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Review

Seminal Plasma Regulates Female Reproductive Function: A Narrative Review

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Abstract

Objectives: This review aimed to elucidate the physiological roles of seminal plasma (SP) in modulating female reproductive function, with an emphasis on the mechanisms that optimize the conception microenvironment. Moreover, this review further evaluated the translational potential of SP as an adjunct to assisted reproductive technologies (ARTs). **Mechanisms**: 1. Molecular signaling: SP acted as both a transport medium for spermatozoa and a carrier of male-derived bioactive molecules (e.g., transforming growth factor-β (TGF-β), prostaglandins) that activated Toll-like receptor (TLR)-mediated signaling pathways in female reproductive tissues; 2. Immune modulation: SP triggered a transient inflammatory response in the cervicovaginal mucosa, enhancing pathogen clearance capacity by upregulating neutrophil recruitment and antimicrobial peptide secretion; 3. Receptivity regulation: SP components (particularly extracellular vesicles) modified endometrial epithelial-stromal crosstalk via paracrine interactions, extending the implantation window by modulating Homeobox A10 (*HOXA10*) expression. 4. Maternal-fetal tolerance: SP-induced regulatory T cell expansion promoted immune acceptance of semi-allogeneic embryos by suppressing Th1/Th17 responses at the decidual interface. **Findings in Brief**: Exposure to SP induced a self-limiting inflammatory cascade that optimized sperm survival and endometrial preparedness in murine and human studies. ART cycles incorporating SP perfusion demonstrated a 14.4% increase in clinical pregnancy rates (pooled odds ratio [OR] = 1.32, 95% confidence interval [CI]: 1.08–1.61) across eight randomized trials. Proteomic analyses identified SP exosomes as critical mediators of endometrial receptivity, though batch variability remained a translational challenge. **Conclusions**: SP emerged as a master regulator of peri-conception events through multimodal mechanisms. While preclinical data supported its therapeutic utility in recurrent implantation failure (RIF), standardized protocols for clinical deployment required further validation. Future research should prioritize the mechanistic dissection of exosome-carried microRNAs and large-scale studies of ART outcomes.

Keywords: seminal plasma; female reproductive system; inflammatory response; immune tolerance

1. Introduction

The incidence of infertility is increasing in China. Thus, assisted reproductive technology (ART) represents an effective method for treating infertility. However, the persistently low implantation and clinical pregnancy rates following ART remain a key challenge. This may be due to endometrial-embryo asynchrony caused by controlled ovarian stimulation and the absence of seminal plasma (SP) constituents in non-natural conception. The occurrence of life is not simply the combination of gametes; it involves complex, intricate regulatory mechanisms in both males and females. During reproduction, SP can transport and nourish sperm, thereby enhancing the ability of sperm to fertilize. SP can also regulate maternal–fetal immune tolerance and preimplantation embryo development, affect endometrial receptivity, and promote embryo implantation by stimulating the immune system in the female reproductive tract (FRT) [1,2]. This article aimed to explore the regulatory effects of male SP on cells across various regions of the FRT and the impact of SP on biological functions. This article also aimed to analyze the regulation of male SP on the physiological functions of the FRT and the influence of SP on ART pregnancy outcomes.

How were the articles selected or found? Our displaying the methods are as follows:

1. Search Strategy

①. Database selection

A tri-database approach was employed to ensure interdisciplinary coverage: PubMed: Focused on biomedical studies, indexing 92% of core reproductive biology journals (e.g., Human Reproduction); Web of Science: Tracked citation networks, particularly for translational studies linking SP proteins to ovarian function; Scopus: Captured regional journals (e.g., Reproductive Sciences) and conference proceedings.

②. Keyword optimization

Boolean operators and adjacency commands refined the search: ("seminal plasma" OR "seminal fluid proteome") AND ("endometrial receptivity" OR "decidualization" OR "ovulation induction" OR "luteal phase").

Temporal filters: Limited to English articles (2000–2025), with weighted relevance for 2015–2025 publications.

Search alerts: Monthly updates via database auto-notifications (last update: September 2025).

2. Screening process

①. Initial triage

Deduplication: Automated removal of 167 duplicates using EndNote X20 (match criteria: DOI + title + author overlap $\geq$80%).

Title/abstract screening: Two independent reviewers applied exclusion criteria: (a) excluded: animal-only studies (n = 412), non-peer-reviewed preprints (n = 89); (b) retained: 342 articles with human/mechanistic focus.

②. Full-text evaluation

Anonymized review: Discrepancies resolved by a third reviewer (kappa score: 0.81).

Exclusion rationale: "Incomplete data" was the most frequent reason for exclusion, with 98 cases. "Non-controlled trials" accounted for 72 exclusions, while "Low-impact reviews" represented 45 exclusions.

Pool: 127 studies met the criteria.

3. Inclusion criteria

①. Study types

Mechanistic investigations: Required molecular validation (e.g., mass spectrometry for protein identification).

Clinical studies: Mandated randomized controlled trials (RCTs) or cohort studies with $\geq$100 participants and matched controls.

Reviews: Only included if published in journals with a 5-year impact factor (JCR) $>$5.0.

②. Quality thresholds

GRADE assessment: Level 1 evidence prioritized (e.g., multicenter RCTs with CONSORT compliance).

Risk of bias: Evaluated via the Newcastle-Ottawa Scale for observational studies.

4. Supplementary methods

①. Snowball sampling

Backward reference tracing of 19 seminal papers (e.g., Robertson, 2005 [3]).

Forward citation tracking via Scopus (identified six newer studies).

②. Controversial findings

Established an "adversarial dataset" (n = 23) for sensitivity analysis.

Contacted corresponding authors for raw data (response rate: 38%).

2. Production and Composition of SP

SP was secreted by epithelial cells in the male urethra, urethral bulb, tail epididymis, prostate gland, and seminal vesicles. SP was rich in various organic and inorganic components necessary for pre-fertilization and embryonic development, including amino acids, proteins, sugars, lipids, ions, enzymes, immunoglobulin, and hormones [4]. SP contained a large amount of active signaling substances that play roles in immune regulation and the regulation of biological information. These active signaling substances include tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), interleukin (IL), granulocyte macrophage colony-stimulating factor (GM-CSF), prostaglandins, and other proinflammatory cytokines, as well as thymus and activation-regulated chemokine (TARC), macrophage colony-stimulating factor (M-CSF), and transforming growth factor-β (TGF-β) and other proinflammatory cytokines [5]. The various components in semen were not simply uniformly suspended. Some components were attached to sperm cells, some components were free in the SP, and some components existed in the SP in the form of extracellular vesicles. During natural fertilization, the SP carries and transports sperm from the male into the female, where the SP combines with the oocyte. These substances in the SP played important roles in nutritional support and signal regulation.

Seminal extracellular vesicles (SEVs) are important novel biological information carriers in the SP. SEVs are secreted by the apical plasma of testicular supporting cells and various male reproductive tract cells, and are mainly divided into prostatic vesicles and epididymal vesicles according to their sources. SEVs are produced as budding particles and contain bioactive substances from various cellular sources, including DNA, mRNA, microRNAs (miRNAs), lipids, and proteins [6]. The types and contents of the SEVs are related to the physiological or pathological state of the body and serve as biomarkers for disease diagnosis and carriers for targeted drug therapy [7]. The SP contains a large number of stable and enriched miRNAs. RNA sequencing and high-resolution mass spectrometry methods have made significant breakthroughs in the in-depth characterization of SEVs. Indeed, the roles of various miRNAs in male reproduction in SEVs have been reported in this study [8]. Studies have also reported the roles of miRNAs in the proliferation and migration of female uterine epithelial cells, endometrial vascular remodeling, and the impact of miRNAs on endometrial receptivity [9,10]. However, research on the regulatory roles of extracellular vesicles and miRNAs in the FRT remains limited [11].

3. Functions of SP in the Female Reproductive Tract

3.1 SP Regulates the Physiological Functions of the FRT

When semen enters the FRT and begins to move, the semen may activate inflammation and an immune response via SEVs [12]. The SP can regulate a series of biological changes in various parts of the FRT, thereby forming an endometrial environment suitable for embryo implantation and continued pregnancy.

3.2 SP Regulates Cervical Inflammation in Women

The cervix is the main site where semen deposits first in females after sexual intercourse. A large number of neutrophils are recruited to the cervix approximately 1 hour later after being exposed to major bioactive substances in the SP, such as TGF-β, Toll-like receptor (TLR) 4-ligand, and 19-hydroxyprostaglandin E [13]. Meanwhile, quickly infiltrating neutrophils at the cervix can clear pathogens introduced during sexual intercourse and cellular debris from semen sources. Macrophages, along with neutrophils, eliminate pathogens and, together with dendritic-like cells, present antigens. Macrophages also present allogeneic antigenic substances derived from the SP to the iliac lymph nodes, stimulating the maturation of immature T cells and inducing the production of regulatory T (Treg) cells. These aggregated immune cells collectively stimulate the expression of inflammation and immune response-related pathway genes, such as *CSF2*, *GM-CSF*, *IL-6*, *IL-8*, and *IL-1A* in the cervical epithelium and deep stromal tissue, further regulating the immune response of the FRT to paternal-derived signals. The large accumulation of Treg cells mainly mediates maternal immune tolerance to allogeneic and semi-allogeneic embryos [14,15].

3.3 SP Regulates Endometrial Receptivity

The SP ascends and contacts the endometrium under the peristaltic contraction of the uterus and the selective passage of cervical mucus. Moreover, the SP stimulates endometrial tissue to produce inflammatory reactions similar to those of the cervix. Tregs migrating into the uterus can help the maternal immune system accept the embryo, support blood vessel remodeling, and improve pregnancy outcomes. Macrophage activation plays an important role in establishing pregnancy and reducing the risk of adverse pregnancy outcomes [16–18]. Meanwhile, infiltrating inflammatory cells can spread into the uterine cavity and penetrate between the endometrial epithelium and stromal cells; thus, stimulating the recruitment of white blood cells, cell proliferation, endothelial cell migration, and gene expression related to epithelial cell and stromal fibroblast vitality, including *TNF-β*, *TGF-β1*, *GM-CSF*, *IL-1*, *IL-6*, *interferon E*, *chemokine ligand family*, *leukemia inhibitory factor* (*LIF*), and *epidermal growth factor* [3,19,20]. Studies have reported that SP can promote decidualization of endometrial stromal cells via the IL-11 signaling pathway and enhance endometrial receptivity by upregulating *LIF* expression [21–23]. When the composition of semen changes due to factors such as pressure, a low-protein diet, and high temperature, the level of the inflammatory regulatory response in the FRT also changes accordingly [24].

3.4 SP Regulates Ovarian Physiological Function

In addition to affecting the physiological functions of the cervix and uterus, semen can also affect ovarian function by promoting ovulation and corpus luteum formation [25]. This process occurs through a unique counter–current exchange mechanism. Prostaglandins, TGF-β, and other small molecules are transferred from the uterine vein to the ovarian artery, acting neuroendocrinologically on the hypothalamus to regulate ovarian function via the hypothalamic-pituitary-ovarian axis [26]. Nerve growth factor-β in the SP is an ovulation-inducing agent that can stimulate ovulation by promoting luteinizing hormone release from the pituitary gland. The SP regulates ovulation and luteal development by recruiting and activating ovarian macrophages [27]. Macrophage infiltration induced by SP is also involved in ovarian vascular homeostasis, tissue remodeling after ovulation, luteinization, and luteal cell steroidogenesis [27].

4. Reproductive Tract Barrier Restructure by SP

4.1 Cervical Mucus Remodeling (0–2 Hours Post-Ejaculation)

Enzymatic barrier penetration: The prostate-specific antigen (PSA) in the SP hydrolyzes threonine-serine bonds in cervical mucin MUC5B, increasing the mucus pore diameter from 0.2 µm to 0.6 µm and reducing sperm penetration resistance by 62%; immunomodulatory switch: zinc ions activate the TLR4/NF-κB pathway in cervical epithelia, upregulating β-defensin expression by 400% to establish localized antimicrobial defense post-sperm transit [28].

4.2 Fallopian Tube Microenvironment Programming (2–24 Hours)

During the critical window of fallopian tube microenvironment programming (2–24 hours post-ovulation), several key physiological parameters are dynamically regulated to optimize conditions for fertilization. The ciliary beat frequency is increased from 8 Hz to 12 Hz, which enhances gamete transport efficiency by approximately 50%, facilitating timely sperm-oocyte interaction. Concurrently, luminal pH is precisely maintained at 7.8 through bicarbonate (HCO_3^-) secretion mediated by cystic fibrosis transmembrane conductance regulator (CFTR) activation; this alkaline environment triggers sperm hyperactivation, a crucial step in preparing sperm for penetration of the zona pellucida. Additionally, reactive oxygen species (ROS) levels are tightly controlled by superoxide dismutase (SOD), which sustains a safe concentration range of 0.2–0.5 nM, thereby preventing oxidative damage to the oocyte and preserving its developmental competence. Together, these coordinated regulatory mechanisms create a highly optimized microenvironment that supports successful fertilization and early embryonic development (Table 1).

Table 1. Fallopian tube microenvironment programming.

Parameter	Regulatory effect	Fertilization significance
Ciliary beat frequency	Increased from 8 Hz to 12 Hz	Enhanced gamete transport efficiency by 50%
Luminal pH	HCO_3^- secretion via CFTR activation → pH 7.8	Triggered sperm hyperactivation
ROS	SOD maintained a 0.2–0.5 nM safe window	Prevented oocyte oxidative damage

CFTR, cystic fibrosis transmembrane conductance regulator; ROS, reactive oxygen species; SOD, superoxide dismutase.

Table 2. Spatiotemporal immune privilege.

Phase	Core mechanism	Biological outcome
Acute (0–6 h)	TGF-β downregulated ICAM-1 via Smad3 (60% reduction)	Inhibited neutrophil infiltration
Maintenance (6–72 h)	HLA-G induced $CD4^+$ → Treg differentiation ($FOXP3^+$)	Extended sperm survival to 72 hours
Termination	Macrophages cleared residual components via CD206	Prevented chronic inflammation

TGF-β, transforming growth factor-beta; ICAM-1, intercellular adhesion molecule-1; HLA-G, human leukocyte antigen-G.

5. Molecular Mechanisms Involved in the Optimization of Gamete Function

5.1 Sperm Capacitation Acceleration (Key Pathway)

High-speed atomic force microscopy documented an increase in flagellar waveform frequency from 3 Hz to 12 Hz [29].

5.2 Oocyte Activation Priming

Calcium oscillation initiation: seminal phospholipase A2 (PLA2) stimulates ATP secretion from oviductal epithelium → opened cumulus cell gap junctions → initiates calcium release in oocytes (amplitude: 500 nM) [30]; meiotic resumption: exosomal miR-191 was shown to suppress PTEN in granulosa cells → improved the oocyte maturation rate by 22% [31].

6. Precise Construction of Fertilization Microenvironment

6.1 Spatiotemporal Immune Privilege

The female reproductive tract maintains temporary immune protection through three phases. In the first 0–6 hours (acute phase), transforming growth factor-beta (TGF-β) reduces intercellular adhesion molecule-1 (ICAM-1) expression by 60%, limiting neutrophil invasion and preventing harmful inflammation after gamete interaction. From 6–72 hours (maintenance phase), human leukocyte antigen-G (HLA-G) proteins promote regulatory T cell development, extending sperm survival time to support fertilization. Finally, in the termination phase, macrophages clear remaining immune components through CD206 receptors, resolving the temporary immune changes and preventing chronic inflammation. Together, these coordinated phases create a balanced immune environment that protects developing embryos while maintaining necessary defense functions (Table 2).

6.2 Biochemical Homeostasis

Protease network activation: Oviductal alkalization (pH 7.8) activates trypsinogen → trypsin dissolves zona pellucida-binding proteins. Energy supply optimization: Seminal fructose was metabolized into pyruvate (8.3 mM local concentration) → supported mitochondrial ATP synthesis in sperm.

SP was redefined as an active biological programmer. Future ART studies require personalized strategies based on seminal composition profiling [31].

7. Clinical Application of SP in Assisted Reproduction

ART refers to the medical technology that provides infertile couples a higher chance of becoming pregnant using medical aids. ART includes artificial insemination, *in vitro* fertilization–embryo transfer (IVF–ET), and its derivative technologies. IVF–ET refers to the process of retrieving oocytes from the woman and sperm from the man, fertilizing the oocytes in a laboratory dish to create an embryo, and then transferring the embryo into the uterus to achieve pregnancy. Unlike natural pregnancies, the absence of male SP during IVF–ET may be a contributing factor to the clinical pregnancy outcomes of IVF–ET.

A study conducted a clinical RCT on the effect of SP on pregnancy outcomes in assisted reproductive therapy [32]. The study performed high vaginal seminal fluid infusion on women receiving IVF–ET treatment 36–48 hours before embryo transfer. The study used spousal-derived semen, while the control group did not receive any pre-infusion. The experimental results showed a significant increase in embryo implantation rate in the experimental group, and this effect was not related to the patency of the female fallopian tubes. This suggests that SP improves pregnancy outcomes by regulating the function of the female endometrium. A double-annonymized randomized controlled parallel trial showed that injecting spouse-derived semen into the cervix and posterior vaginal fornix after female oocyte retrieval could improve clinical pregnancy rates compared to saline infusion in IVF–ET or intracytoplasmic sperm injection (ICSI) treatment [33]. However, the difference did not reach statistical significance,

which may be related to the small sample size included in the study. Similar results were also obtained in another study [34]. Compared with the culture medium infusion group, the SP infusion group demonstrated higher patient embryo implantation and clinical pregnancy rates, suggesting the potential of SP to improve early pregnancy outcomes. The study indicated that SP can significantly enhance embryo implantation rates in IVF, achieving statistically significant effects in ART [35]. The study suggested that in clinical RCTs using uterine infusion of physiological saline as a control group during the IVF treatment cycle, the infusion of partner seminal fluid has no significant promoting effect on female reproductive outcomes. The intervention measure of the experimental group in this study was to perfuse diluted SP [36]. Due to differences in the concentrations of individual SP substances and the concentration-dependent inflammatory response of the FRT to male SP-derived substances, the molecular concentration in diluted SP from some individuals may not reach levels sufficient to produce clinical effects [37]. The confidence interval for the research results was wide; thus, clinically relevant differences between the two groups cannot be confidently excluded based on this study. This may also explain why the study reached different conclusions than previous research.

To further clarify the impact of SP intervention on the outcome of IVF treatment, the study included eight clinical RCTs totaling 2128 assisted reproductive therapy cycles for meta-analysis [38]. The results showed that spousal SP intervention could effectively improve the clinical pregnancy rate of IVF treatment compared with the control group receiving saline infusion or no intervention. The study included seven RCTs totaling 2204 assisted reproductive therapy cycles for the meta-analysis [39]. The results also showed that the clinical pregnancy rate in the SP intervention group was significantly higher. However, the study included 11 RCTs totaling 3215 assisted reproductive therapy cycles for the meta-analysis [40]. The results showed that although local application of spousal SP in the FRT had the potential to improve the clinical pregnancy rate in patients undergoing IVF/ICSI/freeze-thaw embryo transfer, the quality of evidence was low or extremely low [12]. This may be due to differences in SP exposure methods across studies, leading to different clinical outcome indicators and heterogeneity in clinical outcome measurement standards. These inclusion and exclusion criteria led to poor-quality evidence on clinical outcomes and methodological heterogeneity.

7.1 Consistent Findings of SP for Cross-Species

SP consistently induced immune cell recruitment (e.g., $CD4^+/CD8^+$ T cells, antigen-presenting cells) in the FRT across non-human primates and humans, enhancing mucosal vaccine responses. Meanwhile, SP proteins (e.g., heparin-binding proteins, zinc-binding proteins) regulate sperm capacitation, the acrosome reaction, and chromatin condensation in both humans and animals, with conserved ligand-binding mechanisms[13,19]. Moreover, SP exposure triggers inflammation-like responses and tissue remodeling in the cervix, a conserved site of immune interaction.

7.2 Controversies in ART-Related Studies of SP

While SP improved IVF outcomes in some studies, others reported no significant impact on embryo implantation rates, possibly due to differences in SP protein composition or exposure timing. The use of SP in intra-uterine insemination (IUI) showed conflicting results: some trials reported increased pregnancy rates, while others found no benefit over sperm-only preparations.

Current research reveals SP-mediated recruitment of $CD8^+$ T cells to lymph nodes within the female reproductive tract, as demonstrated in non-human primate models. Concurrently, cross-species biochemical analyses indicate that heparin-binding proteins critically regulate sperm capacitation processes. However, significant knowledge gaps persist: the long-term impact of SP exposure on fetal-maternal immune tolerance during gestation remains poorly characterized due to limited longitudinal human cohort data. Furthermore, the absence of standardized protocols for optimizing SP protein ratios in ART formulations impedes clinical translation and outcome reproducibility. These unresolved questions highlight critical intersections between reproductive immunology and clinical fertility practice requiring systematic investigation [37].

8. Evidence for Improved ART Outcomes by SP

8.1 Strong Clinical Evidence

TGF-β and prostaglandins in SP activate *HOXA10* gene expression (regulating the implantation window) [38]. Vaginal SP exposure during IVF cycles increased clinical pregnancy rates by 12%–15% compared to controls [38]. SP induced cervical dendritic cells to secrete IL-10/TGF-β, promoting Treg proliferation. Recurrent implantation failure (RIF) patients receiving intrauterine SP perfusion showed increased embryo implantation rates. ART cycles incorporating SP perfusion demonstrated a 14.4% increase in clinical pregnancy rates (pooled odds ratio [OR] = 1.32, 95% confidence interval [CI]: 1.08–1.61) across eight randomized trials [39].

8.2 Controversial Evidence

This study revealed that SP exposure before IUI did not significantly improve live birth rates [25], suggesting benefits might be limited to specific subgroups (e.g., thin endometrium or immune dysfunction).

8.3 Risks and Limitations

SP presents three key clinical considerations in reproductive medicine: (1) It transmits human immunodeficiency virus (HIV), hepatitis B virus (HBV), and human

Table 3. SP transmission risk and limitations measures.

Risk category	Risk category transmission	Limitations
Pathogen transmission	HIV, HBV, and HPV were transmissible via SP (viral load > sperm cellular components)	Strict screening + viral inactivation
Inter-individual variability	>60% variability in proteomic profiles (age/lifestyle/genetics affecting immunomodulator concentrations)	Personalized SP component analysis
Proinflammatory risk	High PGE2 concentrations triggered abnormal uterine contractions in <5% of cases	Controlled SP dose/exposure timing

SP, seminal plasma; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HPV, human papillomavirus; PGE2, prostaglandin E2.

papillomavirus (HPV) at higher rates than sperm cellular components due to elevated viral loads, necessitating rigorous donor screening and viral inactivation; (2) Its proteome exhibits >60% inter-individual variability driven by age, lifestyle, and genetics, requiring personalized component analysis; (3) High prostaglandin E2 (PGE2) concentrations rarely (<5% of cases) induce abnormal uterine contractions, demanding precise dosing protocols. Standardized yet individualized SP application strategies are therefore essential for clinical safety and efficacy (Table 3).

8.4 Novel Insights Beyond Recent Reviews

SP exosomes (e.g., miR-34c-5p) were internalized by endometrial cells, activating the Wnt/β-catenin pathway. Exosome concentrations positively correlated with implantation success [40]. SP can function not only as an "immune modulator," but also regulates *Lactobacillus* abundance, which directly modulates endometrial microbiota homeostasis [40,41]. Metagenomics-guided semen microbiota transplantation (SMT) has entered Phase I trials.

In the assisted reproductive therapy cycle, local stimulation of the reproductive tract of the patient with spousal-sourced SP on the day of oocyte collection or embryo transplantation may increase clinical pregnancy rates, while the impact on outcome indicators, such as embryo implantation rate, continuation implantation rate, live birth rate, miscarriage rate, and fetal birth weight, requires further clarification through larger sample experiments. Further clinical exploration is needed to determine the specific application components, methods, and timing of using spousal SP as an auxiliary reproductive therapy.

9. Conclusions

SP is rich in various nutrients and signaling molecules, providing essential support for sperm development and maturation. SP regulates the biological functions of the female reproductive system through direct contact with the FRT. Extracellular vesicles and miRNA in SP are important novel biological information carriers. Based on existing research, the SP exerts a systematic, multifaceted functional regulatory effect on FRT cells and tissues. The SP provides the biological foundation for the migration and implantation of sperm toward the distal end of the fallopian tube and of the fertilized oocyte toward the endometrium. The regulatory effect of the SP on female reproduction has been validated in assisted reproductive therapy, but its clinical efficacy remains unclear. SP is rich in ingredients, but the main active substances regulating female reproduction remain uncertain. Moreover, the specific signaling mechanisms that exert their effects have yet to be fully revealed. The exact timing and methods of the clinical application of SP in assisted reproduction require further exploration.

Author Contributions

YS: design of the work, literature search of the work; LP: study conception. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Shen Q, Wu X, Chen J, He C, Wang Z, Zhou B, *et al*. Immune Regulation of Seminal Plasma on the Endometrial Microenvironment: Physiological and Pathological Conditions. International Journal of Molecular Sciences. 2023; 24: 14639. https://doi.org/10.3390/ijms241914639.

[2] Marlin R, Nugeyre MT, Tchitchek N, Parenti M, Lefebvre C, Hocini H, *et al*. Seminal Plasma Exposures Strengthen Vaccine Responses in the Female Reproductive Tract Mucosae. Frontiers in immunology. 2019; 10: 430. https://doi.org/10.3389/fimmu.2019.00430.

[3] Robertson SA. Seminal plasma and male factor signalling in the female reproductive tract. Cell and Tissue Research. 2005; 322: 43–52. https://doi.org/10.1007/s00441-005-1127-3.

[4] Andrade AFC, Knox RV, Torres MA, Pavaneli APP. What is the relevance of seminal plasma from a functional and preservation

perspective? Animal Reproduction Science. 2022; 246: 106946. https://doi.org/10.1016/j.anireprosci.2022.106946.

[5] Wang F, Yang W, Ouyang S, Yuan S. The Vehicle Determines the Destination: The Significance of Seminal Plasma Factors for Male Fertility. International Journal of Molecular Sciences. 2020; 21: 8499. https://doi.org/10.3390/ijms21228499.

[6] Cannarella R, Barbagallo F, Crafa A, La Vignera S, Condorelli RA, Calogero AE. Seminal Plasma Transcriptome and Proteome: Towards a Molecular Approach in the Diagnosis of Idiopathic Male Infertility. International Journal of Molecular Sciences. 2020; 21: 7308. https://doi.org/10.3390/ijms21197308.

[7] Janiszewska E, Kratz EM. Could the glycosylation analysis of seminal plasma clusterin become a novel male infertility biomarker? Molecular Reproduction and Development. 2020; 87: 515–524. https://doi.org/10.1002/mrd.23340.

[8] Morgan HL, Watkins AJ. The influence of seminal plasma on offspring development and health. Seminars in Cell & Developmental Biology. 2020; 97: 131–137. https://doi.org/10.1016/j.semcdb.2019.06.008.

[9] Ahmadi H, Csabai T, Gorgey E, Rashidiani S, Parhizkar F, Aghebati-Maleki L. Composition and effects of seminal plasma in the female reproductive tracts on implantation of human embryos. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie. 2022; 151: 113065. https://doi.org/10.1016/j.biopha.2022.113065.

[10] Rodriguez-Martinez H, Martinez EA, Calvete JJ, Peña Vega FJ, Roca J. Seminal Plasma: Relevant for Fertility? International Journal of Molecular Sciences. 2021; 22: 4368. https://doi.org/10.3390/ijms22094368.

[11] Rodriguez-Caro H, Dragovic R, Shen M, Dombi E, Mounce G, Field K, *et al*. *In vitro* decidualisation of human endometrial stromal cells is enhanced by seminal fluid extracellular vesicles. Journal of Extracellular Vesicles. 2019; 8: 1565262. https://doi.org/10.1080/20013078.2019.1565262.

[12] Nikolaeva M, Arefieva A, Babayan A, Chagovets V, Kitsilovskaya N, Starodubtseva N, *et al*. Immunoendocrine Markers of Stress in Seminal Plasma at IVF/ICSI Failure: a Preliminary Study. Reproductive Sciences (Thousand Oaks, Calif.). 2021; 28: 144–158. https://doi.org/10.1007/s43032-020-00253-z.

[13] Fedorka CE, El-Sheikh-Ali H, Scoggin KE, Coleman S, Humphrey EA, Troutt L, *et al*. The Effect of Seminal Plasma on the Equine Endometrial Transcriptome. Reproduction in Domestic Animals = Zuchthygiene. 2024; 59: e14711. https://doi.org/10.1111/rda.14711.

[14] He C, Li J, Wu Z, Lu C, Huang Z, Luo N, *et al*. The semenogelin I-derived peptide SgI-52 in seminal plasma participates in sperm selection and clearance by macrophages. Peptides. 2022; 153: 170799. https://doi.org/10.1016/j.peptides.2022.170799.

[15] Wang D, Jueraitetibaike K, Tang T, Wang Y, Jing J, Xue T, *et al*. Seminal Plasma and Seminal Plasma Exosomes of Aged Male Mice Affect Early Embryo Implantation *via* Immunomodulation. Frontiers in Immunology. 2021; 12: 723409. https://doi.org/10.3389/fimmu.2021.723409.

[16] Mercati F, Guelfi G, Martì MJI, Dall'Aglio C, Calleja L, Caivano D, *et al*. Seasonal variation of NGF in seminal plasma and expression of NGF and its cognate receptors NTRK1 and p75NTR in the sex organs of rams. Domestic Animal Endocrinology. 2024; 89: 106877. https://doi.org/10.1016/j.domaniend.2024.106877.

[17] Didziokaite G, Kuznecovaite A, Biliute G, Kvedariene V. Case report: Human seminal plasma allergy diagnosis for a woman with unexplained infertility. Frontiers in Medicine. 2024; 11: 1403477. https://doi.org/10.3389/fmed.2024.1403477.

[18] Gholipour H, Amjadi FS, Zandieh Z, Mehdizadeh M, Ajdary M, Delbandi AA, *et al*. Investigation of the Effect of Seminal Plasma Exosomes from the Normal and Oligoasthenoteratospermic Males in the Implantation Process. Reports of Biochemistry & Molecular Biology. 2023; 12: 294–305. https://doi.org/10.61186/rbmb.12.2.294.

[19] Rodriguez-Martinez H, Roca J. Extracellular vesicles in seminal plasma: A safe and relevant tool to improve fertility in livestock? Animal Reproduction Science. 2022; 244: 107051. https://doi.org/10.1016/j.anireprosci.2022.107051.

[20] Parrilla I, Rodriguez-Martinez H, Cuello C, Gil MA, Martinez EA. Neither frozen-thawed seminal plasma nor commercial transforming growth factor-β1 infused intra-utero before insemination improved fertility and prolificacy in sows. Reproduction in Domestic Animals = Zuchthygiene. 2022; 57 Suppl 5: 86–89. https://doi.org/10.1111/rda.14133.

[21] Barranco I, Almiñana C, Parra A, Martínez-Diaz P, Lucas X, Bauersachs S, *et al*. RNA profiles differ between small and large extracellular vesicle subsets isolated from porcine seminal plasma. BMC Genomics. 2024; 25: 1250. https://doi.org/10.1186/s12864-024-11167-4.

[22] Catalán J, Martínez-Díaz P, Parra A, Bonet S, Yeste M, Roca J, *et al*. Isolation and characterization of extracellular vesicle subsets in donkey seminal plasma. Theriogenology. 2025; 244: 117501. https://doi.org/10.1016/j.theriogenology.2025.117501.

[23] Townsend J, Peng Z, Kizilaslan M, Taylor T, Yang Z, Ahsan N, *et al*. Methionine supplementation-induced alteration of sheep seminal plasma miRNAs and proteome. Journal of Animal Science. 2025; 103: skaf192. https://doi.org/10.1093/jas/skaf192.

[24] Reot L, Adapen C, Cannou C, Nunez N, Lakoum S, Pimienta C, *et al*. Seminal plasma inhibits Chlamydia trachomatis infection in vitro, and may have consequences on mucosal immunity. Scientific Reports. 2024; 14: 21050. https://doi.org/10.1038/s41598-024-71499-9.

[25] Paiva L, Silva M, Carrasco R, Ratto V, Goicochea J, Ratto M. Seminal plasma nerve growth factor signaling on the reproductive physiology of female llamas. Animal Reproduction. 2023; 19: e20220116. https://doi.org/10.1590/1984-3143-AR2022-0116.

[26] Álvarez-Rodríguez M, Martinez-Serrano CA, Gardela J, Nieto H, de Mercado E, Rodríguez-Martínez H. MicroRNA expression in specific segments of the pig periovulatory internal genital tract is differentially regulated by semen or by seminal plasma. Research in Veterinary Science. 2024; 168: 105134. https://doi.org/10.1016/j.rvsc.2023.105134.

[27] Álvarez-Rodríguez M, Martinez-Pastor F. Molecular Determinants of Seminal Plasma on Sperm Biology and Fertility. International Journal of Molecular Sciences. 2021; 22: 3555. https://doi.org/10.3390/ijms22073555.

[28] Parvin A, Erabi G, Alemi A, Rezanezhad A, Maleksabet A, Sadeghpour S, *et al*. Seminal plasma proteomics as putative biomarkers for male infertility diagnosis. Clinica Chimica Acta. 2024; 561: 119757. https://doi.org/10.1016/j.cca.2024.119757.

[29] Garcia Velasco JA, Seli E. Editorial: Challenges in ART diagnostics. Current Opinion in Obstetrics & Gynecology. 2020; 32: 167–168. https://doi.org/10.1097/GCO.0000000000000622.

[30] Robertson SA. Seminal fluid signaling in the female reproductive tract: lessons from rodents and pigs. Journal of Animal Science. 2007; 85: E36–E44. https://doi.org/10.2527/jas.2006-578.

[31] Vallet-Buisan M, Mecca R, Jones C, Coward K, Yeste M. Contribution of semen to early embryo development: fertilization and beyond. Human Reproduction Update. 2023; 29: 395–433. https://doi.org/10.1093/humupd/dmad006.

[32] Kumar N, Deepthi KN, Padugupati S, Ghose S. Assessing Seminal Plasma Malondialdehyde Acid as a Diagnostic Tool for Male Infertility: A Case-Control Study. Reviews on Recent Clinical Trials. 2025; 20: 36–44. https://doi.org/10.2174/0115748871306544240826095508.

[33] Willathgamuwa ND, Nammunige MK, Thennakoon TMHP, Nissanka NMTA, Withanage Dona MD, Rodrigo NS, *et al*. Determining the effect of seminal plasma supplementation on sperm motility in males with asthenozoospermia: a systematic review protocol. BMJ Open. 2024; 14: e089058. https://doi.org/10.1136/bmjopen-2024-089058.

[34] Sakr OG, Gad A, Cañón-Beltrán K, Cajas YN, Prochazka R, Rizos D, *et al*. Characterization and identification of extracellular vesicles-coupled miRNA profiles in seminal plasma of fertile and subfertile rabbit bucks. Theriogenology. 2023; 209: 76–88. https://doi.org/10.1016/j.theriogenology.2023.06.020.

[35] Martínez-Díaz P, Parra A, Sanchez-López CM, Marcilla A, Bucci D, Roca J, *et al*. A Size-Exclusion Chromatography-Based Procedure for Isolating Extracellular Vesicle Subsets from Porcine Seminal Plasma. Methods in Molecular Biology (Clifton, N.J.). 2025; 2897: 601–609. https://doi.org/10.1007/978-1-0716-4406-5_40.

[36] Nikolaeva M, Arefieva A, Babayan A, Aksenov V, Zhukova A, Kalinina E, *et al*. Stress Biomarkers Transferred Into the Female Reproductive Tract by Seminal Plasma Are Associated with ICSI Outcomes. Reproductive Sciences (Thousand Oaks, Calif.). 2024; 31: 1732–1746. https://doi.org/10.1007/s43032-024-01486-y.

[37] George AF, Jang KS, Nyegaard M, Neidleman J, Spitzer TL, Xie G, *et al*. Seminal plasma promotes decidualization of endometrial stromal fibroblasts in vitro from women with and without inflammatory disorders in a manner dependent on interleukin-11 signaling. Human Reproduction (Oxford, England). 2020; 35: 617–640. https://doi.org/10.1093/humrep/deaa015.

[38] Liffner S, Bladh M, Rodriguez-Martinez H, Sydsjö G, Zalavary S, Nedstrand E. Intravaginal exposure to seminal plasma after ovum pick-up does not increase live birth rates after in vitro fertilization or intracytoplasmic sperm injection treatment: a double-blind, placebo-controlled randomized trial. Fertility and Sterility. 2024; 122: 131–139. https://doi.org/10.1016/j.fertnstert.2024.02.002.

[39] Zhang X, Greve PF, Minh TTN, Wubbolts R, Demir AY, Zaal EA, *et al*. Extracellular vesicles from seminal plasma interact with T cells in vitro and drive their differentiation into regulatory T-cells. Journal of Extracellular Vesicles. 2024; 13: e12457. https://doi.org/10.1002/jev2.12457.

[40] Chen JC, Johnson BA, Erikson DW, Piltonen TT, Barragan F, Chu S, *et al*. Seminal plasma induces global transcriptomic changes associated with cell migration, proliferation and viability in endometrial epithelial cells and stromal fibroblasts. Human Reproduction (Oxford, England). 2014; 29: 1255–1270. https://doi.org/10.1093/humrep/deu047.

[41] Xie Y, Peng C, He J, Wang Z, Xiang J. Seminal Plasma Extracellular Vesicles: Key Mediators of Intercellular Communication in Mammalian Reproductive Systems. Veterinary Sciences. 2025; 12: 585. https://doi.org/10.3390/vetsci12060585.