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SP and Uterine Immunity: A Timing-Based Perspective on Implantation and Reproductive Success: A narrative review

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ABSTRACT

Seminal plasma plays a multifaceted role in reproduction, extending beyond sperm transport to the modulation of female reproductive tract immunity. Rich in prostaglandins, cytokines, and extracellular vesicles, SP influences endometrial receptivity, embryo implantation, and the immunological dialogue that sustains early pregnancy. This narrative review synthesizes current evidence on the dual actions of SP, supportive and disruptive, on implantation and pregnancy outcomes, with emphasis on the timing of exposure and its implications for reproductive success. A structured literature search of PubMed, Scopus, SCIENCEDIRECT and Web of Science (1990–2025) identified mechanistic, animal, and human studies exploring SP-mediated immune signaling, endometrial response, and implantation outcomes. SP can promote regulatory immune adaptation, angiogenesis, and trophoblast invasion that favor implantation. However, exposure outside the receptive window or under inflammatory conditions may trigger pathological cytokine activation linked to implantation failure, PE, and other gestational complications. Evidence from human and animal models highlights the importance of temporally

controlled SP exposure. In assisted reproduction (ART), where natural SP contact is absent, these mechanisms offer translational insight for improving uterine receptivity. The impact of SP on implantation depends critically on timing and maternal immune context. Understanding this balance may guide novel strategies to enhance natural and assisted conception outcomes while minimizing inflammation-associated complications.

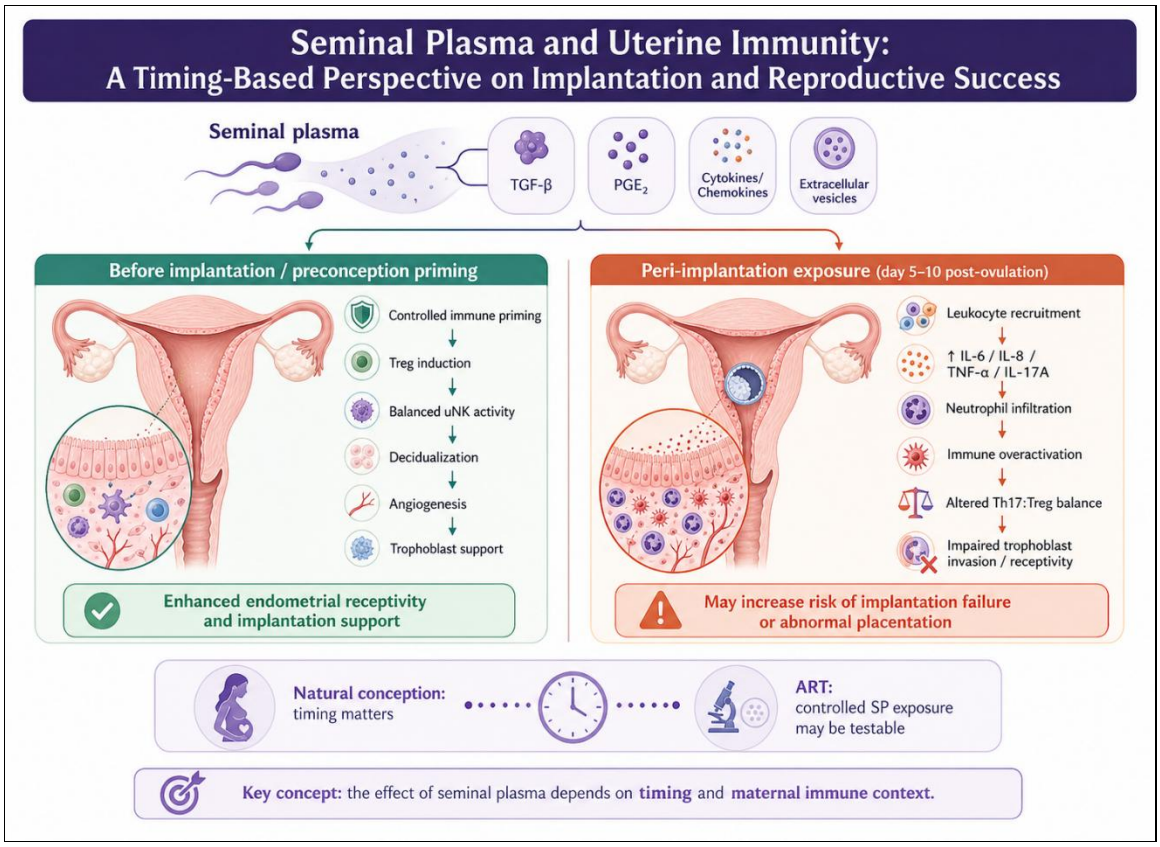

Fig 1) graphical abstract

Keywords: Embryo Implantation; Endometrium/immunology; Inflammation; Reproductive Techniques, Assisted; SP; Uterus/immunology

INTRODUCTION

Insemination is no longer viewed merely as the delivery of sperm into the female reproductive tract. Although this continues to be its primary function, research indicates that semen also interacts with female reproductive tissues, influencing implantation, pre-implantation embryo development, and the health of offspring (Bromfield, 2014). During ejaculation, sperm from the epididymides mix with secretions from the prostate, seminal vesicles, and seminiferous tubules, forming seminal plasma (SP) (Szczykutowicz et al., 2019). This fluid, released before and during ejaculation, constitutes the non-cellular component of semen, aiding in the transport of sperm and its interaction with the female reproductive environment (Talluri et al., 2017).

Under normal conditions, SP-mediated signaling contributes to endometrial decidualization and the modulation of key immune cells, including macrophages, natural killer cells, regulatory T cells, and dendritic cells (Szczykutowicz et al., 2019). Yet deviations in SP composition, driven by factors such as advanced paternal age, obesity, or metabolic stress, have been associated with heightened pro-inflammatory signaling and dysregulated uterine immunity (Shen et al., 2023). Experimental evidence indicates that SP can activate the γδ T cell/IL-17A axis, upregulating cytokines such as IL-1β and TNF-α and chemokines including CXCL1, CXCL2, and CCL20 (Sharkey et al., 2017). Such immune perturbations, when mistimed during the peri-implantation period, may predispose to implantation failure, miscarriage, or pregnancy complications such as PE (Song et al., 2016). Exposure to SP induces a controlled, transient inflammatory response characterized by leukocyte infiltration and the release of cytokines and chemokines(Adefuye et al., 2016; Ahmadi et al., 2022; Sharkey, 2012). While controlled inflammation is essential for implantation (Dekel et al., 2014), The implantation site is already a controlled battlefield, an "open wound" where the embryo must break through the maternal tissue to embed itself (Dekel et al., 2010a). This process requires a precise, finely-tuned inflammatory response to manage the invasion and subsequent repair (Dekel,

2014). The additional, potent inflammatory surge from SP is akin to pouring gasoline on a carefully controlled fire. It overwhelms the delicate balance, creating a state of excessive inflammation. Excessive or prolonged inflammation, whether from repeated SP exposure or altered SP composition, can overwhelm local immune regulation, impair maternal tolerance to the semi-allogeneic embryo, and disrupt the cellular cross-talk necessary for normal trophoblast invasion and placental formation. In assisted reproduction (e.g. IVF or ICSI with embryo transfer), the female genital tract is deprived of natural exposure to SP, creating a "blank slate" environment. This deviation from natural physiology offers a unique context in which to test whether timed reintroduction of SP (or its components) can modulate endometrial immune readiness and improve implantation in ART cycles.

This review explores the dualistic role of SP in modulating the uterine immune landscape, how it can both facilitate and hinder implantation depending on timing, dose, and composition. We further propose a novel and testable concept: that limiting SP exposure during the peri-implantation window, through short-term sexual abstinence, could reduce aberrant inflammation, enhance uterine receptivity, and ultimately improve reproductive success, particularly among individuals with recurrent implantation failure or unexplained pregnancy loss.

2. SP Composition and Its Mechanisms in the Female Reproductive Tract (FRT)

SP is a complex fluid that plays a crucial role in reproduction, providing essential energy substrates such as simple sugars for sperm function. It also contains a wide variety of enzymatic and non-enzymatic antioxidants that protect sperm from oxidative stress. Furthermore, its rich composition of chemokines, cytokines, and prostaglandins contributes to immune modulation, regulates inflammation, and supports overall reproductive health processes *(Owen & Katz, 2005)*

2.1 Energy Substrates and Antioxidants

Simple sugars such as fructose and glucose serve as key energy sources for sperm motility (Juyena & Stelletta, 2012; Talluri et al., 2017). Mammalian sperm rely on metabolic energy for various functions, with motility being one of the most crucial. ATP production in sperm primarily occurs through mitochondrial oxidative phosphorylation and glycolysis; however, the relative contribution of these pathways varies across species. In humans, glycolysis plays a significant role in ATP generation, with fructose and glucose, both present in SP, acting as essential substrates that fuel this process and support sperm function (Ferramosca & Zara, 2014; Rees et al., 1990; Williams & Ford, 2001). Several studies have demonstrated that glucose, specifically, is essential for optimal capacitation and fertilization in human sperm. It plays a crucial role in enabling sperm to penetrate the zona pellucida, as it supports hyperactivated motility, a key factor for successful fertilization. Fructose also provides an important energy source, particularly during sperm motility and survival within the female reproductive tract, ensuring sperm have the energy required to reach and fertilize the oocyte (K et al., 1991).

In addition to energy substrates, SP contains enzymatic antioxidants such as superoxide dismutase, catalase, and glutathione peroxidase, as well as non-enzymatic antioxidants including vitamins C and E, zinc, and selenium. These agents counteract reactive oxygen species (ROS) generated during immune cell infiltration after coitus (Aitken & Baker, 2006). Without sufficient antioxidant defense, oxidative stress may lead to lipid peroxidation, DNA fragmentation, and impaired mitochondrial function in both sperm and endometrial cells, creating a hostile environment for fertilization or implantation (Ibrahim et al., 2024; Y. Wang et al., 2025). Oxidative and endothelial biomarkers commonly measured in pregnancy include MDA, 8-isoprostane, protein carbonyls, TAC, SOD/CAT/GPx and ADMA; prior work from our group has summarized assay heterogeneity and reported ADMA elevation in pre-eclampsia (Bansal et al., 2025; Ibrahim et al., 2024; Mahdy et al., 2022). This paradox, where SP offers both protection and potential harm, underscores the importance of timing and uterine conditions in determining whether its immunometabolic influence is beneficial or detrimental.

2.2 Proteins and Structural Factors

SP contains a wide array of proteins, many of which are essential for sperm function, stability, and interaction with the female reproductive tract (Turunen et al., 2022). Some of these proteins originate from blood plasma through exudation into the male genital tract, while others are synthesised and secreted by reproductive organs, forming SP-specific proteins (Juyena & Stelletta, 2012). Blood-derived proteins such as prealbumin, albumin, globulin, transferrin, α-antitrypsin, β-lipoprotein, β-glycoprotein, orosomucoid, kininogen, peptide hormones, and immunoglobulins (IgG, IgA, and IgM) have been identified and characterised. These proteins help regulate the osmotic pressure and pH of SP and facilitate the transport of ions, lipids, and hormones, contributing to an optimal environment for sperm survival and function (Manjunath et al., 2007; Perumal, 2012).

The most abundant structural proteins in human SP include semenogelin I (SEMG1) and semenogelin II (SEMG2), which form a coagulum around ejaculated spermatozoa immediately after ejaculation, regulating their mobility (Anamthathmakula & Winuthayanon, 2020; Juyena & Stelletta, 2012). These semenogelins are subsequently degraded by prostate-specific antigen (PSA), a serine protease, leading to liquefaction of the semen and the release of motile sperm. This regulated liquefaction process is critical for proper sperm progression through cervical mucus (Anamthathmakula et al., 2022; Anamthathmakula & Winuthayanon, 2020).

Another group of proteins in SP includes enzymes such as dipeptidyl peptidase IV (DPP-IV), aminopeptidases, and extracellular matrix-degrading proteases, which play roles in remodeling the cervical epithelium and promoting sperm ascent through the female tract. Moreover, a number of SP proteins are actively involved in immune signaling. CD38, TGF-β-binding proteins, and prostasomes carry surface ligands that interact with endometrial epithelial cells to modulate maternal immune tolerance and cytokine production (Anamthathmakula et al., 2022).

Together, these proteins not only facilitate sperm survival and function but also act as mediators between the paternal antigenic load and the maternal immune system, reinforcing the view that SP is not a passive carrier fluid, but a biologically active modulator of reproductive success.

2.3 Cytokines and Chemokines

SP is a potent immunological fluid, containing a broad spectrum of cytokines and chemokines that initiate and regulate immune signaling in the female reproductive tract following intercourse (Sharkey et al., 2017). These molecules include both pro-inflammatory and anti-inflammatory agents, such as interleukin (IL)-6, IL-8, tumor necrosis factor-alpha (TN F-α), granulocyte-macrophage colony-stimulating factor (GM-CSF), and transforming growth factor-beta (TGF-β) (Ahmadi et al., 2022; Shen et al., 2023). TGF-β, one of the most abundant cytokines in SP, plays a pivotal role in modulating the maternal immune response by inducing regulatory T cells (Tregs), which are essential for immune tolerance toward the semi-allogeneic embryo (Wen et al., 2023).

Seminal fluid contains a wide range of cytokines, chemokines, and growth factors, primarily in the soluble fraction of a SP. While cytokines regulate numerous reproductive processes, their precise roles in SP and their effect on male fertility and fecundity remain under investigation (Lyons et al., 2023)**.** Pro-inflammatory cytokines such as (Interleukins) IL-1, IL-6, IL-8, TNF-α , IFNγ, and GM-CSF are present in SP, contributing to inflammatory responses in the female reproductive tract. These cytokines, together with chemokines, promote the recruitment of antigen-presenting cells (APCs) and lymphocytes, initiating an immune reaction against paternal antigens introduced by semen (Nederlof et al., 2017; Sharkey et al., 2017). A delicate balance between pro-inflammatory and immunoregulatory factors in SP is essential for promoting immune tolerance in the female reproductive tract and facilitating implantation (Sharkey et al., 2017). Seminal fluid cytokines play a pivotal role in modulating the female immune response after coitus, triggering molecular and cellular adaptations that prepare the immune system to support pregnancy and tolerate paternal antigens expressed by the conceptus (Sharkey et al., 2017). SP triggers the recruitment of immune cells and cytokine production in the female reproductive tract (FRT), initiating physiological processes that support fertilisation, implantation, and pregnancy (Ahmadi et al., 2022). Upon exposure to SP, cervical and endometrial epithelial cells upregulate the production of pro-inflammatory cytokines, including IL-6, GM-CSF, and chemokines such as CXCL1 and CXCL8, facilitating the recruitment of leukocytes such as neutrophils and macrophages to the site (Sharkey et al., 2012). SP plays a crucial role in clearing pathogens and debris from the uterine cavity after mating, fostering pre-implantation embryo development, and enhancing uterine receptivity by upregulating embryo attachment molecules and angiogenic factors (Nederlof et al., 2017). However, imbalances in SP composition may disrupt these processes, potentially leading to pregnancy loss or complications later in gestation (Dekker et al., 1998; Schjenken & Robertson, 2015; Sharkey et al., 2017).

SP cytokines are known to significantly influence pregnancy by modulating the immune environment within the female reproductive tract (Lyons et al., 2023). These cytokines trigger the recruitment of immune cells such as macrophages and dendritic cells, which regulate inflammation, immune tolerance, and angiogenesis (Crants et al., 2024). This local immune activation supports implantation by clearing pathogens, enhancing angiogenesis, and promoting endometrial remodeling (Crants et al., 2024). However, excessive or mistimed cytokine responses can lead to an inflammatory environment that impairs endometrial receptivity and trophoblast invasion (Chan & Robertson, 2025; Pantos et al., 2022).

Prostaglandins

SP is a potent source of prostaglandins, including prostaglandin E2 (PGE2), prostaglandin F2α (PGF2α), and prostaglandin D2 (PGD2), which play immunomodulatory and vasoactive roles in the female reproductive tract immediately after coitus (Andrade et al., 2024). Emerging evidence suggests that during sexual intercourse, seminal fluid prostaglandins, including PGE2, PGE1, PGE3, and PGF2, actively participate in key reproductive stages (Luo et al., 2024; Mayoral Andrade et al., 2020; Sales et al., 2002). These stages include pre-implantation, implantation (apposition, adhesion, invasion), and decidualization, as well as other molecular processes critical for embryo implantation and maintenance (Andrade et al., 2020).

Research has shown that PGE2 not only promotes tumor formation but also stimulates angiogenesis in endometrial epithelial cells (Battersby et al., 2007). Additionally, prostaglandins in SP can activate inflammatory pathways, leading to the recruitment of immune cells such as macrophages and neutrophils (Andrade et al., 2024). In cases where SP composition is abnormal, this heightened inflammatory response may impair the endometrium's ability to support implantation, increasing the risk of pregnancy complications such as implantation failure or miscarriage (Rodriguez-Martinez et al., 2021; Shen et al., 2023). Prostaglandins also modulate local immune responses. PGE_2 downregulates pro-inflammatory cytokines and

suppresses the cytotoxicity of uNK cells, helping to establish maternal immune tolerance at the implantation site (F. Wang et al., 2021). Disruption in prostaglandin production or signaling, whether due to SP imbalance, cyclooxygenase (COX) inhibition, or timing mismatch, can impair decidualization, vascular adaptation, and immune tolerance, leading to implantation failure or early miscarriage (Salleh, 2014).

Influence of SP on Pre-implantation, implantation Stage, and Uterine Environment Dynamics:

Exposure to SP is thought to influence offspring health (Ahmadi et al., 2022). After coitus, SP is deposited in the cervix, initiating significant cellular changes within the female reproductive tract (FRT). Within four hours, leukocytes, primarily neutrophils, followed by macrophages, are recruited to the cervix, peaking at 12 hours and resolving by 24 hours (Bromfield, 2014). Vaginal insemination triggers an inflammation-like response in the ectocervix, altering leukocyte populations and gene expression within the stratified epithelium and deeper stromal tissues (Adefuye et al., 2016).

The initial response to semen deposition involves the recruitment of immune cells to the exposed area, along with the production of pro-inflammatory cytokines, including interleukin (IL)-6 and granulocyte-macrophage colony-stimulating factor (GM-CSF) (Ahmadi et al., 2022). Semen deposited in the lower female reproductive tract (FRT) rapidly reaches the upper FRT due to peristaltic contractions (Ahmadi et al., 2022). In response to SP exposure, both endometrial epithelial cells (eEC) and endometrial stromal fibroblasts (eSF) upregulate the expression of pro-inflammatory cytokines such as tumour necrosis factor-α (TNF-α), IL-1β, IL-6, and leukemia inhibitory factor (LIF) (Adefuye et al., 2016).

During the pre-implantation phase, the uterine environment undergoes crucial changes to prepare for embryo implantation (Yanaihara et al., 2005). A balanced interplay among uterine secretions, immune responses, and local microenvironmental factors, such as pH, is essential for facilitating sperm migration and establishing endometrial receptivity (Cooper & Rompalo, 2013). Normal fetal development depends on the formation of a robust placenta to sustain the fetus (Robertson et al., 2018). Implantation and placental development represent critical windows of vulnerability, during which pregnancy loss and complications frequently arise. In humans, implantation typically occurs around days 8 to 9 post-ovulation, approximately 4 to 5 days after fertilization (Aplin & Ruane, 2017). Once the blastocyst hatches from the zona pellucida, its trophoectoderm layer mediates attachment to the uterine epithelium. This initial adhesion is followed by trophoblast differentiation and invasion into the endometrium. High implantation failure rates are observed in both natural conception and IVF (Aplin & Ruane, 2017). This phenomenon may result from multiple factors, with immunological imbalances in the endometrium being a primary contributor (Simon & Laufer, 2012).

SP triggers the recruitment of immune cells into the endometrial epithelium (von Wolff et al., 2007). In response to chemotactic agents present in SP, approximately 50 million leukocytes, primarily neutrophils, migrate into the uterine lumen within an hour after coitus (Taylor, 1982). Paternal antigens, including soluble human leukocyte antigen-G (sHLA-G) and soluble HLA class-I molecules with potential regulatory functions, are also found in SP. During implantation, the embryo expresses paternally inherited alloantigens, which can elicit an inflammatory response that may compromise reproductive success (Robertson et al., 2018). Immunological interactions in the uterus triggered by SP exposure demonstrate the recruitment of immune cells (neutrophils, macrophages, uNK cells), modulation through cytokines and HLA-G, and potential clinical outcomes (Robertson et al., 2018). These antigens are processed by maternal antigen-presenting cells (APCs) and subsequently presented to T cells. HLA-G plays a crucial role by inducing T-cell apoptosis, suppressing the cytotoxic activity of NK cells, and simultaneously promoting the proliferation and cytokine secretion of uNK cells. As the predominant immune cell population in the endometrium during implantation and early pregnancy, uNK cells are essential for angiogenesis and successful implantation (Rajagopalan et al., 2005). As illustrated in Figure 2. *Immunomodulatory Effects of SP on Endometrial Receptivity*, SP plays a dual role in modulating the uterine environment through both beneficial immunotolerance mechanisms and potentially adverse inflammatory or oxidative pathways.

UNK cells are the predominant leukocyte population in the endometrium during the implantation window and play a critical role in regulating trophoblast invasion (Moffett-King, 2002). These cells contribute significantly to angiogenesis during embryo implantation by expressing key growth factors, such as vascular endothelial growth factor (VEGF), which are essential for blood vessel formation (Rizov et al., 2017). Studies have shown that the absence of uNK cells can lead to histopathological abnormalities at implantation sites, particularly in the decidualization zone (Guimond et al., 1997). Furthermore, research indicates that insufficient uNK cell activation, triggered by paternally inherited conceptus antigens, is associated with gestational complications such as recurrent spontaneous abortion, fetal growth restriction, PE, and preterm labor (Rätsep et al., 2015). Interestingly, an in-vitro study has demonstrated that human SP can significantly suppress the activity of NK cells in peripheral blood leukocytes, suggesting a complex interaction between SP and immune modulation in the female reproductive tract (Ribeiro et al., 2021).

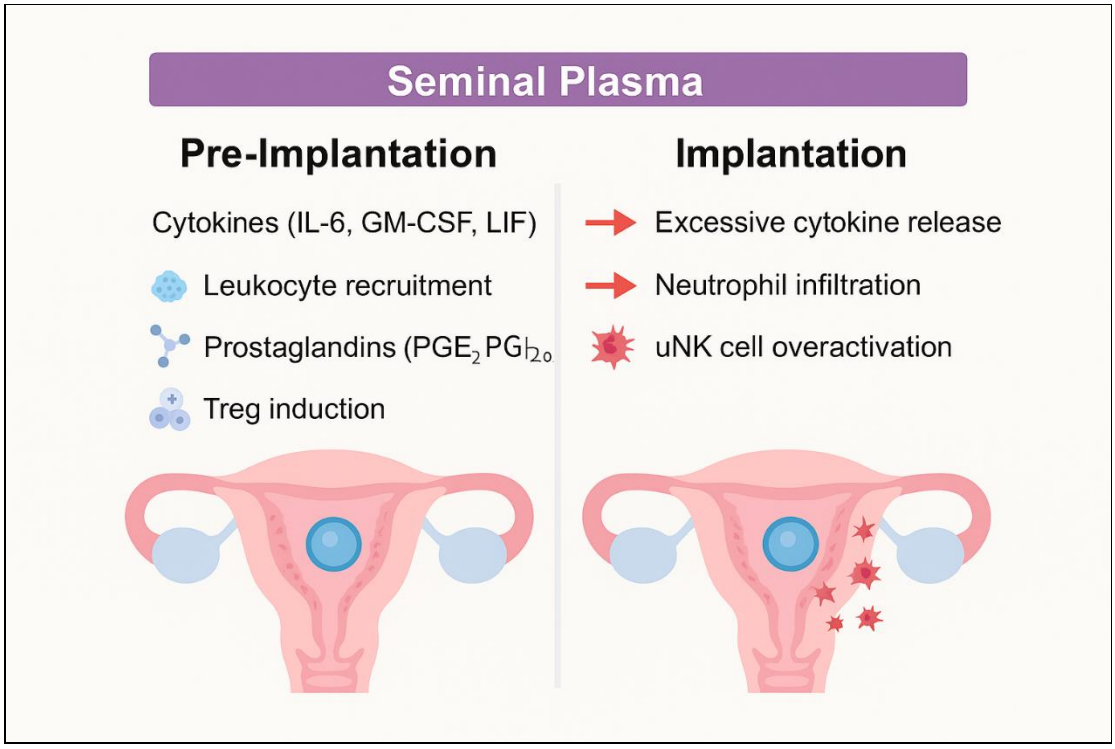

Figure 2. Immunomodulatory Effects of SP on Endometrial Receptivity

Approximately half of all human embryo implantations result in failed pregnancies, with causes ranging from genetic or metabolic abnormalities in the embryo to poor uterine receptivity. A significant proportion of early spontaneous abortions is linked to inadequate endometrial receptivity (Dekel et al., 2010b). Embryo implantation begins with the apposition of the blastocyst to the uterine endometrium, followed by its attachment to the endometrial surface epithelium (Sharkey et al., 2012). This process has been likened to an "open wound" that requires a robust inflammatory response (Mor et al., 2011). As the blastocyst breaches the uterine epithelial lining to implant, it creates a site of cellular invasion, death, and repair (Dekel et al., 2010b). Exposure to SP during coitus has been shown to induce significant changes in leukocyte populations within the cervix, triggering an inflammatory response that extends from the stratified epithelial layer into the deeper stroma of the ectocervix (Dekel et al., 2010b). Notably, this inflammatory reaction is absent in cases where coitus does not occur or when condoms are used, thereby supporting the role of SP in modulating immune responses in the female reproductive tract (Sharkey et al., 2012).

We hypothesise that sexual intercourse during the implantation window, when blastocyst implantation is most likely, may negatively impact reproductive success. During this period, SP is introduced into the female reproductive tract, releasing potent inflammatory mediators, including leukocytes, T cells, TNF, and prostaglandins, mainly PGE2 (Samuelsson, 1963; Templeton et al., 1978). Prostaglandins are strong chemotactic factors for neutrophils and can amplify the immune response at the implantation site, which Mor G. et al. describe as an "open wound." This heightened immune activity may disrupt the delicate balance required for successful implantation, potentially leading to implantation failure (Chan & Robertson, 2025; Dekel et al., 2010b; Pantos et al., 2022).

Furthermore, uNK cells are essential for implantation, trophoblast invasion, and placentation (Greenwood et al., 2000; Le Bouteiller & Piccinni, 2008). Studies have demonstrated that in the absence of uNK cells, trophoblasts fail to reach the endometrial vasculature, leading to pregnancy termination (Hanna et al., 2006). Ribeiro's research further supports this by showing that human SP significantly suppresses NK cell activity, reinforcing the hypothesis that SP negatively impacts implantation. This suppression may impair trophoblast invasion, leading to inadequate placentation and increasing the risk of pregnancy complications such as miscarriage, PE, intrauterine growth restriction (IUGR), and preterm birth syndrome (PTBs). Seminal fluid may also influence reproductive tract vasculature. In vitro studies using HeLa cells show that SP upregulates pro-angiogenic factors like IL-8 and GRO (Guo et al., 2019). Notably, women lacking prior exposure to a partner's seminal fluid, such as those using donor sperm/eggs or conceiving early in a relationship, face a higher risk of PE (Sadat et al., 2012). This suggests that seminal fluid may mitigate PE risk by promoting endometrial vascular remodeling, which is often impaired in the condition (Chan & Robertson, 2025).

5. Clinical Implications and Translational Perspectives

The evolving understanding of SP as an immunologically active fluid with both beneficial and harmful potential opens new avenues for reproductive health interventions. While SP primes maternal immunity and prepares the uterus for implantation, its timing and dosage are critical**,** especially in couples struggling with infertility, recurrent implantation failure (RIF), or pregnancy complications.

5.1 ART, RPL, and Timing of Intercourse

In (ART), especially IVF (IVF), SP exposure has been proposed as a beneficial immunomodulatory adjuvant (Chicea et al., 2013). Exposure to SP before embryo transfer has been shown in some studies to enhance endometrial receptivity, increase the expression of implantation-associated cytokines (e.g., GM-CSF, IL-6, LIF), and improve pregnancy rates (Ahmadi et al., 2022; Shen et al., 2023). However, this benefit is strictly phase-dependent.

In the context of assisted reproduction (ART), the uterine environment is uniquely devoid of natural SP exposure, which may render the endometrium immunologically 'blind' to paternal antigens. Several randomized controlled trials and meta-analyses have aimed to restore SP exposure around oocyte retrieval or embryo transfer. A meta-analysis of seven RCTs (n = 2,204) found a statistically significant increase in clinical pregnancy rate (RR ~1.23) with SP application, though live birth effects were not proven (data heterogeneous) (Crawford et al., 2015). The *Cochrane Review* similarly concluded that evidence is insufficient to confirm effects on live birth or miscarriage in ART, though low-quality evidence suggests improved clinical pregnancy rates (Ata et al., 2018). Biomarker-based work is emerging, suggesting intravaginal SP may boost implantation potential in ART cycles (van den Berg et al., 2024). These findings make ART a fertile testing ground for your timing hypothesis: because ART cycles circumvent natural SP exposure, they offer a relatively controlled intervention setting to test whether timed SP reintroduction can modulate uterine immunity and improve pregnancy outcomes.

5.2 Abstinence During Implantation Window: A Novel Strategy

Emerging hypotheses, including the one advanced in this review, suggest that avoiding sexual intercourse during the implantation window (days 5–10 post-ovulation) may reduce uterine inflammation, enhance immune balance, and improve embryo attachment (Steiner et al., 2014). Such a strategy would aim to preserve the decidual immune microenvironment by avoiding post-coital leukocyte infiltration, cytokine spikes, and prostaglandin-driven uterine contractions, all of which could disrupt embryo attachment (Glasser et al., 1987; Pantos et al., 2022; Salleh, 2014). Consistent with this timing-based hypothesis, Ibrahim et al. conducted a single-centre pilot randomized controlled trial comparing peri-implantation sexual abstinence for 14 days post-ovulation with non-abstinence and reported no early low-lying placenta in the abstinence arm compared with 5/24 cases (20.8%) in the non-abstinence arm; however, the difference was not statistically significant, and the findings should be interpreted as hypothesis-generating rather than definitive (Ibrahim et al., 2025). As shown in

Figure ***3****:* Explained hypothesis Mechanistic and observational data suggest that peri-implantation exposure may provoke local leukocyte recruitment and transient cytokine/prostaglandin responses; whether these perturbations affect clinical implantation outcomes remains to be tested in controlled trials), SP exposure during this critical window can lead to leukocyte infiltration, cytokine surges, and prostaglandin-induced uterine contractions, potentially disrupting embryo-endometrial synchrony and impairing implantation outcomes. affects implantation and live birth outcomes; details will be prospectively registered and reported.

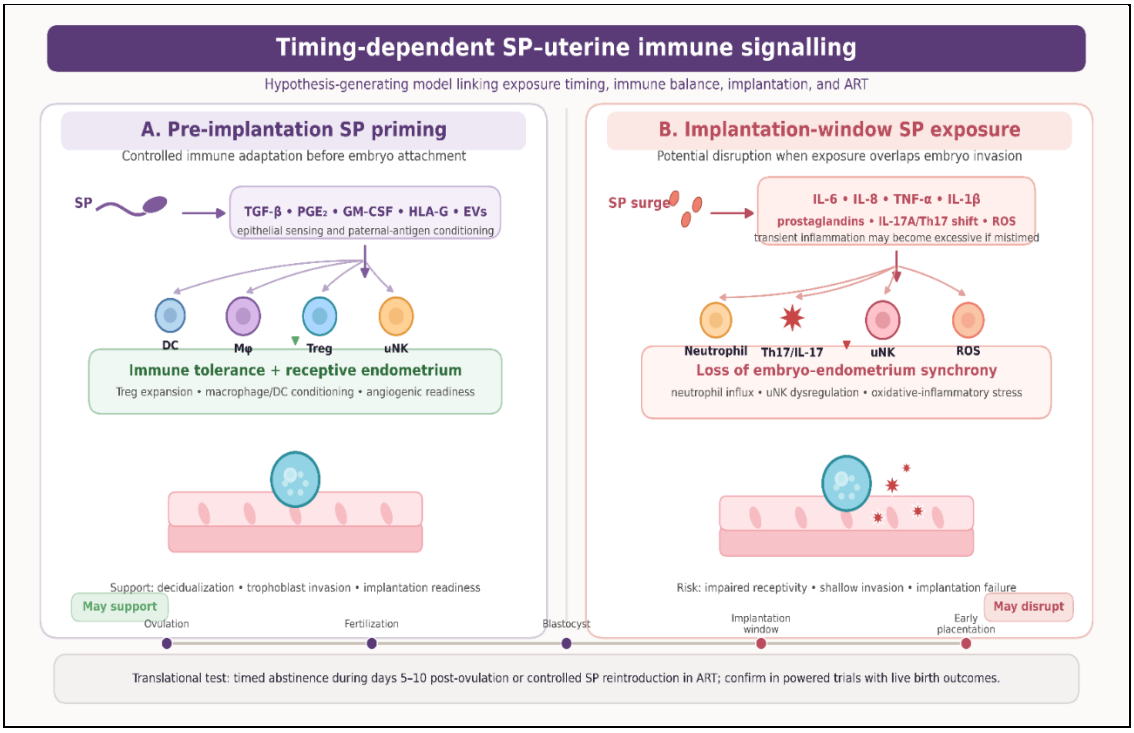

Figure 3: Explained hypothesis: Conceptual model: temporal separation between SP exposure and implantation. Mechanistic and observational data suggest that peri-implantation SP exposure may provoke local leukocyte recruitment and transient cytokine/prostaglandin responses. Preliminary randomized evidence is compatible with this timing-based model, but current clinical data remain underpowered and require confirmation in larger, adequately controlled trials

6. DISCUSSION

This narrative review synthesizes mechanistic, animal, and human evidence showing that SP has a dual immunomodulatory role in the female reproductive tract: when exposure occurs before implntation SP promotes maternal immune adaptation (decidualization, regulatory T-cell expansion, angiogenesis) that supports embryo implantation, whereas peri-implantation exposure can provoke a transient but potent pro-inflammatory response (↑IL-6, IL-8, TNF-α, IL-17A and altered Th17:Treg balance) that may disrupt trophoblast invasion, impair endometrial receptivity, and increase the risk of implantation failure or adverse placentation (Bromfield, 2014; Sharkey et al., 2012; Shen et al., 2023). Human observational data (e.g., reduced fecundability with intercourse during the implantation window) (Steiner et al., 2014) and epidemiologic links between limited preconception SP exposure and PE provide translational context (Saftlas et al., 2014), while ART studies that apply SP around transfer report increased clinical pregnancy but inconsistent effects on live birth, underscoring the phase- and context-dependent nature of SP effects (Crawford et al., 2015).

These main findings align with and extend prior work. Mechanistic and animal studies described by Robertson and colleagues and Bromfield demonstrate how SP components such as TGF-β and prostaglandins prime tolerogenic pathways and expand Treg populations, mechanisms that plausibly underlie improved implantation after prior SP exposure (Bromfield, 2014; Robertson et al., 2009). Conversely, in vitro and animal reports implicating IL-6, TNF-α, and IL-17A signaling in impaired trophoblast invasion and shallow placentation support the notion that timing matters, an immune stimulus that primes tolerance at one timepoint may be disruptive if delivered during the peri-implantation wound-healing/invasion phase (du Fossé et al., 2023; Shen et al., 2023; Song et al., 2016)

Clinical data are mixed but informative. Several trials and meta-analyses in ART suggest that intravaginal or intracervical application of SP around oocyte retrieval or embryo transfer can increase clinical pregnancy rates, though evidence for improved live birth is lacking and heterogeneity is high (Ata et al., 2018; Crawford et al., 2015). Observational epidemiology similarly gives a nuanced picture: cumulative preconception SP exposure has been linked to lower PE risk(Saftlas et al., 2014), indicating a beneficial priming effect before pregnancy, while peri-implantation intercourse has been associated with reduced fecundability in at least one cohort, suggesting a potential adverse effect of mistimed exposure (Steiner et al., 2014). More recently, preliminary randomized evidence from Ibrahim et al. extended this hypothesis into a clinical abstinence model, showing a lower point estimate of early low-lying placentation after peri-implantation abstinence, although the small sample size, wide confidence intervals, and non-significant result preclude causal inference. Taken together, these data

support a timing-based framework in which the same SP signals produce beneficial or harmful outcomes depending on when they encounter the endometrium and the maternal immune milieu.

From a translational perspective, ART cycles represent an attractive and ethically feasible setting to test timing hypotheses: because natural SP contact is absent, peri-transfer SP application can be precisely timed and randomized, and endpoints (implantation, clinical pregnancy, live birth) are straightforward to measure. Future trials should be adequately powered, prospectively registered, and include live birth as the primary outcome; secondary outcomes should include implantation rate, miscarriage, and standardized immune biomarkers (endometrial cytokine panels, Treg/Th17 ratios, uNK cell phenotype). Patient subgroups most likely to benefit from timing interventions, women with recurrent implantation failure (RIF), recurrent pregnancy loss (RPL), or evidence of endometrial inflammation, should be prioritized for stratified analyses (Moreno et al., 2023; Zhou et al., 2021)

Important caveats and limitations temper clinical recommendations. Much of the mechanistic evidence derives from animal models or in vitro systems and may not fully recapitulate human peri-implantation dynamics; existing human clinical studies are heterogeneous in SP preparation, route of application, timing relative to transfer, and outcome reporting. Standardized SP assays and preparation protocols are lacking, making cross-study comparisons difficult. There is also a potential trade-off: while limiting peri-implantation SP exposure could reduce deleterious acute inflammation for some couples, insufficient prior SP exposure might theoretically increase risks such as PE in susceptible patients (Ibrahim et al., 2025). Finally, behavioural interventions (sexual abstinence during the implantation window) have psychological and relational consequences that must be considered in shared decision-making.

In summary, SP is a biologically active fluid with both foundational and potentially disruptive immunological actions. The evidence compiled here supports a hypothesis-generating, timing-based model: optimal reproductive outcomes may depend not only on the presence of SP but also on when the endometrium is exposed. Carefully designed randomized trials, particularly in ART settings, are needed to determine whether peri-implantation abstinence or controlled SP reintroduction can improve implantation and live birth outcomes, and to identify which patients are most likely to benefit. Until then, clinical recommendations should remain cautious and individualized, balancing biological plausibility with the current limitations of human evidence.

7. CONCLUSION

SP is far more than a vehicle for sperm transport, it is a biologically active modulator of immune responses, uterine receptivity, and implantation success. While early exposure to SP supports immune tolerance, decidualization, and vascular remodeling, mistimed exposure, particularly during the implantation window, can lead to inflammatory overstimulation, impaired trophoblast invasion, and adverse pregnancy outcomes including implantation failure, miscarriage, and PE.

This review highlights a compelling and underexplored hypothesis: that avoiding SP exposure during the implantation window may preserve uterine immune balance and improve reproductive outcomes in select clinical populations. Supported by evidence from murine studies, in vitro models, and emerging clinical data, this hypothesis warrants formal evaluation in well-designed prospective studies. If validated, such a strategy could offer a simple, cost-free, and non-pharmacologic intervention to support fertility, especially in individuals facing immune-related implantation barriers or unexplained pregnancy loss. Future research should aim to refine the optimal timing of SP exposure and explore personalized reproductive strategies based on immune profiling. In the era of precision medicine, reconsidering the timing of intercourse may be a key step toward optimizing maternal-fetal immune dialogue and improving pregnancy success.

Authors' contributions:

Ola Hamad Salah Rashid, Abubakar Ibrahim, Wasan Hamad Jasim, and Manar Al-Hoda Zaid Mahmood Al-Faqheri: Conceptualization, Methodology, Writing – Original Draft, Project Administration.

Nik Ahmad Zuky Nik Lah and Abubakar Ibrahim: Conceptualization, Methodology, Supervision, Writing – Review & Editing.

Engku Husna Engku Ismail: Investigation, Validation, Final Review and Approval.

Nik Syamim Firdaus Nik Ahmad Zuky: Writing – Review & Editing.

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All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

Conflict of interests

The author declares no competing interests.

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Author Expertise and Central Hypothesis

Members of the author group have previously published related work on oxidative stress, pregnancy complications, and pre-eclampsia mechanisms (Ibrahim et al., 2024; Mahdy et al., 2022; Bansal et al., 2025).

The Ssecondary aim of this hypothesis-driven review is to explore whether peri-implantation exposure to SP contributes causally to the pathogenesis of pre-eclampsia (PE) by triggering oxidative–inflammatory pathways at the maternal–fetal interface. The authors propose that mistimed or excessive SP–mediated immune activation during the peri-implantation window may initiate a cascade of local oxidative stress, impaired trophoblast invasion, and abnormal placentation that ultimately predisposes to PE. This hypothesis is biologically plausible and supported by evidence linking oxidative stress to PE, as well as by prior work from the author team on oxidative stress and pregnancy biomarkers

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