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Endometrial immune profiling: Bridging pre-eclampsia research with infertility solutions

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ABSTRACT

Assisted reproductive technologies (ART) are now widely recognized as a key therapeutic option for individuals experiencing infertility. Despite these technological improvements, ART success rates remain suboptimal. One emerging area of interest is the endometrial immune profiling, which involves the characterization of endometrial immune cells and biomarkers to assess local immunological conditions that may influence implantation and pregnancy outcomes before conception. In this review, we will discuss how the endometrial biomarkers selected prior to pregnancy to characterize the immune environment during the implantation window are directly linked to some immune key factors known to be crucial in the human placentation. Strong published evidence demonstrates that physiological transformation with remodeling of the uteroplacental spiral arteries is a key player to successful placentation and normal placental function. Poor remodeling of the uteroplacental spiral arteries, therefore, is associated with early-onset preeclampsia (PE) and several other major obstetrical syndromes, including fetal growth restriction, placental abruption, and spontaneous preterm premature rupture of membranes. In the future, endometrial immune profiling prior to conception could serve as a valuable indicator to predict high obstetrical risk and/or prevent some pregnancy-related pathology based on a better understanding of the underlying mechanisms.

1. Introduction

Assisted reproductive technologies (ART) have recently come into focus as a key therapeutic tool for individuals experiencing infertility. Despite the. As of 2018, the live birth rate (LBR) per initiated treatment cycle was approximately 30 % for women under the age of 35, with a marked decline observed as maternal age increases (European Ivf Monitoring Consortium, 2022). Although ART has substantially increased the chance of conception for many individuals struggling with infertility, the consistently modest success rates highlight the urgent need for ongoing research and innovation. An estimated 15 % of couples attempting natural conception are affected by infertility (Mascarenhas et al., 2012). Additionally, a recent report from the World Health Organization further underscores that about 1 in 6 couples of reproductive age experience infertility in their lifetime (World Health Organization. Infertility – Fact Sheet. Published 22 May 2024).

One emerging area of interest is endometrial immune profiling, which involves the characterization of immune cells and biomarkers within the endometrial lining to assess local immunological environment that may influence implantation, subsequently pregnancy outcomes. This strategy shows promise in identifying endometrial immune dysregulation as an important factor in infertility or pregnancy loss and provides a foundation for developing personalized treatment (Ledee et al., 2020b).

In this review we aim at discussing how endometrial immune biomarkers selected prior to pregnancy to categories the endometrial immune profiling during the implantation window is directly linked to some key immune factors know to be a major player in the human placentation. It has been documented that physiological transformation with remodeling of the uteroplacental spiral arteries is a crucial process to ensure normal placental function. Poor remodeling of uteroplacental spiral arteries is linked to early-onset preeclampsia (PE) and other major obstetrical syndromes (Staff et al., 2022; Zhang et al., 2023).

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2. From mice to humans: foundational discoveries in reproductive immunology

The 1990s marked a pivotal period in reproductive immunology, with groundbreaking insights into how the maternal immune system accommodates the genetically distinct embryo during implantation. Much of this progress stemmed from studies using murine models, which provided a controlled framework to investigate immune tolerance in pregnancy.

In 1996, Y. S. Loke et al., at identified a specialized population of immune cells—uterine natural killer (uNK) cells—present in large numbers within the endometrium during the implantation window and has an essential role in successful implantation and early pregnancy development (King et al., 1996). These cells were shown to secrete cytokines and angiogenic factors that facilitate vascular remodeling in the uterus, which in turns supporting embryonic growth (King et al., 1996). Furthermore, uNK cell function is hormonally regulated, and thus any dysregulation in their number or activity may lead to implantation failure or recurrent pregnancy loss in murine models. This research significantly shifted attention from the adaptive immune response to the central role of the innate immune system in reproductive success. Fig. 1

T. Wegmann and G. Chaouat, using abortion-prone mouse strains, further deepened our understanding of uterine immunity and its immunological mechanisms (Wegmann et al., 1993) by shedding the light on the uterine immune privilege and the presence of uNK cells, highlights their role in promoting maternal-fetal tolerance. Furthermore, the Immunotrophism, a novel concept, underscored the immune system's regulatory influence on embryonic development (Wegmann, 1987). Moreover, a Th2-biased immune shift was identified as critical for implantation and pregnancy maintenance, though subsequent findings nuanced this view, highlighting the necessity of a balanced Th1/Th2 cytokine milieu (Chaouat et al., 2004).

These publications laid the groundwork for investigating immunological factors in infertility and their relevance in ART. Such efforts culminated in a more refined understanding of how the immune landscape governs implantation outcomes and the success of early pregnancy (Moffett and Loke, 2006).

3. Translation to humans: understanding human implantation and its specificity

Human implantation represents a uniquely intricate process that requires the synchronized interaction of the embryo with a hormonally primed, immunologically receptive endometrium (Aplin, 2000). Unlike other mammals, human implantation is characterized by extensive decidualization prior to embryo arrival, deeply invasive trophoblast behavior, and a finely tuned maternal immune tolerance (Gellersen et al., 2007; Huang et al., 2023).

Implantation unfolds in three sequential phases: apposition, adhesion, and invasion, which are followed by placentation. During the apposition and adhesion stages, the blastocyst orients themselves establish molecular contact with the luminal epithelium of the endometrium. This interaction is mediated by specific adhesion molecules, such as integrins and selectins on the blastocyst, and their corresponding ligands on the endometrial surface (Singh and Aplin, 2009). Concurrently, the endometrium increases vascular permeability and secretory activity, creating a supportive environment for embryonic development (Massri et al., 2023).

The adhesion phase is often described as a pseudo-inflammatory event, as it triggers the release of pro-implantation mediators such as cytokines and chemokines (Salamonsen et al., 2007). This transient inflammatory-like state prepares the endometrium for the next phase—invasion—during which extravillous trophoblast (EVT) cells penetrate the decidua and remodel maternal spiral arteries. Notably, endovascular EVTs invade the arterial lumens, replacing maternal endothelial cells to establish a low-resistance, high-capacity blood flow system essential for fetal development (Ashkar et al., 2003; Brosens et al., 1995; Ledee et al., 2023).

Implantation in humans typically occurs 6–7 days post-ovulation, within a narrow window of implantation (WOI). During this period, endometrial receptivity is orchestrated by ovarian hormones, leading to structural and immunological changes (Acosta et al., 2000; Gellersen et al., 2007). A crucial component of this transformation is the modulation of the local immune environment, particularly a shift from adaptive to innate immune dominance.

Within WOI, there is a reduction in adaptive immune cells (e.g., B and T lymphocytes) and an increase in innate immune populations, including uNK cells, macrophages, and dendritic cells (Zhang et al., 2016). This shift is instrumental in establishing a state of immune tolerance toward the semi-allogeneic embryo, which expresses paternal antigens foreign to the maternal immune system.

At the cytokine level, this immune adaptation involves a transition toward a Th2-dominant profile, favoring anti-inflammatory responses. Regulatory immune cells promote tissue remodeling and vascular adaptation while suppressing pro-inflammatory Th1 responses. Uterine immune cells, including uNK cells, dendritic cells, macrophages, and

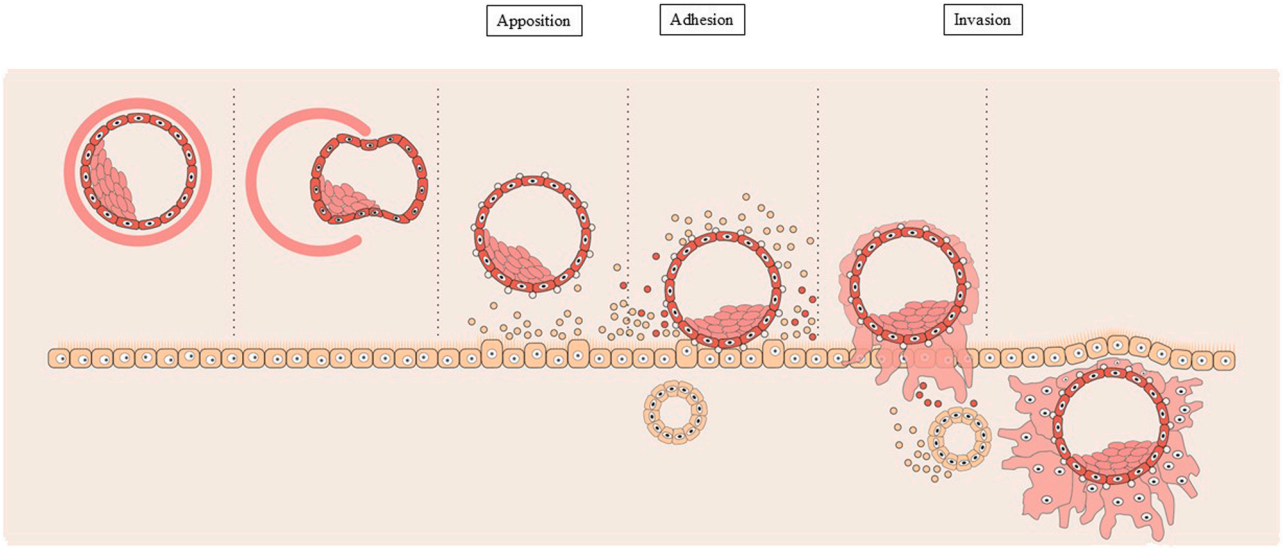

Fig. 1.

regulatory T cells (Tregs), differ functionally from their peripheral counterparts (Koopman et al., 2003; lockwood et al., 2013). For example, uNK cells, highly abundant in early pregnancy, display unique phenotype and secrete factors essential for trophoblast invasion and vascular remodeling (Manaster and Mandelboim, 2010; Zhang et al., 2010; Feyaerts et al., 2018).

Dendritic cells and macrophages also contribute by fostering immune tolerance through the induction of Tregs, resulting in ant-inflammatory cytokine release including IL-10 and TGF-β (Blois et al., 2008; Lash et al., 2016)., reinforcing the Th2-biased environment necessary for implantation and placental development (Kallikourdis and Betz, 2007; Aluvihare et al., 2004).

The remodeling of spiral arteries by invading trophoblasts is a hallmark of human implantation (Wei et al., 2022). This involves the replacement of smooth muscle and endothelial cells in maternal arteries with fetal trophoblasts, establishing a hemodynamic state optimal for fetal growth (Ashkar et al., 2003; Brosens et al., 1995). Importantly, this transformation is preceded by a controlled destabilization of spiral arteries, a step that prepares the maternal vasculature for EVT invasion (Sato et al., 2012).

Impaired spiral artery remodeling can result from immune dysregulation, ultimately leading to complications such as pre-eclampsia (PE) or fetal growth restriction. While the exact mechanisms underlying failed remodeling are not fully elucidated, aberrant cytokine signaling and dysfunctional immune cell interactions—particularly involving uNK and trophoblast cells—are considered key contributors (Zhang et al., 2023).

4. Selecting key-immune targets to define the uterine immune profile

To better understand how the endometrium prepares for embryo implantation—and to identify potential immunological disruptions that may impair this process—we evaluated specific immune-related biomarkers during the mid-luteal phase. The selected targets were not chosen for their exclusivity, given the redundancy among cytokines and growth factors in the endometrial microenvironment, but rather for their ability to reveal critical aspects of the local immune milieu. These included the Th1/Th2 cytokine balance, spiral artery destabilization, and uNK cell mobilization and maturation. To this end, we quantified the mRNA expression levels of those selected biomarkers by RT-qPCR (Ledee et al., 2011). Two composite ratios—IL-18/TWEAK and IL-15/Fn-14—were developed as integrative biomarkers. The IL-18/TWEAK ratio provides insights into the angiogenic profile and Th1/Th2 balance, while the IL-15/Fn-14 ratio reflects the maturation status and functional activity of uNK cells. These were complemented by an assessment of $CD56^{+}$, a specific biomarker of uNK cell density.

4.1. Interleukin (IL)-18

IL-18 is a pro-inflammatory cytokine involved in immune regulation, tissue remodeling, and angiogenesis. In the reproductive context, IL-18 is expressed in the endometrium during the WOI and is implicated in trophoblast invasion, uNK cell modulation, and placental vascularization (Novick et al., 2013; Yoshino et al., 2001; Tokmadzic et al., 2002; Ledee et al., 2025). While IL-18 supports physiological implantation processes, its aberrant or excessive expression has been associated with adverse pregnancy outcomes including PE among others(Cift et al., 2013; Huang et al., 2005).

Immunologically, IL-18 exhibits dual functionality within the Th1/Th2 paradigm. It typically promotes Th1 responses—characterized by IFN-γ and TNF-α production and cytotoxic T cell activation—but can also enhance Th2-associated cytokines such as IL-5 and IL-13, depending on the cytokine milieu (Ledee-Bataille et al., 2005; Li et al., 2009). (Nakanishi, 2018). This context-dependent behavior underscores its nuanced role in shaping immune tolerance during implantation.

4.2. IL-15

IL-15 is implicated plays a key role in reproductive immunology by promoting the survival, proliferation, and differentiation of uNK cells (Laskarin et al., 2005; Ashkar et al., 2003; Verma et al., 2000; Manaster et al., 2008). It influences the local secretion of secondary mediators such as IL-6 and TNF-α, both of which are important in implantation and placental development. IL-15 expression during WOI supports the establishment of a receptive immune landscape within the endometrium. Strong evidence has demonstrated the upregulation of IL-15 and its receptor IL-15Rα in the endometrial stromal cells during the WOI, thereby facilitating the activation of uNK cells and subsequently promoting a favorable environment for embryo implantation.

4.3. TNF-like weak inducer of apoptosis (TWEAK) and fibroblast growth factor-inducible 14 (Fn-14)

TWEAK is a member of the TNF superfamily that binds to its receptor Fn-14, which is expressed on various cell types, including uNK cells (Qi et al., 2016; Maecker et al., 2005). The TWEAK/Fn-14 axis participates in angiogenesis, inflammation, and apoptosis, and plays a crucial role in regulating uNK cell cytotoxicity during implantation (Ledee et al., 2011; Petitbarat et al., 2010).

Functionally, TWEAK modulates the local immune response by influencing the expression of cytokines such as IL-15 and IL-18 (Petitbarat et al., 2011, 2009). contributing to the controlled activity of uNK cells, balancing cytotoxicity with tissue remodeling to support embryo invasion and tolerance. This axis thus represents a significant node in the local immunoregulatory network during early pregnancy.

4.4. Cluster of differentiation (CD56)

CD56 is a well-established surface marker for uNK cells and is routinely used to quantify their recruitment to the endometrium during the WOI (Chen et al., 2025). However, in our investigations, enumeration of $CD56^{+}$ cells alone provided limited insight into the functional immune environment. While cell presence indicates mobilization, a deeper understanding of implantation physiology requires concurrent evaluation of the molecular signals guiding uNK cell differentiation and function.

5. From implantation to PE: longitudinal hypothesis

In the context of endometrial immune profiling, it is important to acknowledge that many of the foundational hypotheses were originally derived from murine studies, particularly from the abortion-prone CBA × DBA/2 mouse model. Initially described as an immunological model for investigating the mechanisms underlying recurrent miscarriage, it was only two decades later that this model was also recognized as a relevant model for studying PE (Chaouat et al., 2005; Ahmed et al., 2010).

Similarly, the endometrial immune environment and our biomarkers were studied not only in the context of repeated implantation failure and recurrent pregnancy loss, but also in the context of PE.

5.1. Decidual NK cells (dNK) In PE

PE is a major pregnancy complication characterized by maternal hypertension and proteinuria, affecting 5–8 % of pregnancies worldwide and contributing significantly to maternal and perinatal morbidity and mortality (Steegers et al., 2010; Creanga et al., 2017). PE is classified as early-onset (before 34 weeks) or late-onset (after 34 weeks), with early-onset PE more closely linked to poor placentation and spiral artery remodeling due to inadequate trophoblast invasion (Cartwright et al., 2017; Chaiworapongsa et al., 2014).

dNK cells are central to spiral arteries remodeling through their

secretion of cytokines and chemokines (Zhang and Wei, 2021). Dysfunction of these cells or their receptors has been implicated in PE progression and development., It has been demonstrated that women with the Killer-cell immunoglobulin-like receptors (KIR AA) genotype (lacking activating KIRs) are at increased risk when the fetus expresses Human Leukocyte Antigen (HLA)-C2, which strongly interacts with the inhibitory receptor KIR2DL1, leading to excessive suppression of uNK cells, resulting consequently in impaired angiogenesis (Moffett et al., 2016; Hiby et al., 2008). Additionally, it has been reported that HLA-G protects trophoblasts from NK cell-mediated lysis, and its reduced expression has been implicated in severe PE (Pazmany et al., 1996). Furthermore, abnormal expressions and polymorphisms of HLA-G have been shown to be related to PE and recurrent spontaneous abortion (Xu et al., 2020). Natural Killer Group 2 A (NKG2A), an inhibitory receptor found on the surface of NK cells, deletion in mice leads to abnormal vascular remodeling, and genomic studies link inadequate NKG2A education to increased PE risk (Shreeve et al., 2021).

Functional assessments of NK subsets may provide more meaningful insights. Overall, NK cell dysfunction appears to play a significant role in PE pathogenesis (Williams et al., 2009).

5.2. IL-15 and PE

The functional maturity of uNK and dNK cells, which are essential for placentation, has been linked to IL-15 local secretion (Manaster et al., 2008). Increased decidual IL-15 expression has been observed in woman with recurrent miscarriage, suggesting impaired implantation and vascularization of the placenta (Toth et al., 2010). Some reports have also described increased circulating IL-15 levels in the serum of pre-eclamptic mothers compared to healthy controls (Hu et al., 2007). These findings provide evidence that IL-15 may be involved in poor pregnancy outcomes. Sones et al., explored whether dNK cell activation and function were dysregulated before placenta formation in their murine model of PE, BPH/5. These mice spontaneously develop the maternal signs of PE, including hypertension and proteinuria, as well as similar placental defects observed in human pre-eclamptic placentae such as inadequate remodeling of spiral arteries (Davisson et al., 2002). They observed a marked decrease in mature dNK cell numbers at *e5.5* in BPH/5 implantation sites compared to CBA controls. Furthermore, IL-15 mRNA was significantly increased in BPH/5 implantation sites compared to the control group at *e4.5* and *e5.5*.One hypothesis is that high levels of IL-15 may be induced to help promote more dNK cell activation in BPH/5 (Sones et al., 2014). Their hypothesis is that peri-implantation events may lead to early impaired uterine angiogenesis and placental development long before the development of PE in this model.

5.3. IL-18, TWEAK and PE

Regarding IL-18 circulating concentration, no significant difference in IL-18 levels were observed in patients with PE when compared to the control group in eleven studies with 947 participants (Yang et al., 2014). Nevertheless, the biomarker we used is the ratio of IL-18/TWEAK mRNA levels which should reflect a Th-1 deviation (inducing the production of IFN- γ). Circulating IFN-γ was found to be significantly higher in women with PE than that in normotensive pregnant women in 16 studies with 2230 subjects (Yang et al., 2014). More recently, the circulating concentration of IFN- γ at the first trimester was reported to be higher in patients who developed PE, suggesting a Th-1 biased immune activation (Vafaei et al., 2023). Two case-control studies reported a low level of soluble TWEAK at the first trimester of pregnancy in patients who developed PE (Shahid et al., 2019; Yildirim et al., 2016). Additionally, increased IL-18 and IL-12 in PE patients has been observed and proposed a shift in the balance of immune reactivity towards a Th1 phenotype in PE patients(Raghupathy, 2013). Collectively, these findings suggested that baseline TWEAK might serve as an independent variable for prediction of PE (Shahid et al., 2019).

6. Future direction: from uterine immune profiling to poor placentation

The maternal environment at the time of implantation is a key factor in the development of PE. As demonstrated by Robillard and al., metabolic factors, other than diabetes, associated with pre-pregnancy maternal weight were specifically associated with late onset PE (Robillard et al., 2019). Based on this information, they were able to demonstrate in a prospective population study that in overweight and obese women who achieve an optimal gestational weight gain, the rate of term PE (> 37 week's gestation) was significantly decreased (Robillard et al., 2023).

Using uterine immune profiling and precision care tailored to each profile, we demonstrated in extended cohort studies (Ledee et al., 2020a) and a randomized controlled trial (Ledee et al., 2025) that the LBR can be significantly improved when immune dysregulations observed prior to conception are addressed through personalized interventions. As shown in this manuscript, all functional endometrial biomarkers utilized in uterine immune profiling are also valuable for exploring PE.

ARTs are highly suspected to increase the risk of PE in all the recent meta-analysis, so preventive actions would be highly beneficial (Omani-Samani et al., 2020).

Prospective cohort studies involving infertile patients with uterine immune dysregulation should not limit the outcome to LBR alone but should also evaluate all pregnancy-related pathologies occurring during and after delivery, with particular attention to PE.

Preliminary follow-up data indicate that nearly all reported cases of PE occurred in patients with immune over-activation (9 out of 195), while no PE cases were observed among those without immune deregulation (0/36), and only one case occurred in a patient with under-activation who had an oocyte donation (1/97). To validate these findings, more systematic and comprehensive documentation of pregnancy complications throughout gestation is needed to develop a robust and reliable dataset.

CRediT authorship contribution statement

Nathalie Lédée: Writing – original draft, Methodology, Conceptualization. **Nada J.Habeichi:** Writing – review & editing. **Marie Petitbarat:** Writing – review & editing.

Declaration of Competing Interest

"Endometrial Immune Profiling: Bridging Pre-eclampsia Research with Infertility Solutions"

NL initiated the MatriceLAB Innove company and holds a patent covering the endometrial immune tests and the appended recommendations (PCT/EP2013/065355). The remaining authors declare no conflict of interest regarding the publication of this article

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