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How NETosis Shapes the Conversation Between Mother and Fetus: Impacts on Trophoblasts, the Placenta, and Healthy Pregnancy

Cómo la NETosis Moldea la Comunicación Entre la Madre y el Feto: Impactos en el Trofoblasto, la Placenta y el Embarazo Saludable

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SUMMARY: Neutrophil extracellular trap (NET) formation, or NETosis, has emerged as a pivotal factor in the maternal-fetal immune dialogue. During pregnancy, neutrophils infiltrate the decidua and placenta, where their activation must be finely balanced between defending against pathogens and preserving fetal tolerance. Excessive NETosis is increasingly implicated in pregnancy complications by injuring trophoblasts, inciting placental inflammation, and disrupting maternal vascular homeostasis. This review synthesizes clinical, molecular, and immunological evidence on key themes: the dual role of NETosis at the maternal-fetal interface, NETosis-driven placental pathology in preeclampsia and related disorders, metabolic modulation of NETosis in gestational diabetes with downstream trophoblast apoptosis, NETosis as a mediator between maternal inflammatory conditions (autoimmune disease, periodontal disease) and adverse pregnancy outcomes, and the dynamic changes in neutrophil phenotype from early gestation to the pro-NETotic state of the puerperium. We highlight how NET components (DNA, histones, proteases) provoke endothelial damage, complement activation, and thrombo-inflammation in the placenta, while also questioning how evolution may have harnessed NETs for reproductive success. Throughout, we pose unresolved questions, for example, could targeting NETosis or its upstream drivers (like IL-8, ROS, or HMGB1) ameliorate disorders such as preeclampsia without compromising host defense? By integrating insights from recent studies, including those on preeclampsia, gestational diabetes, systemic lupus erythematosus, periodontal disease, and postpartum immunity, this review aims to present a humanized yet authoritative perspective. Understanding NETosis in pregnancy may unlock novel biomarkers and therapies to promote healthier pregnancies and outcomes for both mother and child.

KEY WORDS: Neutrophil extracellular traps (NETs); Pregnancy; Trophoblasts; Placenta.

INTRODUCTION

Pregnancy requires a harmonious immune balance in which the immune system of the mother tolerates the semi-allogeneic fetus while still protecting both against infection (Rackaityte & Halkias, 2020). Neutrophils, as central effectors of innate immunity, are critical participants in this balance and undergo notable changes during gestation. Neutrophils normally help remodel uterine tissues and support placental development, yet they can also become overzealous, contributing to pathology if improperly regulated (Bert *et al*., 2021). A key weapon of neutrophils is the release of neutrophil extracellular traps (NETs), weblike DNA fibers studded with histones and granular enzymes, through a specialized cell-death program known as NETosis. Initially discovered as a pathogen-killing mechanism, NETs are now recognized to drive sterile inflammation when unchecked (Xuan *et al*., 2023; Ji *et al*., 2025).

In normal pregnancy, rising levels of circulating neutrophils and granulocyte colony-stimulating factor (G-CSF) reflect an enhanced innate immune readiness, yet these cells are phenotypically modulated to prevent excessive tissue damage to the fetus (Chaiworapongsa *et al*., 2011; Dutta *et al*., 2024). Remarkably, polymorphonuclear leukocytes have been implicated not only in crucial processes

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like implantation and spiral artery remodeling, but also in pregnancy complications when their functions are dysregulated (Hebeda *et al*., 2022). Abnormal neutrophil activation and NETosis have been reported in conditions such as recurrent fetal loss, preeclampsia, and gestational diabetes mellitus (Bert *et al*., 2021). The presence of NETs at the maternal-fetal interface is a double-edged sword: while NETs can trap microbes to prevent infection spread to the fetus, they can also incite local inflammation, damage placental cells, and even trigger thrombotic events that compromise uteroplacental circulation (Katsi *et al*., 2025).

In this review, we discuss how NETosis shapes the conversation between mother and fetus from clinical, molecular, and immunological perspectives. We focus on five thematic areas that encapsulate the role of NETosis in maternal-fetal interactions during pregnancy. By interrogating each of these areas, we aim to unravel how NETosis contributes to both physiological outcomes and pathological sequelae in pregnancy. This comprehensive view will also highlight emerging hypotheses and questions to spur future research.

MATERIAL AND METHOD

A narrative literature review was conducted to examine how NETosis shapes communication between mother and fetus, with particular attention to its impacts on the trophoblast, placenta, and overall pregnancy health. The review included original research articles, systematic reviews, and meta-analyses retrieved from multiple databases, including Web of Science, PubMed, ScienceDirect, Scopus, and Trip Database. Priority was given to the most recent publications addressing the following themes: NETosis at the maternal-fetal interface and the balance between defense and tolerance; NETosis in preeclampsia and placental dysfunction; NETosis in gestational diabetes and its association with trophoblast apoptosis; NETosis as a link between maternal inflammation, autoimmunity, and pregnancy outcomes; and finally, NETosis in the puerperium, focusing on postpartum immune changes and their implications. Examining these areas clarified how NETosis contributes to both physiological and pathological processes during pregnancy and the postpartum period. This synthesis also highlighted emerging hypotheses and research questions that are likely to guide future investigations.

The maternal-fetal interface (comprised of decidual maternal cells and fetal trophoblasts) is an immunologically unique site where neutrophils are abundant, especially in early pregnancy (Bert *et al*., 2021). Decidual neutrophils and other innate immune cells participate in implantation and placental development, aiding in tissue remodeling and immune tolerance (Hebeda *et al*., 2022). Neutrophils can secrete proteases and vascular endothelial growth factor (VEGF) to facilitate trophoblast invasion of the uterine lining (Nadkarni *et al*., 2016). At the same time, these neutrophils stand guard against invasive microbes that could endanger the fetus (Fell *et al*., 2025). NETosis represents a critical defense strategy in this context: NETs can ensnare and kill bacteria in the decidua and placenta, limiting infection spread at the maternal-fetal boundary (Gomez-Lopez *et al*., 2017). For example, in chorioamnionitis or other intrauterine infections, neutrophils releasing NETs in the amniotic fluid and fetal membranes help contain pathogens but may also contribute to collateral tissue damage and preterm labor (Fig. 1). This begs the question: how do neutrophils decide the threshold for NET release in a way that maximizes antimicrobial action while minimizing harm to fetal tissues? The answer is not fully understood, but hormonal and local signals in pregnancy likely raise this threshold to protect fetal tolerance.

Indeed, normal pregnancy appears to reprogram neutrophils towards a regulated activation state. A recent longitudinal study of healthy pregnant women showed that as gestation advances, maternal neutrophils undergo metabolic shifts (increased glucose use, lipid droplet accumulation) and gradually heighten their baseline reactive oxygen species (ROS) production and NET release capacity (Calo *et al*., 2025). Intriguingly, by term, these neutrophils also exhibit an attenuated response to additional inflammatory stimuli. In other words, pregnancy primes neutrophils for NETosis but simultaneously imposes checks to prevent an overzealous reaction (Giaglis *et al*., 2016). This controlled NETotic potential likely contributes to maternal-fetal tolerance: neutrophils may form NETs sparingly to trap microbes, yet excessive NETosis (and the accompanying inflammation) is actively restrained to avoid damaging the placenta and fetus (Abu-Raya *et al*., 2020). Key modulators in this balancing act include pregnancy hormones (e.g. progesterone, estrogen) and cytokines in the decidual microenvironment that can suppress or delay neutrophil full-scale activation (Wang *et al*., 2024a). Moreover, fetal-derived factors like placental microparticles are continuously shed into the maternal circulation; at low levels they may induce a mild neutrophil activation that is physiological, but if levels spike, they risk triggering pathological NETosis (as discussed in the next section).

Another element at play is the interaction between neutrophils and decidual natural killer (dNK) cells, the other predominant immune cell type in early pregnancy. dNK cells help orchestrate placental development and produce factors that can influence neutrophil behavior. Recent evidence from

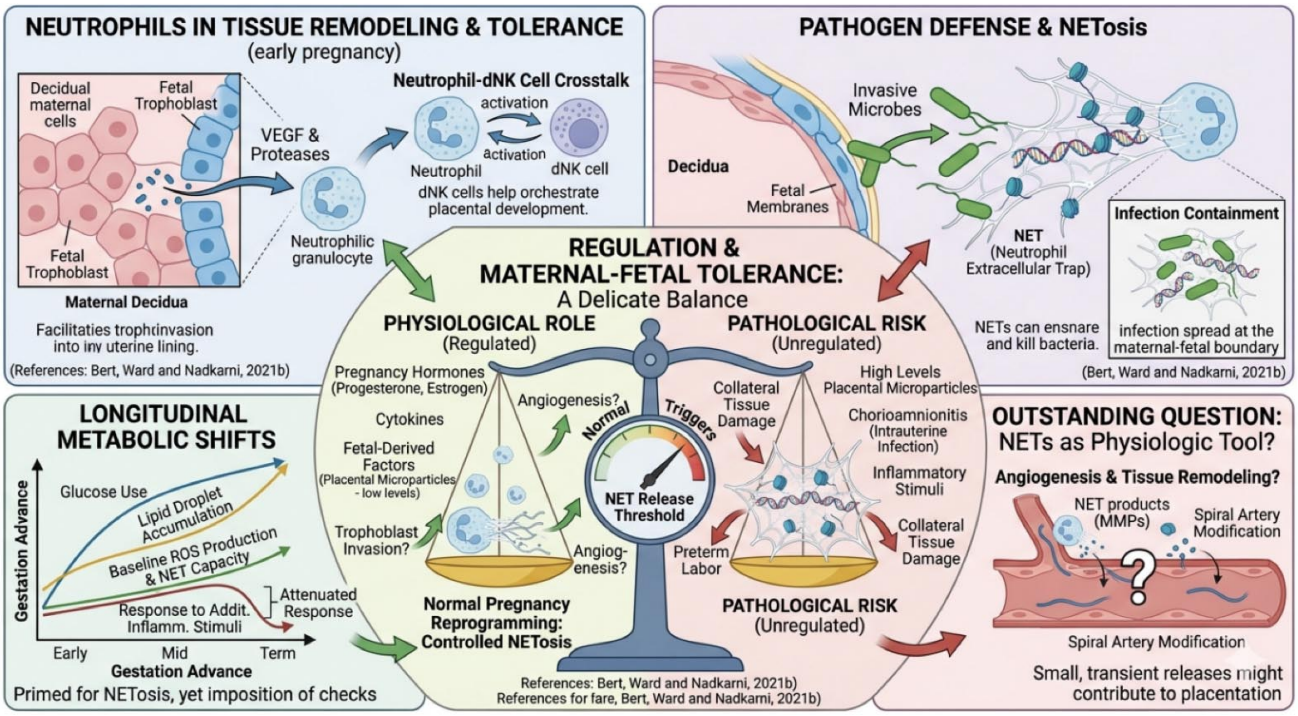


Fig. 1. NETosis in the balance between defense and tolerance at the maternal-fetal interface. Controlled NETosis contributes to maternal–fetal tolerance, tissue remodeling, angiogenesis, and placentation during normal gestation, whereas dysregulated NET formation promotes inflammation, tissue damage, infection-associated pathology, and adverse pregnancy outcomes, including preterm labor. Figure created with the assistance of artificial intelligence (AI)-based design tools.

SLE-affected pregnancies found NETs and dNK cells colocalized in the intervillous space, suggesting crosstalk: NET products might activate dNK cells or viceversa (Liu *et al*., 2023). This interplay highlights a broader concept: NETs do not act in isolation but modulate the local immune conversation. Outstanding question: Could small, transient releases of NETs by decidual neutrophils actually contribute to the normally robust angiogenesis and tissue remodeling needed for placentation? Some researchers hypothesize that NET-derived matrix metalloproteinases or other enzymes could aid trophoblast invasion and spiral artery modification in early pregnancy, turning a typically "pathological" process into a physiologic tool when tightly regulated. Unraveling such dual roles of NETosis remains a fascinating area for further study.

NETosis in Preeclampsia and Placental Dysfunction

Preeclampsia (PE) exemplifies a scenario where NETosis tips from adaptive to pathological. Clinically, PE is characterized by new-onset maternal hypertension and end-organ damage (often with proteinuria) arising after 20 weeks' gestation, rooted in placental maldevelopment and maternal endothelial dysfunction (Hahn *et al*., 2012). An excessive inflammatory response is a hallmark of PE, and neutrophils are central to this hyperinflammation. Studies have found that neutrophils from women with preeclampsia are overly primed, showing higher surface activation markers and greater propensity to undergo NETosis compared to neutrophils from uncomplicated pregnancies. In fact, the first hints that NETs contribute to pregnancy disorders came from observations in preeclamptic placentas: Gupta *et al*. (2005), noted DNA-protein lattices clogging the intervillous space of the placenta, which we now recognize as NETs. These NETs were thought to originate from neutrophils activated by placental debris such as syncytiotrophoblast microparticles (STBM) and proinflammatory cytokines like interleukin-8, which are elevated in PE. Placentally derived microdebris in the maternal circulation can directly trigger neutrophils to release NETs in a dose-dependent manner, establishing a vicious cycle: the stressed PE placenta sheds debris that activates neutrophils, which in turn deposit NETs that further damage the placenta and maternal vessels (Gupta *et al*., 2005; Hahn *et al*., 2012).

Within the placenta, NETs exert multi-faceted damage. NET fibers studded with proteases and histones can physically occlude the narrow maternal blood spaces of the placenta, exacerbating ischemia. They also cause localized oxidative stress and kill surrounding cells (Wang

et al., 2025). A recent study illuminated how NETs impair trophoblast function in PE via the alarmin high-mobility group box 1 (HMGB1) (Lu *et al*., 2025). HMGB1 was found to be significantly elevated in preeclamptic placentas and co-localized with NETs, implicating HMGB1 as a mediator of NET-induced damage. When cultured trophoblast cells were exposed to NET preparations from PE patients, their invasive and migratory capacity plummeted, and they produced excess ROS and inflammatory cytokines (IL-1β, IL-6, IL-8, TNF-α) (Lu *et al*., 2025). Strikingly, blocking HMGB1 with the inhibitor glycyrrhizin rescued the trophoblasts from NET-induced harm (Shen, 2024). This suggests NETs initiate a cascade of trophoblast cell dysfunction through HMGB1 signaling, adding a molecular piece to the PE puzzle. It raises a provocative question: Could neutralizing NET-associated HMGB1 or NETs themselves (for instance, with DNase or anti-histone therapies) ameliorate preeclampsia without compromising antimicrobial defenses? Early experimental evidence offers hope, in a placental explant model, DNase treatment reduced NET deposition and improved vascular flow, though clinical translation remains distant (Hernández González *et al*., 2024; Lu *et al*., 2025).

Beyond trophoblast injury, NETs in PE contribute to systemic endothelial damage and a pro-thrombotic state. NET components like histone H3 and neutrophil elastase are toxic to endothelial cells, causing cell death and denudation of the vessel lining. Autopsies of severe PE cases reveal NETs not only in placental vasculature but also in maternal kidneys, liver, and brain microvasculature, aligning with the multi-organ nature of the disease (Saffarzadeh *et al*., 2012; Ramos *et al*., 2024). Moreover, NETs carry tissue factor and expose phosphatidylserine, providing a scaffold for disseminated intravascular coagulation, a feared complication of severe PE (Lalic-Cosic *et al*., 2021). Mader *et al*., reported that placentas from PE patients are infiltrated with NETs entangled with platelets, and these were associated with decidual vasculitis, fibrin deposition, and microthrombi. Collectively, these findings portray NETosis as a driving force in the pathogenesis of PE: from insufficient spiral artery remodeling due to trophoblast NET-interference, to maternal hypertension and end-organ damage via endothelial toxicity and systemic inflammation (Jiang *et al*., 2021). Clinically, this is evidenced by higher circulating cell-free DNA (a proxy for NETs) in women who develop preeclampsia, often preceding symptom onset. Thus, one can hypothesize that measuring NET biomarkers might allow early identification of women at risk for PE, enabling closer monitoring or preventative interventions (Rafaeli-Yehudai *et al*., 2018).

While PE has no cure except delivery, understanding NETosis opens potential therapeutic avenues. Could targeting upstream neutrophil activators (such as blocking IL-8, NADPH oxidase, or the STBM-neutrophil interaction) reduce NET formation enough to prolong pregnancy in preeclampsia? Small studies suggest antioxidants that reduce neutrophil ROS can decrease NET release, hinting that therapies like N-acetylcysteine or even statins (which have anti-NET effects) might be repurposed in the future (Guillotin *et al*., 2023; Karadzov Orlic & Joksic, 2025). The challenge will be achieving immunomodulation that calms pathological NETosis yet preserves neutrophils' essential role in host defense. As research progresses, PE stands as a paradigm of how an overzealous neutrophil response, an immunological conversation gone awry, can undermine pregnancy health (Aneman *et al*., 2020).

NETosis in Gestational Diabetes: A Link to Trophoblast Apoptosis

Gestational diabetes mellitus (GDM), a glucose intolerance first recognized in pregnancy, provides another window into NETosis-mediated materno-fetal stress (Vokalova *et al*., 2018). GDM creates a hyperglycemic and pro-inflammatory intrauterine environment, and it has been associated with a range of adverse outcomes, including fetal overgrowth, placental dysfunction, and an increased risk of preeclampsia in the mother. Neutrophils from GDM patients exhibit an "activated" phenotype with elevated basal ROS production and a heightened tendency to form NETs (Zgutka *et al*., 2024). In fact, one study reported significantly increased NETosis in women with GDM compared to healthy pregnant controls. The mechanistic connection between high blood sugar and NETosis is an area of active investigation. Hyperglycemia can directly induce NET release by triggering oxidative stress; excess glucose drives the neutrophil NADPH oxidase to generate ROS, a known requirement for NET formation (Wang *et al*., 2019). Consistently, diabetic conditions are linked to elevated citrullinated histone H3 via peptidylarginine deiminase 4 (PAD4) and increased neutrophil elastase activity, priming neutrophils for NETosis.

A novel insight into GDM-associated NETosis is the role of adipokines, particularly adiponectin. Adiponectin, an anti-inflammatory hormone, is typically reduced in GDM patients. Low adiponectin removes a brake on neutrophils, it normally suppresses neutrophil NADPH oxidase and ROS generation. Shen *et al*. (2021), demonstrated that hypoadiponectinemia in GDM is causally linked to excessive NET formation. In their cellular signaling study, adding adiponectin in vitro curtailed NET release from neutrophils by dampening ROS production, whereas neutrophils in low-adiponectin conditions showed robust NETosis via p38 MAPK and ERK1/2 pathways. This positions adiponectin as a molecular rheostat tuning neutrophil reactivity in GDM (Vokalova *et al*., 2018). The downstream consequences of

NETosis in GDM are particularly concerning for the placenta. The same study found that NETs derived under GDM-like conditions directly induce apoptosis in trophoblast cells. Specifically, NET exposure activated the intrinsic (mitochondrial) apoptotic pathway in trophoblasts, characterized by cytochrome c release and caspase-3 activation, a process mediated by ERK1/2 signaling (Katsi *et al*., 2025). The result is placental villous trophoblast attrition, which can impair nutrient and gas exchange to the fetus.

Trophoblast apoptosis and shallow invasion are key features of placental pathologies in GDM, potentially explaining the higher incidence of preeclampsia and fetal growth restriction in diabetic pregnancies (Xie *et al*., 2024). NETosis offers a unifying mechanism: hyperglycemia and low adiponectin provoke NET release; NETs inflict damage on trophoblasts and possibly endothelial cells in placental vessels, thereby exacerbating placental dysfunction (Guillotin *et al*., 2023). Consistent with this, GDM placentas have been observed to be larger yet morphologically abnormal, with increased inflammation and deposits of DNA/protein consistent with NETs. Could therapies that restore adiponectin levels or inhibit NETosis improve placental health in GDM? It is tantalizing to consider. Thiazolidinediones (TZDs) used in type 2 diabetes can raise adiponectin; however, their use in pregnancy is limited by safety concerns (López-Quintero *et al*., 2022). Antioxidant supplements or targeted inhibition of PAD4 (to block histone citrullination) are theoretical options to reduce NETosis. An intriguing hypothesis is whether tight glycemic control alone can normalize neutrophil behavior. Some small studies suggest that neutrophil activation markers subside when maternal blood sugars are well-controlled, but whether this translates to reduced NET burden in vivo remains unknown (Zambrano *et al*., 2025).

From an immunological perspective, GDM creates a state of chronic, low-grade inflammation akin to metabolic syndrome, sometimes dubbed "metaflammation". Neutrophils in GDM not only form more NETs but also secrete higher levels of pro-inflammatory cytokines (e.g., IL-1β, IL-8) and proteases. This can skew the maternal immune milieu towards a Th1-like inflammatory profile, counteracting the Th2/Treg environment that normally dominates pregnancy (Manoj *et al*., 2025). As such, NETosis in GDM could be contributing to the breakdown of immune tolerance, at least partially. One might ask: Do NETs act as adjuvants that activate maternal dendritic cells or T cells in GDM, potentially increasing the risk of autoimmunity or thyroid dysfunction postpartum? These considerations bridge the gap between metabolic and immune adaptations in pregnancy. In summary, GDM highlights how a metabolic disturbance can spill over into exaggerated NETosis, thereby harming the placenta. Unraveling this connection further may not only help manage GDM but also yield insight into non-GDM pregnancies where subclinical metabolic stress (like obesity) could similarly amp up NET-mediated damage.

NETosis Linking Maternal Inflammation and Autoimmunity to Pregnancy Outcomes

The impact of NETosis in pregnancy is not confined to gestational syndromes; it also serves as a bridge between pre-existing maternal conditions and adverse pregnancy outcomes. Two contexts illustrate this especially well: maternal autoimmune diseases (such as systemic lupus erythematosus and antiphospholipid syndrome) and maternal infections/inflammatory disorders (such as periodontal disease) (Aslanian-Kalkhoran *et al*., 2024). In both scenarios, maternal neutrophils are often pre-primed for NETosis, and pregnancy can amplify their pathogenic potential at the maternal-fetal interface.

Systemic Lupus Erythematosus (SLE) and Antiphospholipid Syndrome (APS): Women with SLE or APS face higher rates of miscarriage, preeclampsia, and fetal growth restriction, largely due to placental insufficiency (Erton *et al*., 2022). Lupus neutrophils are intrinsically prone to NET formation, a proinflammatory low-density granulocyte subset in lupus has been shown to spontaneously release NETs decorated with immunostimulatory molecules. These NETs can damage endothelial cells and expose intracellular antigens, fueling the autoimmune process (Salemme *et al*., 2019). During pregnancy, the placenta becomes a prime target of lupus-related NETosis. A study by Jiang *et al*. (2021), found an abundance of NETs infiltrating the placentas of patients with active SLE. The NET deposition was accompanied by fibrin (clot) formation and inflammatory infiltrates, and was linked with poor placental perfusion and lower birth weights. Notably, SLE placentas in that study also showed higher numbers of $CD56^{+}CD16^{+}$ dNK cells amidst the NETs, suggesting that NETosis might perturb the normal NK cell regulatory functions and incite a local immune attack (Tay *et al*., 2020). Mechanistically, lupus autoantibodies (such as anti-DNA or anti-histone antibodies) may stabilize NETs or reduce their clearance, prolonging their harmful presence. Additionally, neutrophils in SLE express surface toll-like receptors that can be triggered by immune complexes, driving further NET reléase (Yu & Su, 2013). The end result is a placenta peppered with NETs that mirror lupus's systemic vasculopathy, complete with tissue necrosis, thrombosed vessels, and inflammatory cell infiltrates.

In antiphospholipid syndrome, where antiphospholipid (aPL) antibodies cause thromboses and pregnancy loss, NETosis is a key pathological mediator (Zaiema *et al*., 2024).

aPL antibodies can bind to trophoblast cells and activate complement, generating C5a which potently stimulates neutrophils via C5a receptors. Redecha *et al*. (2007), demonstrated in mouse models that this cascade leads neutrophils to undergo NETosis and release tissue factor-rich NETs, causing placental thrombosis and fetal demise. NETs have been found in the placental bed of APS patients, where they directly damage trophoblasts and incite apoptosis. Yalavarthi *et al*. (2015), observed that neutrophils from APS patients show higher baseline NET release, and these NETs can induce trophoblast cell death and an inflammatory stromal response. Thus, in autoimmune conditions, NETosis forms a pathogenic link between maternal circulation and placental injury (Katsi *et al*., 2025). It is sobering to consider that therapies like heparin and hydroxychloroquine, used in APS and SLE pregnancies, might exert some of their beneficial effects by dampening NET formation or accelerating NET clearance (as both can interfere with DNA-protein interactions). This therapeutic angle, targeting NETs in autoimmune pregnancies, prompts further exploration: Could NET-inhibiting strategies, such as PAD4 inhibitors or DNAse supplements, complement conventional therapy to further reduce pregnancy risks in SLE/APS? Initial research in mice is encouraging, but safety in human pregnancy must be proven (Zambrano *et al*., 2025).

Periodontal Disease and Distant Inflammation: Chronic periodontal disease (gum inflammation and infection) is a perhaps unexpected but illustrative example of how a localized maternal inflammatory condition can affect pregnancy via systemic NETosis (Wen *et al*., 2023). Periodontitis tends to worsen during pregnancy due to hormonal and immune shifts, and it has been epidemiologically linked to adverse outcomes like preterm birth, low birth weight, and preeclampsia (Tsikouras *et al*., 2024). One hypothesis is that oral pathogens or their products (endotoxins, outer membrane vesicles) translocate into the maternal bloodstream and eventually reach the placenta, triggering inflammation there (Orsaria *et al*., 2021). Neutrophils are at the forefront of periodontal inflammation, and in pregnant individuals with periodontal disease, they display exaggerated activation profiles. Calo *et al*. (2025), found that pregnant women with worse gingival inflammation had neutrophils that produced more ROS and released more NETs upon stimulation. They demonstrated that gingival crevicular fluid from periodontitis patients (especially rich in Porphyromonas gingivalis components) could induce neutrophils to undergo NETosis in vitro, linking oral inflammation to systemic neutrophil priming. Over the course of pregnancy, neutrophils progressively shifted toward this pro-NETotic, pro-inflammatory state in concert with any escalation in periodontal disease (Calo *et al*., 2025).

The placental implication is that maternal neutrophils activated by chronic periodontal infection may home to the placenta or release NETs into the circulation that deposit in the placenta, contributing to a pro-inflammatory milieu (AlSharief & Alabdurubalnabi, 2023). Case studies have indeed isolated oral bacteria within placental tissues, and animal models show that inducing periodontal disease can lead to placental inflammatory lesions. NETs could be the missing mechanistic link: a systemic vehicle by which oral infection translates to placental damage (Wen *et al*., 2023). NET-associated proteases (like neutrophil elastase and MMP-8) can degrade decidual extracellular matrix, potentially leading to premature rupture of membranes and preterm labor (one reason periodontitis is tied to preterm birth). Additionally, NETs provide a surface for platelet aggregation and coagulation; women with severe periodontitis have higher levels of coagulation markers and a propensity for thrombin generation, which in pregnancy could mean placental intervillous thromboses (Wang *et al*., 2024b).

From a clinical standpoint, these insights reinforce the importance of dental health in pregnancy. Might treating periodontitis (through deep cleaning or antibiotics) not only improve oral health but also reduce NETosis and inflammation systemically, thereby protecting the pregnancy? It remains an open question, but one worth investigating (Castaño-Suárez *et al*., 2024). The periodontal case exemplifies a broader phenomenon: maternal inflammatory states, whether autoimmune or infectious, can escalate NETosis, which in turn becomes a common pathway of placental injury. It underscores NETosis as a potential "unifier" in the pathology of diverse conditions like SLE, APS, infection, and even stress-related inflammation (Marder *et al*., 2016). Each of these scenarios sees neutrophils as messengers carrying distress signals into the maternal-fetal interface, sometimes literally in the form of extruded NETs that spark local havoc. An important area of future research is identifying if any maternal biomarkers of NETosis (such as cell-free nucleosomes or neutrophil activation markers) could serve as early warning signs for placental dysfunction across these disparate conditions (Sundet *et al*., 2026).

NETosis in the Puerperium: Postpartum Immune Shifts and Implications

While pregnancy itself alters neutrophil behavior, the story does not end at delivery. The early postpartum period (puerperium) is accompanied by dramatic immunological shifts, essentially an "immune reboot" as the body transitions from a tolerant, pro-pregnancy state to one focused on wound healing and infection control after

childbirth (Wu & Jin, 2025). Neutrophils in the puerperium have recently been shown to exhibit a highly pro-NETotic phenotype, which has significant implications for maternal health. Giaglis *et al*. (2021), reported that within 48 hours after delivery, women's neutrophils release NETs more readily and in greater quantity than neutrophils either from late pregnancy or non-pregnant controls. Remarkably, even without any exogenous stimulation, postpartum neutrophils demonstrated increased spontaneous NET formation, evidenced by higher baseline levels of extracellular DNA–MPO complexes in culture. When stimulated with PMA (a potent NETosis trigger), these postpartum neutrophils formed NETs far more vigorously than those from pregnant or never-pregnant women (Metzler *et al*., 2014). This hyper-responsive state was corroborated by molecular changes: postpartum neutrophils contained elevated levels of PAD4 (the enzyme driving histone citrullination), citrullinated histone H3, neutrophil elastase, and MPO transcripts. In essence, the neutrophils of new mothers are locked and loaded for NET release (Metzler *et al*., 2014).

Why would evolution favor a surge in NETosis capability right after childbirth? One reason may be the need for enhanced protection against postpartum infections. The hours and days after delivery involve exposure to potential pathogens (especially at the placental implantation site and in lactational tissues) and a high risk of puerperal infections (Giaglis *et al*., 2016). Augmented NET formation could provide an immediate, robust antimicrobial shield during this vulnerable window (Fell *et al*., 2025). Additionally, delivery is accompanied by hemostatic challenges, the uterine vasculature must clot effectively to prevent hemorrhage. NETs are known to promote thrombosis by providing a scaffold for platelets and coagulation factors (NETs can carry tissue factor and stimulate fibrin deposition) (Martinod & Wagner, 2014). Thus, a pro-NETotic neutrophil phenotype postpartum might contribute to the rapid clotting needed to stanch bleeding from the placental bed. In fact, (Giaglis *et al*., 2021) noted that NETs generated postpartum carried tissue factor (TF) and coincided with elevated markers of coagulation in maternal blood. This paints NETs as a double agent: aiding in postpartum hemostasis on one hand, but potentially raising the risk of pathological thromboses on the other (Xu *et al*., 2022).

Indeed, the postpartum period is associated with a heightened risk of venous thromboembolism (VTE), up to 3-5-fold higher than in pregnancy itself (Xu *et al*., 2025). The pro-thrombotic NETosis observed postpartum provides a plausible immunothrombotic mechanism for this risk. One striking finding was that neutralizing G-CSF (which is elevated during pregnancy) could blunt pregnancy plasma's ability to induce NETs, but it did not fully suppress postpartum plasma-induced NETosis (Giaglis *et al*., 2021). This indicates that by postpartum, additional factors beyond G-CSF drive neutrophils to NETosis. The candidates include high levels of circulating cell-free DNA and placental microparticles released en masse at delivery (Yuen *et al*., 2024; Sundet *et al*., 2026). The study showed that microparticle-rich postpartum serum could trigger NET release from even non-pregnant neutrophils, whereas microparticle-depleted serum was far less potent. This suggests that placental microparticles (tiny membrane-bound vesicles from placental tissues shed into blood) act as a "secondary hit" to neutrophils, unleashing NETs in the absence of the pregnancy hormones that previously kept them in check (Sundet *et al*., 2026).

The concept of NETs at the nexus of thrombosis and immunity is perhaps most evident in the puerperium. Clinicians must navigate the fine line: on one side, an insufficient NETosis response could leave a new mother susceptible to sepsis or subinvolution of the uterus (poor healing), whereas an excessive NETosis response might manifest as thromboembolic events or post-surgical complications (Shields *et al*., 2023). This trade-off raises a critical question: Should we, and can we, modulate NETosis in the immediate postpartum period to improve outcomes? For example, in women with pre-existing risk factors for thrombosis, would administering NET inhibitors reduce VTE without increasing infection risk? Or conversely, in cases of immunosuppression, could stimulating NETosis help prevent infection? Such interventions are not yet in reach, but simply recognizing the postpartum immune recalibration is a step forward (Kamel *et al*., 2014). Research into postpartum NETosis might also explain clinical observations like the flare of autoimmune diseases (such as lupus) that some women experience after delivery, possibly due to the intense NET-driven inflammation rebound as pregnancy's immune suppression lifts (Silver *et al*., 2023).

In summary, the puerperal rise in NETosis exemplifies how dynamic and context-dependent neutrophil behavior is across the timeline of pregnancy (Fell *et al*., 2025; Xu *et al*., 2025). It closes the loop on the maternal-fetal conversation: after the baby is born, the mother's immune system shifts gears, and NETs are very much part of the new dialog focused on maternal recovery (Wu & Jin, 2025). Understanding this phase is important, as complications like postpartum hemorrhage, infection, and thrombosis remain leading causes of maternal morbidity and mortality (Fig. 2). NETosis, it appears, is a common denominator in each of these outcomes, and thus a compelling target for ongoing research in obstetric medicine (Yunas *et al*., 2025).

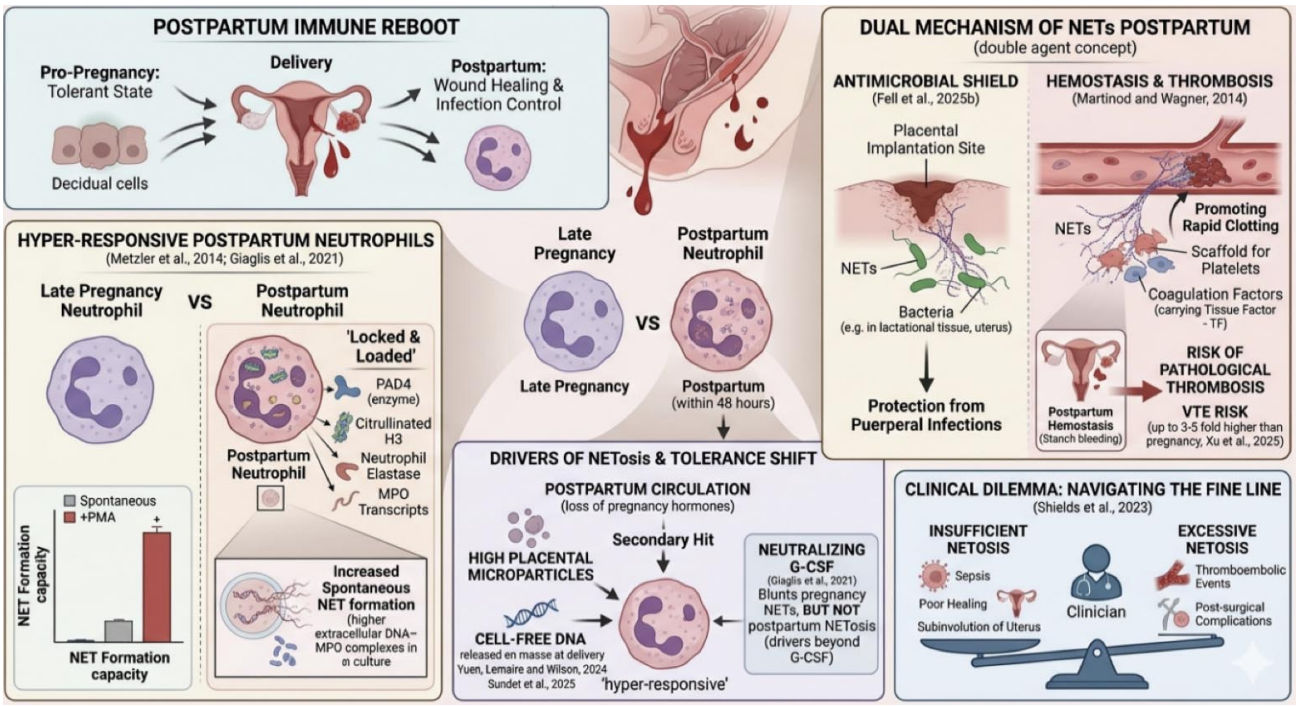


Fig. 2. Schematic overview of postpartum neutrophil reprogramming and the dual role of neutrophil extracellular traps (NETs) after parturition. Enhanced postpartum NETosis may contribute to antimicrobial defense and uterine protection, while excessive or dysregulated NET formation can promote thromboinflammation and postpartum complications. Figure created with the assistance of artificial intelligence (AI)-based design tools.

CONCLUSIONS

Neutrophil extracellular trap formation is a powerful form of communication in the maternal-fetal context, one that can be beneficial or destructive. In this review, we identified five key dimensions through which NETosis shapes pregnancy outcome: Immune Modulation at the Maternal-Fetal Interface: NETosis provides antimicrobial defense yet is normally restrained to preserve fetal tolerance. Neutrophils adapt during pregnancy to prevent unwarranted NET release, highlighting a delicate immunological poise. Placental and Vascular Injury in Preeclampsia: Excessive NETosis, triggered by placental factors, drives inflammation, endothelial damage, and coagulopathy in preeclampsia. NETs harm trophoblasts (e.g., via HMGB1) and propagate a feed-forward loop of placental insufficiency. This establishes NETs as central players in the pathogenesis of hypertensive disorders of pregnancy. Metabolic Influence of NETosis in GDM: Hyperglycemia and low adiponectin levels in gestational diabetes tip neutrophils into an overactive state. The resulting NETs promote placental oxidative stress and trophoblast apoptosis, linking metabolic dysregulation to impaired placental function. Managing neutrophil activation may be a novel angle to mitigate GDM's impact on pregnancy. NETs as Mediators of Maternal Condition Impact: Maternal autoimmune diseases (SLE/APS) and chronic infections (periodontal disease) utilize NETosis as a conduit to affect pregnancy. Autoantibodies and inflammatory stimuli heighten NET release, which in turn causes thrombotic and inflammatory damage at the maternal-fetal interface. This convergence on NETs across disparate conditions underscores their relevance as a unifying therapeutic target. Postpartum NETosis Surge: The early puerperium sees a notable upswing in neutrophil NET-forming propensity. While evolutionarily geared to protect against infection and hemorrhage, this pro-NETotic state may predispose to postpartum thrombosis and autoimmune flares. Understanding and modulating this response could improve postpartum care. From a clinical perspective, these insights paint NETosis as a potential biomarker and drug target for pregnancy complications. Measuring NET markers (e.g., cell-free DNA, citrullinated histones) in maternal blood might help predict or diagnose conditions like preeclampsia or impending preterm birth. Therapies that safely temper NETosis, such as recombinant DNase, PAD4 inhibitors, or blockers of neutrophil activators, could transform the management of obstetric disorders that currently have limited treatment options besides delivery. Yet, any therapeutic modulation must tread carefully: NETs also serve critical roles in host defense, especially in the context of pregnancy

when the maternal immune system is already tolerant. Key hypothesis: Tailored, temporally targeted NET-inhibiting strategies (for example, a short course of DNase during a severe preeclampsia flare) might quell the storm without long-term immunosuppression, but this remains to be tested in trials. On a molecular level, unraveling NETosis in pregnancy has broader implications for immunology and vascular biology. It compels us to consider how phenomena like oxidative stress, endothelial activation, and complement activation intersect in the unique immunological environment of pregnancy. NETs sit at this crossroads, engaging innate immunity, coagulation, and even autoimmunity. For immunologists, pregnancy is a natural experiment in tolerance versus immunity; NETosis might be one of the linchpins that when tilted to one side yields tolerance and successful gestation, and when tilted to the other yields inflammation and pathology.

In conclusion, NETosis profoundly influences the connection between mother and fetus, with impacts ranging from molecular (trophoblast signaling, cytokine release) to clinical (preeclampsia, preterm birth, fetal growth). This review, drawn from contemporary research and expert interpretation, underscores NETs as both biomarkers of distress and instigators of damage in pregnancy. By posing critical questions and synthesizing current knowledge, we aim to stimulate further research into therapeutic modulation of NETosis. The hope is that in the near future, clinicians might confidently say they can dial down the neutrophil's fury when it threatens maternal or fetal health, thereby tilting the scales toward a healthy pregnancy outcome.

VACA-MERINO, V.; SÁNCHEZ, R. & ZAMBRANO, F. Cómo la NETosis moldea la comunicación entre la madre y el feto: Impactos en el trofoblasto, la placenta y el embarazo saludable. *Int. J. Morphol., 44(4)*:1406-1416, 2026.

RESUMEN: La formación de trampas extracelulares de neutrófilos (NET, por sus siglas en inglés), o NETosis, ha surgido como un factor clave en el diálogo inmunológico materno-fetal. Durante el embarazo, los neutrófilos se infiltran en la decidua y la placenta, donde su activación debe mantener un equilibrio preciso entre la defensa frente a patógenos y la preservación de la tolerancia fetal. La NETosis excesiva se asocia cada vez más con complicaciones del embarazo, ya que daña los trofoblastos, provoca inflamación placentaria y altera la homeostasis vascular materna. Esta revisión sintetiza la evidencia clínica, molecular e inmunológica sobre temas clave: el papel dual de la NETosis en la interfaz materno-fetal; la patología placentaria mediada por NETosis en la preeclampsia y trastornos relacionados; la modulación metabólica de la NETosis en la diabetes gestacional y su repercusión en la apoptosis del trofoblasto; la NETosis como mediador entre condiciones inflamatorias maternas (enfermedades autoinmunes, enfermedad periodontal) y resultados adversos del embarazo; y los cambios dinámicos en el fenotipo de los neutrófilos desde la gestación temprana hasta el estado pro-NETótico del puerperio. Destacamos cómo los componentes de las NET (ADN, histonas, proteasas) provocan daño endotelial, activación del complemento y tromboinflamación en la placenta, al tiempo que planteamos interrogantes sobre cómo la evolución pudo haber aprovechado las NET para el éxito reproductivo. A lo largo del texto, formulamos preguntas aún no resueltas; por ejemplo, ¿podría la intervención sobre la NETosis o sus desencadenantes (como IL-8, ROS o HMGB1) mitigar trastornos como la preeclampsia sin comprometer la defensa del huésped? Al integrar hallazgos de estudios recientes —incluidos aquellos sobre preeclampsia, diabetes gestacional, lupus eritematoso sistémico, enfermedad periodontal e inmunidad posparto—, esta revisión busca ofrecer una perspectiva que sea, a la vez, humana y rigurosa. Comprender la NETosis durante el embarazo podría permitir el descubrimiento de nuevos biomarcadores y terapias para fomentar embarazos más saludables y mejores resultados tanto para la madre como para el hijo.

PALABRAS CLAVE: Trampas extracelulares de neutrófilos (NET); Embarazo; Trofoblastos; Placenta.

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