decreased serum C3/C4; placental C4d deposition; aPL antibodies activate complement via β_2GPI.	Elevated plasma NET markers (e.g., MPO-DNA); aPL-sensitized neutrophils exhibit enhanced NETosis.	Strong/Established Mechanism	Well-established association. aPL-induced complement activation and NETosis synergistically promote immunothrombosis and placental infarction, representing a key pathogenic pathway in this defined autoimmune subset.
Systemic Lupus Erythematosus (SLE)	Hypocomplementemia correlates with disease activity; immune complex deposition activates the classical pathway.	Elevated NET levels with impaired clearance; NETs expose autoantigens (e.g., LL-37, DNA).	Strong Clinical Association/Plausible Mechanistic Contribution	Well-documented clinical association. The complement-NETosis axis is hypothesized to exacerbate local injury and disrupt immune tolerance at the maternal-fetal interface, contributing to the elevated EPL risk in active SLE.
Preeclampsia (PE)	Elevated complement activation products (e.g., C5a); complement deposition in placental tissue.	Increased NET markers in maternal circulation and placenta; NETs impair spiral artery remodeling.	Strong/Central Pathogenic Mechanism	Strong association. Complement and NETosis are considered central drivers of placental ischemia, endothelial dysfunction, and systemic inflammation, which can lead to secondary pregnancy loss.
Infection (e.g., Parvovirus B19)	Pathogen components activate the lectin or alternative complement pathways.	Many pathogens are potent inducers of NETosis.	Hypothetical/Potential Trigger	A plausible trigger. Infection may ignite the complement-NETosis axis, disrupt fetal-maternal tolerance, and precipitate an inflammatory cascade that could result in pregnancy loss, illustrating one potential pathway among many.
Idiopathic Recurrent Pregnancy Loss (RPL)	Elevated serum C5a in some cohorts; polymorphisms in complement genes (e.g., mannose-binding lectin deficiency).	Abnormal NETs levels detected in endometrial tissue or blood in subsets of patients.	Emerging/Speculative Hypothesis	An emerging research focus. Dysregulation of this axis is proposed as a potential mechanism underlying a proportion of "unexplained" cases, highlighting the mechanistic heterogeneity of EPL.

This table summarizes available evidence, which varies from established pathogenic pathways (e.g., in APS) to more speculative hypotheses (e.g., in idiopathic RPL). This underscores that EPL is a heterogeneous syndrome where the relevance of the complement-NETosis axis, among other mechanisms, depends on the specific etiological context.

gistic interplay that can disrupt the delicate immune homeostasis at the maternal-fetal interface. As illustrated in Fig. 1, under physiological conditions, a tightly regulated balance supports pregnancy, whereas in EPL, various triggers may initiate a vicious cycle involving excessive complement activation and NET formation, leading to inflammation, thrombosis, and placental failure. The following sections delve into the molecular mechanics of this proposed cascade (4.1, 4.2) and the evidence supporting it across different clinical contexts.

4.1 Molecular Mechanisms of Complement Activation-Induced NETosis

The pathological roles of complement and NETosis, detailed separately in preceding sections, converge in a synergistic interplay across various etiologies of EPL. As summarized in Table 1, the evidence supporting this axis exists on a spectrum—from well-established mechanistic links in defined conditions like antiphospholipid syndrome (APS), to more hypothetical associations in idiopathic cases. This spectrum underscores the heterogeneous nature of EPL, wherein the complement-NETosis pathway may represent one operative mechanism among others, depending on the underlying disease context (Table 1).

As a central component of innate immunity, the complement system generates bioactive cleavage products that recruit and activate neutrophils, thereby inducing the formation of NETs, a process known as NETosis. Specifically, the complement-derived anaphylatoxin C5a binds to its receptor C5aR1, triggering neutrophil activation and promoting NET release. Studies have shown that C5aR1 activation upregulates key NETosis-associated proteins in neutrophils, including NE, citrullinated histone H3 (CitH3), peptidylarginine deiminase 4 (PAD4), and MPO. The C5aR1 signaling pathway also regulates NET formation through the Rap1a/B-Raf/ERK cascade. In addition, direct membrane injury caused by the membrane attack complex (MAC, C5b-9) on neutrophils can induce NETosis. MAC insertion triggers rapid intracellular calcium influx, which promotes histone H3 citrullination a critical initiating event in NET formation [56]. Concurrently, reactive oxygen species (ROS) serve as key downstream effectors in complement-mediated NETosis. Complement activation therefore initiates a sequential cascade: calcium influx and histone citrullination, followed by NADPH oxidase activation and ROS generation, ultimately leading to NET release [57]. Collectively, these mechanisms form a coordinated molecular network through which complement activation drives NET formation, elucidating the mechanistic link between complement signaling and neutrophil functional responses.

Under various pathological conditions, such as severe infections and autoimmune diseases, complement-mediated NETosis is generally upregulated. Studies in patients with severe COVID-19 have shown that elevated levels of the complement cleavage product C5a and the membrane attack complex C5b-9 are significantly and positively correlated with circulating MPO-DNA complexes, a well-established marker of NETosis. These findings indicate that complement activation substantially contributes to immune-inflammatory responses by inducing NETosis [42,57]. Furthermore, the complement component C1q has been shown to induce NET formation in LPS-preactivated neutrophils. This process involves a transcription-dependent mechanism and requires the cooperative engagement of the scavenger receptor SCARF1 and complement receptor 3 (CR3) [58]. Collectively, these observations suggest that complement-derived mediators activate neutrophils through specific cell surface receptors and intracellular signaling pathways. This activation results in ROS production and alterations in calcium signaling, which in turn promote NETosis.

In summary, the molecular mechanism by which complement activation induces NETosis is multifaceted, involving multiple interdependent pathways and synergistic events. Key components include C5a-mediated neutrophil activation via C5aR1, MAC-induced plasma membrane disruption and calcium influx, histone H3 citrullination, and NADPH oxidase-dependent ROS generation. These signaling cascades act in concert to drive NET release, establishing a critical pathophysiological basis for inflammatory and immune dysregulation. In the context of EPL, particularly in autoimmune-associated subsets such as antiphospholipid syndrome (APS), complement activation-induced NETosis has been implicated in impairing embryo implantation and compromising pregnancy maintenance by mediating local inflammation and aberrant immune activation, representing a pivotal molecular event in APS-related pregnancy pathology [29]. The contribution of this axis to the pathogenesis of non-APS or idiopathic EPL warrants further investigation.

4.2 Mechanisms by Which NETosis Potentiates Complement System Activation

NETs are complex, web-like structures composed of nuclear components, including DNA and histones, as well as various cytoplasmic proteins. Upon release, surface-exposed nucleic acids and histones, which carry charged molecular motifs, can directly trigger complement system activation. Studies have shown that histones and DNA on NETs activate both the classical and alternative complement pathways, leading to the cleavage and deposition of key complement components, including C3 and C5 [29]. This NET-mediated complement activation extends beyond initial cascade events and further promotes assembly of the membrane attack complex (MAC, C5b-9), significantly amplifying local inflammatory responses and tissue damage.

The bidirectional interplay between NET-driven complement activation and complement-induced NETosis establishes a self-reinforcing positive feedback loop that in-

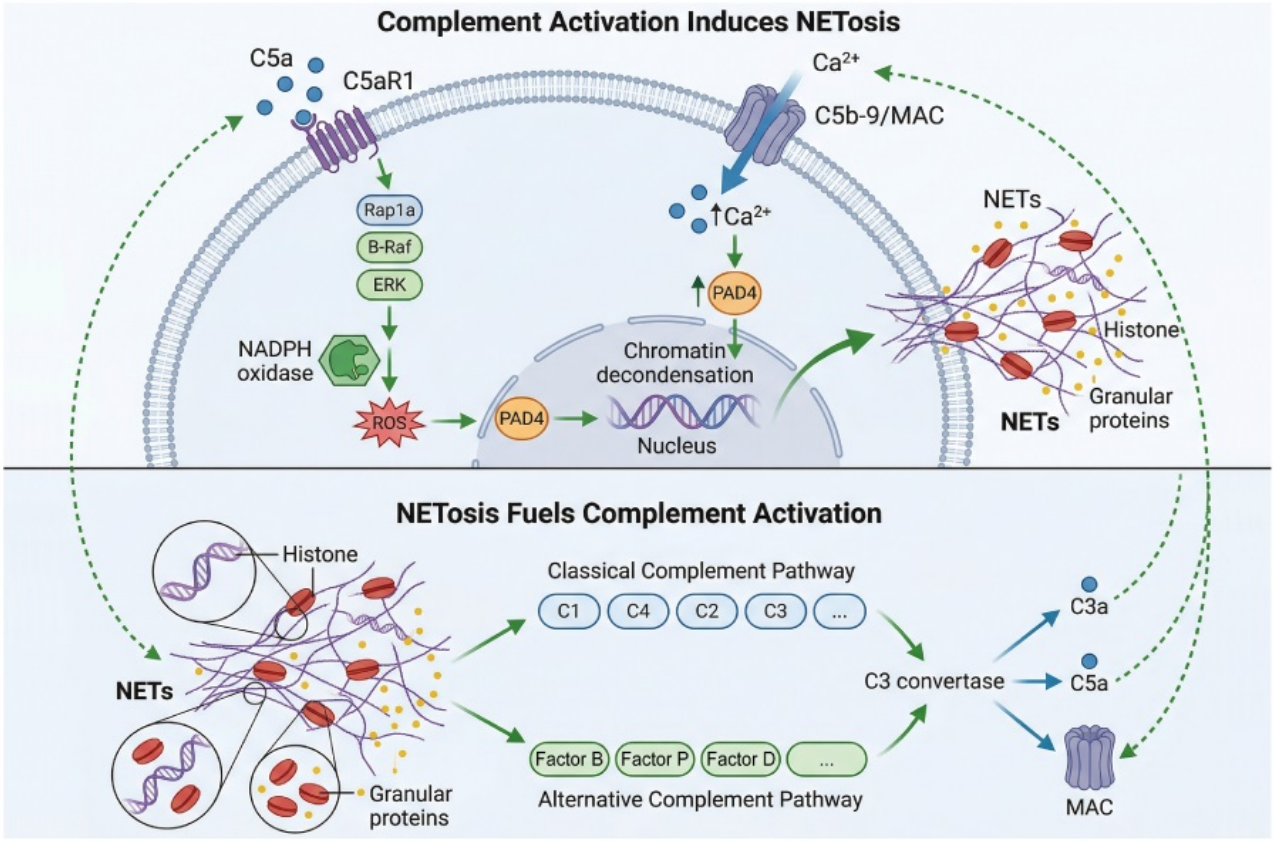

Fig. 2. Proposed molecular model of the self-amplifying feedback loop between complement activation and NETosis in early pregnancy loss (EPL). This schematic integrates key molecular interactions. Complement activation products (e.g., C5a, MAC) induce NETosis via specific receptors (e.g., C5aR1) and downstream signaling (upper). In turn, released NET components (e.g., histones, DNA) can activate the classical and alternative complement pathways, generating more effector proteins (lower). This creates a vicious cycle that may drive inflammation, immunothrombosis, and tissue damage at the maternal-fetal interface. It is critical to note that the *in vivo* relevance and dominance of this loop likely vary across the heterogeneous etiologies of EPL (as summarized in Table 1), and its role in idiopathic cases remains a testable hypothesis. Note: The *in vivo* significance and relative contribution of this proposed loop across different EPL subtypes require further experimental validation. Created in BioRender. Ma, J. (2026) https://BioRender.com/382paup.

tensifies immune-inflammatory responses. For example, in autoimmune conditions such as APS, aberrant NET formation not only directly triggers complement activation but is also amplified by activated complement products. This creates a sustained pathological cycle that exacerbates vascular endothelial injury and thrombosis [14,39]. Complement regulatory proteins, such as platelet-derived thrombospondin-1 (TSP-1), can inhibit alternative pathway activation, highlighting the complexity of NET-complement crosstalk and its key role in maintaining immune homeostasis [59].

In the context of EPL, the reciprocal interaction between NETs and the complement system can severely disrupt the local immune microenvironment, causing tissue damage. NET-triggered complement activation initiates a cascade of pathological events, including vascular endothelial injury, microthrombosis, and localized inflammation, which collectively compromise the maternal-fetal interface and impair embryonic development and implantation [18]. Additionally, NET components such as histones exhibit intrinsic cytotoxicity toward endothelial cells. This cytotoxicity acts synergistically with complement-mediated injury, further amplifying inflammation in the endometrium and placenta [43]. Consequently, the self-amplifying positive feedback loop between NETs and complement activation proposed as a pivotal pathological mechanism driving the onset and progression of EPL, as integrated in the molecular model shown in Fig. 2.

It is particularly worth emphasizing that autoimmune pregnancy loss represented by APS provides the most direct human disease model and supporting evidence for the formation of a vicious cycle between NETosis and the complement system in EPL [14]. Therefore, this self-amplifying positive feedback loop is considered a key pathological mechanism in APS-related pregnancy loss. As illustrated in Fig. 2, this loop represents a compelling, yet context-dependent, pathological hypothesis for EPL more broadly. While strongly supported by direct evidence in defined con-

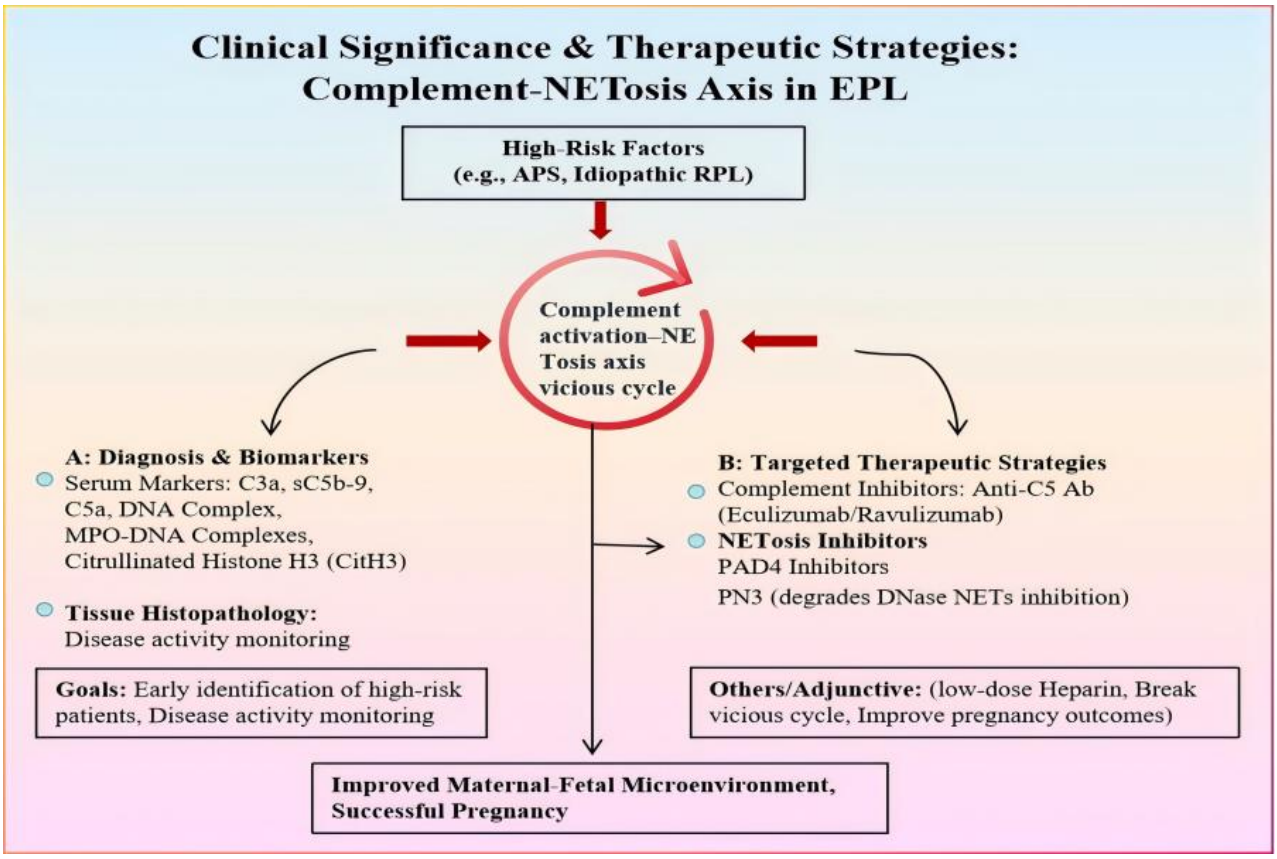

Fig. 3. Proposed clinical implications and therapeutic strategies targeting the complement-NETosis axis in early pregnancy loss (EPL). This schematic illustrates the potential central role of the complement-NETosis cycle in EPL pathology and outlines corresponding prospective diagnostic and therapeutic approaches. In high-risk settings (e.g., APS), this axis may serve as a key target for clinical intervention. (A) Diagnostic and prognostic biomarkers. Over-activation of this axis generates biomarkers with potential diagnostic value, including serum complement activation products (C3a, C5a), NETosis markers (MPO-DNA, CitH3), and tissue evidence of complement deposition and NET formation. (B) Targeted therapeutic strategies. Interventions aim to disrupt the vicious cycle. These include complement inhibitors (e.g., anti-C5 monoclonal antibodies), NETosis inhibitors (e.g., PAD4 inhibitors, recombinant DNase), and adjunctive therapies like heparin. Many of these agents, while mechanistically compelling, remain in preclinical or early clinical investigation for EPL. Their application would likely be tailored to specific patient subgroups (e.g., those with evidence of axis activation), reflecting the mechanistic heterogeneity of EPL.

ditions like APS (see Table 1), its operation and relative contribution in other EPL contexts, particularly idiopathic recurrent pregnancy loss, remain to be directly confirmed in relevant experimental models of pregnancy. Future research should aim to dissect the presence and weight of this loop among other coexisting mechanisms across different patient subgroups, which is essential for understanding the mechanistic heterogeneity of EPL.

5. Conclusion

These integrated diagnostic and therapeutic approaches ultimately improve the maternal-fetal microenvironment and support successful pregnancy outcomes.

EPL, as a highly heterogeneous and etiologically complex obstetric complication, requires a comprehensive understanding of its underlying pathophysiological mechanisms to inform and optimize clinical management. This review focuses on two pivotal immune processes complement system activation and NETosis and systematically analyzes their intricate interplay in the pathogenesis of EPL, including the mechanisms by which they jointly drive autoimmune dysregulation and thrombosis. This integrated perspective not only deepens our understanding of the immunopathological basis of EPL but also provides novel theoretical insights and strategic directions for future diagnostic and therapeutic interventions.

The complement system, a fundamental component of innate immunity, plays an essential role in host defense against pathogens. However, its dysregulated activation has been firmly established as a key contributor to various immune-mediated diseases. Evidence reviewed here shows that aberrant complement activation in EPL not only directly triggers localized and systemic inflammatory re-

sponses but also amplifies inflammatory cascades and promotes prothrombotic conditions through the induction of NETosis. NETosis, serving as a critical interface between innate immunity and coagulation pathways, is particularly prominent in autoimmune settings and has emerged as a central mechanism in the development of EPL. The bidirectional, self-amplifying feedback loop between complement activation and NETosis underscores the pivotal role of this molecular axis in both maintaining and disrupting immune homeostasis during pregnancy.

However, the specific molecular mechanisms underlying the interplay between the complement system and NETosis remain incompletely understood and require further investigation. Some studies emphasize the direct role of the complement cleavage product C5a in neutrophil activation, highlighting the therapeutic potential of complement inhibitors in modulating NETs and NETosis. In contrast, other evidence suggests that NETosis is a multifactorial process regulated by a complex network of cytokines and microenvironmental signals, implying that single-target interventions may have limited clinical efficacy. These divergent findings underscore the need for future basic research and clinical trials to adopt integrated, multi-target, and multi-pathway strategies to achieve more precise and effective therapeutic outcomes.

From a clinical translation perspective, both the complement system and NETosis serve not only as central drivers in the pathophysiology of EPL but also as promising diagnostic biomarkers and therapeutic targets. Dynamic monitoring of serum complement components, including C3, C5, and C5b-9, along with NETosis-related markers such as MPO-DNA complexes and circulating histones, may enable the early and accurate identification of high-risk pregnant individuals. This, in turn, facilitates the development of personalized intervention strategies. At the same time, the advancement of therapeutics targeting complement inhibition, for example, anti-C5 monoclonal antibodies, and NETosis modulation offers promising avenues for novel treatment options in EPL. These approaches have the potential to significantly improve pregnancy outcomes and reduce the incidence of adverse obstetric complications.

As summarized in Fig. 3, this proposed complement-NETosis axis not only provides a framework for understanding disease heterogeneity but also unveils specific avenues for clinical translation. Targeting this axis encompasses both the identification of high-risk patients through biomarker profiling and the application of mechanistically-informed therapeutic strategies.

In summary, the synergistic interaction between complement activation and NETosis in EPL pathogenesis not only deepens our understanding of reproductive immunopathology but also opens a new frontier in immunomodulatory therapy. Future research should focus on comprehensively elucidating the regulatory network within the complement-NETosis axis, integrating analyses of clinical patient samples with multidimensional animal models to advance mechanistic insights and accelerate therapeutic innovation. Furthermore, fostering interdisciplinary collaboration will enhance integration across immunology, reproductive medicine, and pharmacology, help reconcile conflicting perspectives, and promote the seamless translation of fundamental discoveries into clinical practice. As visually summarized in the Graphical Abstract, we propose that a self-amplifying 'Complement-NETosis Axis' may be a key, albeit context-dependent, driver of immune dysregulation and tissue injury at the maternal-fetal interface in a subset of EPL cases, offering a unifying framework for future research and therapeutic innovation. Through such comprehensive exploration and sustained scientific effort, we anticipate the achievement of precise prevention and effective management of early pregnancy loss, ultimately improving outcomes for a broad population of patients.

Author Contributions

Material preparation, data collection and analysis were performed by JM, KW, GL and FW. The first draft of the manuscript was written by JM and FW and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Ethical review and approval were not required in our study.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, we used AI and AI-assisted technologies (specifically, ChatGPT and simi-

lar large language models) to assist with language polishing, including spelling and grammar checks. This tool was employed solely to improve the readability and clarity of the manuscript. After using these technologies, the authors thoroughly reviewed, critically evaluated, and edited the content as necessary. The authors take full responsibility for the entire content of this publication, including all scientific interpretations, data accuracy, and conclusions presented. The use of AI-assisted technology was conducted in accordance with the ethical guidelines of our institution and the policies of this journal. It did not contribute to the generation of original scientific data, the formulation of research hypotheses, or the interpretation of results.

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