Am J Clin Exp Immunol 2025;14(4):167-184
www.ajcei.us /ISSN:2164-7712/AJCEI0163843

Review Article

The immunomodulatory role of seminal plasma in endometrial receptivity and embryo implantation

Zahra Kanannejad[1], Nassim Kheshtchin[1,2], Hesamedin Nabavizadeh[1,3]

[1]Allergy Research Center, Shiraz University of Medical Sciences, Shiraz, Iran; [2]Department of Immunology, Shiraz University of Medical Sciences, Shiraz, Iran; [3]Department of Allergy and Clinical Immunology, Namazi Hospital, Shiraz, Iran

Received February 11, 2025; Accepted June 9, 2025; Epub August 15, 2025; Published August 30, 2025

Abstract: Successful implantation and pregnancy rely on complex interactions between the embryo and the maternal reproductive tract. Seminal plasma components, including proteins, cytokines, and growth factors, are pivotal in enhancing endometrial receptivity and inducing maternal immune tolerance to the developing conceptus. Exposure to seminal plasma facilitates pathogen clearance, supports embryo development, and modulates immune responses by altering the endometrial transcriptome and promoting regulatory T cell (Treg) expansion. Proteomic studies have identified seminal plasma factors involved in these processes. Changes in the immunomodulatory components of seminal plasma can diminish its positive effects on the endometrium, potentially resulting in reduced fertility and increased risk of adverse pregnancy outcomes. This review explores how seminal plasma influences maternal immune responses and highlights the clinical implications, particularly its potential to improve outcomes in assisted reproductive technologies (ART) like in vitro fertilization (IVF). Understanding the molecular dialogue between seminal plasma and the endometrium may lead to new strategies for enhancing fertility and promoting healthy pregnancy.

Keywords: Fertility, seminal plasma, embryo implantation, maternal immune tolerance, regulatory T-cell

Introduction

The successful establishment of pregnancy is a complex and delicate process that requires a harmonious interplay between the embryo and the maternal immune responses in the uterine environment [1]. The old concept that pregnancy is associated with immune suppression has created a myth of pregnancy as a state of immunological weakness and, therefore, of increased susceptibility to infectious diseases [2]. However, recent evidence underscores that the immune system during pregnancy is highly active, balancing the dual roles of fostering a supportive environment for fetal development and protecting both mother and fetus from pathogens.

A critical component of this dynamic interplay is the role of seminal plasma in modulating endometrial receptivity and inducing maternal tolerance to the semi-allogenic conceptus. Seminal plasma is a complex mixture of biomolecules such as proteins, lipids, carbohydrates, and signaling molecules. Seminal plasma serves as a protective and nourishing environment for sperm while also playing an essential role in facilitating communication between the male and female reproductive tissues. Seminal plasma is instrumental in preparing the female reproductive tract for pregnancy [3, 4]. Upon deposition in the female reproductive tract, seminal plasma triggers immune responses that help pathogen clearance, enhance tissue remodeling, and establish maternal tolerance. This immune tolerance induction by seminal plasma has implications for improving outcomes in assisted reproductive technology (ART) and managing pregnancy complications.

This review discusses the immunological components of seminal plasma and their interactions with the female reproductive tract, emphasizing their role in shaping maternal immune tolerance and reproductive success.

https://doi.org/10.62347/FNFJ5275

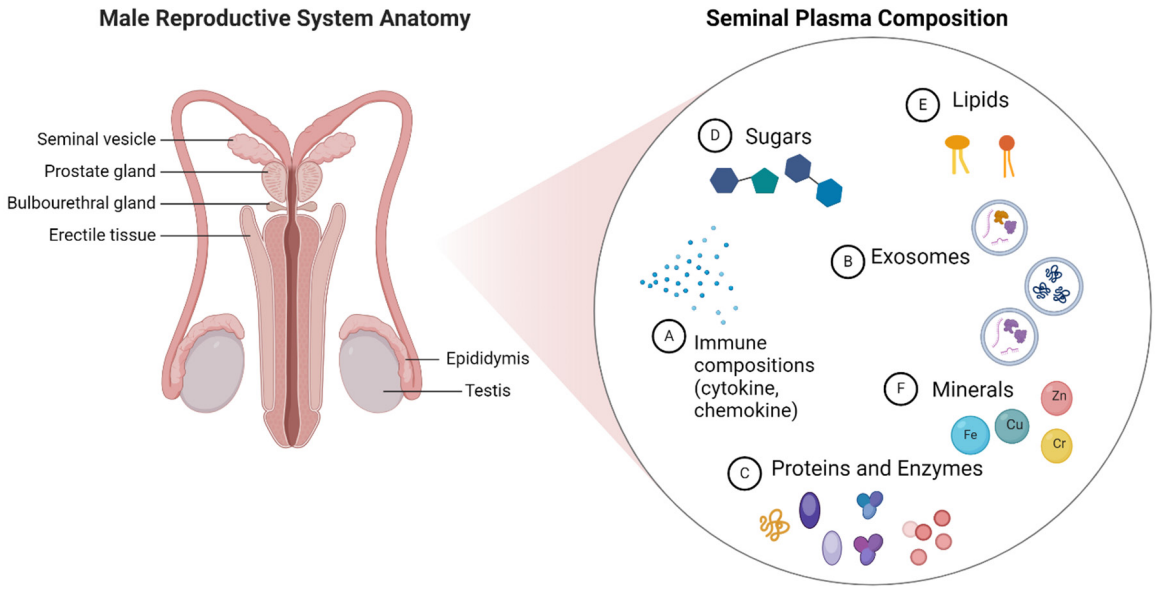

Figure 1. Anatomy of the male reproductive system and composition of seminal plasma. Left: Key anatomical structures involved in seminal plasma production, including the seminal vesicle, prostate gland, bulbourethral gland, epididymis, and testis. Right: Major constituents of seminal plasma: (A) immune factors (cytokines, chemokines); (B) exosomes; (C) proteins and enzymes; (D) sugars; (E) lipids; (F) minerals (Zn, Cu, Fe, Cr).

Seminal plasma

Seminal plasma is a complex biological fluid that contains secretions from the testis, epididymis, prostate, seminal vesicles, and Cowper's glands. It comprises various biochemical components, including exosomes, microRNAs (miRNAs), immunomodulatory agents (cytokines and chemokines), peptides, and proteins (**Figure 1**). Seminal plasma is traditionally considered a medium for sperm transport and protection within the female reproductive tract [5]. Beyond its transport function, seminal plasma facilitates maternal immune adaptation and endometrial receptivity, critical for successful implantation and pregnancy maintenance [6-8]. Here is a summary of seminal plasma components and their roles in modulating female reproductive immune responses.

Immunomodulatory agents

The seminal plasma contains various signaling molecules with immunomodulatory effects that regulate immune responses in the female reproductive tract [9-13]. These molecules influence endometrial gene expression, immune cell recruitment, and local tolerance. Key agents include TGF-β, interleukin (IL)-10, IL-1, IL-6, IL-8, tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), granulocyte-macrophage colony-stimulating factor (GM-CSF), Activin A, prostaglandin E2 (PGE2), and soluble human leukocyte antigen G (sHLA-G) [14, 15]. Their collective actions promote Treg induction, leukocyte activation, and tissue remodeling, which are essential for successful implantation (**Table 1**).

Exosomes

Seminal plasma is a rich source of exosomes and extracellular vesicles that carry proteins, lipids, and nucleic acids, including miRNAs. Examining proteins in seminal exosomes has found a diverse collection of proteins that play a crucial role in the interaction with the female reproductive system. Dysregulation of exosome-associated proteins has been linked to male infertility, particularly in conditions like varicocele. Profiling the exosomal proteome can provide insights into the underlying causes of infertility. Some important proteins can be found in seminal exosomes: RAB27A, KIF5B, CRISP1, SPAG11B, DEFB126, Transferrin, SEMG1, and protease [28]. The result of a study showed that exosome-associated proteins in seminal plasma actively signal to cells of the endometrium and can promote decidualization of endometrial stromal fibroblasts (eSFs) in

Table 1. Key immunomodulatory agents in seminal plasma and their functions

Agent	Type	Primary Functions in Female Reproductive Tract
TGF-β (β1, β2, β3)	Anti-inflammatory cytokine	Induces Tregs, inhibits Th1 responses, enhances GM-CSF, IL-6, LIF expression; promotes immune tolerance [16]
IL-10	Anti-inflammatory cytokine	Suppresses inflammatory responses; promotes immune tolerance [17, 18]
IL-1, IL-6, IL-8, IL-18	Pro-inflammatory cytokines	Stimulate leukocyte recruitment, endometrial gene expression (e.g., LIF), and embryo implantation readiness [19, 20]
TNF-α, IFN-γ	Pro-inflammatory cytokines	Enhance early inflammatory responses; may influence uterine receptivity and local immunity [13, 21]
GM-CSF	Growth factor/cytokine	Promotes endometrial remodeling, leukocyte activation, and embryotrophic support [13, 22, 23]
Activin A, Follistatin	TGF-β superfamily members	Induce cervical inflammation post-coitus; modulate immune response [19, 20]
GDF15	Divergent TGF-β family	Possibly attenuates immune response during coitus [24]
PGE2	Lipid mediator	Promotes Treg development; induces tolerogenic DCs; enhances PTGS2 expression and immune modulation [25]
sHLA-G	Immune checkpoint molecule	Contributes to maternal-fetal tolerance; inhibits NK and T-cell responses [26]
VEGF, EGF, FGF, G-CSF	Growth factors	Support angiogenesis, embryo growth, endometrial receptivity [27]

TGF-β, Transforming Growth Factor Beta; IL, Interleukin; TNF-α, Tumor Necrosis Factor Alpha; IFN-γ, Interferon Gamma; GM-CSF, Granulocyte-Macrophage Colony-Stimulating Factor; GDF15, Growth Differentiation Factor 15; PGE2, Prostaglandin E2; sHLA-G, Soluble Human Leukocyte Antigen-G; VEGF, Vascular Endothelial Growth Facto; EGF, Epidermal Growth Factor; FGF, Fibroblast Growth Factor; G-CSF, Granulocyte Colony-Stimulating Factor; PTGS2, prostaglandin-endoperoxide synthase 2; LIF, leukemia inhibitory factor.

women with and without inflammatory disorders through induction of IL-11 [24].

Researchers have also observed exosomes interact with the female reproductive tract epithelium, influencing gene expression and promoting an immune-tolerant environment [29]. The conditioned medium obtained from human endometrial cells exposed to seminal plasma exosomes stimulates the production of pro-inflammatory cytokines such as IL-1α and IL-6 while reducing the levels of the anti-inflammatory cytokine IL-10 [30]. Another study revealed that seminal exosomes are internalized by human endometrial stromal cells and subsequently induce them to produce IL-8 and IL-6, which are involved in embryo implantation [31]. It suggests seminal exosomes promote a pro-inflammatory uterine environment for implantation [5]. Seminal exosomes also interact with DCs and induce immature, tolerogenic DCs to promote a tolerogenic immune environment. The proteins constituted by seminal exosomes play an essential role in Tregs expansion, which recognizes paternal antigens and contributes to maternal immune tolerance [32].

Proteins

Seminal plasma is rich in a diverse array of proteins, which can be categorized into two main groups: those derived from blood plasma, such as albumin, prealbumin, and globulin, and those synthesized and secreted by the male reproductive organs, including clusterin, plasmin, lactoferrin, pro cathepsin D, and cholesterol transfer protein. These proteins play vital roles in regulating osmotic pressure, maintaining pH balance, and facilitating the transport of ions, lipids, and hormones within the seminal plasma [33]. The composition of seminal plasma proteins is both complex and species-specific. Ongoing research is focused on identifying the active factors within these proteins and understanding their mechanisms of action, particularly in humans.

Seminal plasma roles in pregnancy

Seminal plasma is crucial to pregnancy success by initiating maternal immune responses, facilitating embryo implantation, and modulating gene expression in the endometrium (**Figure 2**).

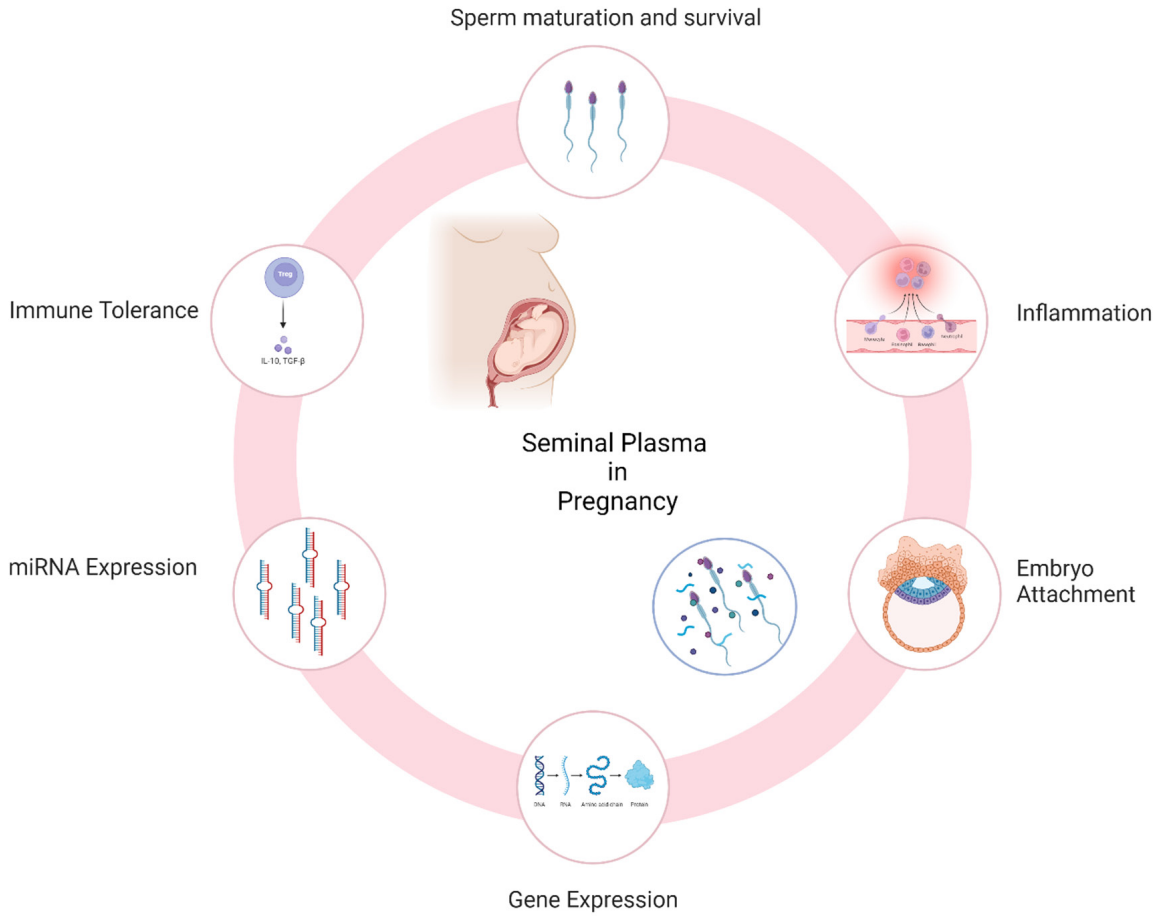

Figure 2. Key roles of seminal plasma in reproductive processes. Seminal plasma influences multiple aspects of female reproductive physiology, including immune activation, sperm maturation and survival, maternal immune tolerance, embryo attachment, and modulation of gene and miRNA expression. These mechanisms collectively support implantation and early pregnancy.

Induction of maternal inflammatory responses

Following deposition in the female reproductive tract, seminal plasma triggers an immune response in females by inducing an influx of inflammatory cells. This intricate process involves the production of GM-CSF, IL-6, IL-1, IL-8, and a diverse array of chemokines [4]. These pro-inflammatory factors stimulate the extravasation and infiltration of macrophages, DCs, and granulocytes into the subepithelial stroma (**Figure 3**).

The maternal inflammatory responses by seminal plasma are diminished when a barrier method such as a condom is used. Bromfield et al. evaluated in mice the consequences for offspring of ablating the plasma fraction of seminal fluid by surgical excision of the seminal vesicle gland [15]. They found that the absence of seminal plasma was associated with down-regulation of the embryotrophic factors LIF, CSF-2, IL-6, and EGF and up-regulation of the apoptosis-inducing factor Trail in the oviduct [15].

The post-mating inflammatory response created by seminal plasma has been extensively studied in humans and animals. In a study conducted on pigs, researchers investigated the effects of seminal plasma exposure on the uterine environment [34, 35]. The findings revealed that seminal plasma elicited a distinct immune response within the uterus, characterized by the upregulation of specific cytokines and chemokines. Notably, the expression of GM-CSF, IL-6, and monocyte chemoattractant protein (MCP)-1 was induced in the uterine tissue. Human studies have also demonstrated

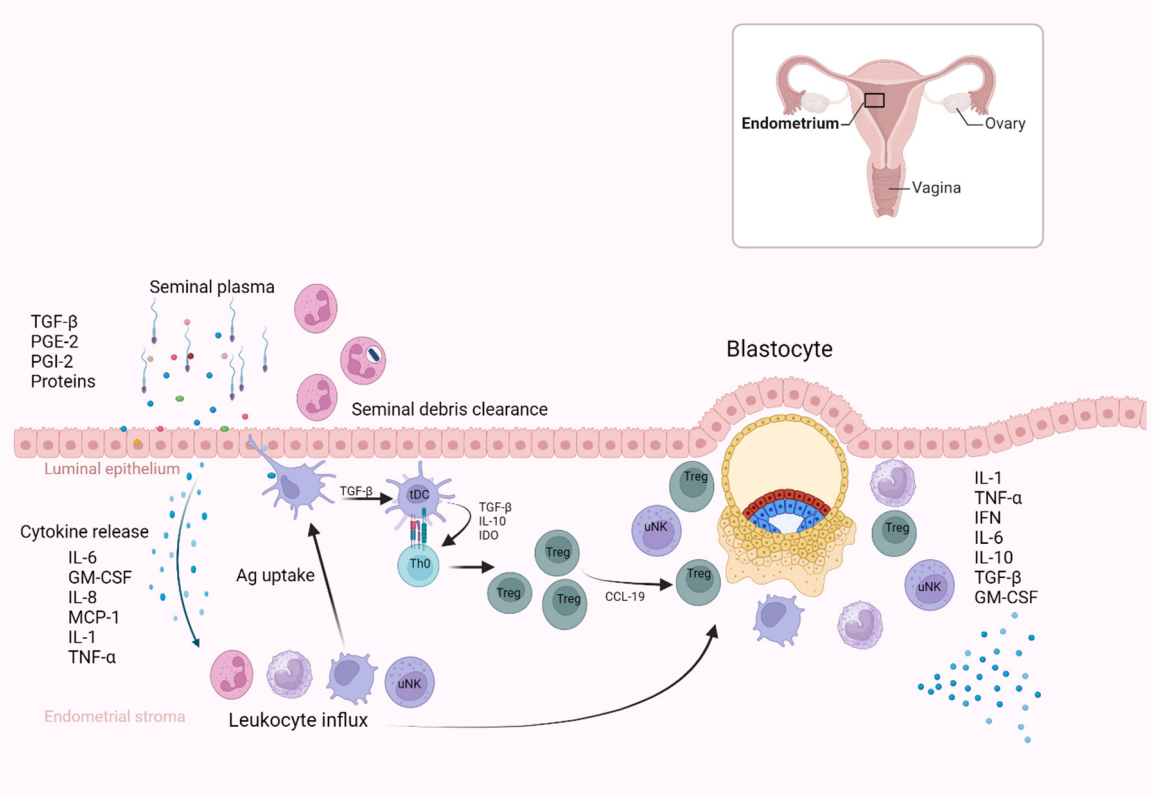

Figure 3. Immune response to seminal plasma in the female reproductive tract. Seminal plasma components such as TGF-β, PGE2, PGI2, and proteins stimulate epithelial cells to produce pro-inflammatory cytokines and chemokines, recruiting immune cells, including neutrophils, macrophages, DCs, and uNK cells. Dendritic cells exposed to TGF-β acquire a tolerogenic phenotype and present antigens to naïve T cells in draining lymph nodes, promoting Treg expansion. These Tregs migrate to the implantation site to support maternal immune tolerance. TGF-β, transforming growth factor beta; PGE2, prostaglandin E2; PGI2, prostaglandin I2; DC, dendritic cell; uNK, uterine natural killer cell; Treg, regulatory T cell.

that sexual intercourse elicits a distinct immune response within the cervical tissues. Sharkey et al. showed an increase in CSF-2, IL-6, IL-8, and IL-1A expression in the human cervix after unprotected intercourse by seminal plasma exposure [36]. This inflammation leads to the robust recruitment of macrophages and dendritic cells to cervical tissue, including the epithelial layers and the underlying stromal compartment [36]. The influx of leukocytes requires direct interaction between seminal plasma and the female reproductive tract tissues, and using a condom during intercourse prevents the development of an inflammatory response [36]. Gutsche et al. conducted an in vitro study to examine the effects of seminal plasma exposure on the mRNA expression of cytokines in human endometrial epithelial and stromal cells [17]. Incubation of epithelial cells with 0.1, 1, and 10% seminal plasma resulted in concentration-dependent stimulation of IL-1β, IL-6, and LIF mRNA expression [17]. Cytokine mRNA expression increased 2-fold for IL-1β, 2.5-fold for IL-6, and 2.2-fold for LIF following stimulation with 10% seminal plasma [17]. Ochsenkühn et al. also found that seminal plasma can increase the expression of IL-1β and TGF-β in human endometrial epithelial cell cultures [37].

Research shows that sperm regulates female reproductive immune responses through seminal plasma components attached to sperm, like sialic acid residues [38]. This mechanism is believed to have an essential role in the dispersion of seminal components by sperm throughout the uterine environment [39]. A contribution of sperm to the regulation of female tract immune responses is indicated in several species. A study conducted in vivo on cows examined the local and systemic immune responses triggered by sperm following artificial insemina-

tion [40]. The results indicated that most sperm were quickly transported to the uterus within one hour, leading to pro-inflammatory responses in neutrophils and peripheral blood mononuclear cells (PBMCs). The upregulation of TNF-α, IL-8, IL-1β, and PGE characterized this response. In humans and mice, evidence showed that sperm signal in conjunction with the seminal plasma fraction elicits a maximal effect. In humans, artificial sperm insemination into the cervix results in an influx of neutrophils into surrounding tissues, potentially through complement activation [4].

Facilitation of embryo attachment

Seminal plasma facilitates embryo implantation and pregnancy success by modulating the maternal uterine environment. A wide range of molecules, such as GM-CSF, LIF, IL-6, TGF-β, TNF-α, TGF-α, insulin, insulin growth factor (IGF)-I and II, EGF, and heparin-binding-EGF (HB-EGF) have been found to contribute to embryo attachment potentially. These molecules are partially regulated by exposure to seminal plasma in the oviductal epithelium [24, 41-43]. Seminal plasma contains a heterogeneous population of extracellular vesicles (EVs) involved in several reproductive physiological processes. EVs carry proteins, lipids, and microRNAs and can modulate endometrial gene expression. The major types of EVs found in seminal plasma are prostasomes (originating from the prostate), epididymosomes (from the epididymis), and Sertoli cell-derived EVs (from testicular cells like Sertoli cells) [44]. These EVs interact with the female reproductive tract epithelium and can modulate gene expression to create an environment conducive to embryo implantation [45]. Specific miRNAs like miR-21-5p encapsulated in seminal EVs can regulate endometrial receptivity and embryo-maternal communication [46]. Specific proteins like spermadhesins and enzymes like paraoxonase type 1 (PON-1) in seminal plasma may also play roles in embryo-endometrial interactions [47].

Induction of endometrial gene expression

Seminal plasma has been shown to modulate gene expression in the female reproductive tract, particularly in the uterus, which is essential for successful pregnancy. Various seminal plasma components, including PGs and TGF-β, mediate these effects.

Seminal plasma components like IL-8 and TGF-β induce LIF and LIF receptor (LIFR) expression [48]. Their expression decreases in individuals with infertility and those suffering from recurrent early abortions, suggesting their involvement in the process of implantation and early pregnancy [49]. Seminal plasma upregulates the expression of these genes, thus enhancing the receptivity of the endometrium for embryo implantation [42, 49-51]. Homeobox A-10 (HOXA-10) is a member of the GATA family of transcription factors and plays a key role in several signaling events during implantation [52]. Seminal plasma has been shown to regulate its expression, which is critical for successful implantation [3, 53]. The human endometrium activates HOXA-10 during the implantation window. Its levels significantly increase during the middle secretory phase of the menstrual cycle [54]. Animal studies have shown that mice lacking the HOXA-10 gene are remarkably infertile and exhibit structural abnormalities in their reproductive systems. Seminal plasma also increases the expression of Mucin-1 (MUC-1), which helps create a tolerogenic environment for the embryo [3, 55-57]. This gene is involved in the innate immune response and prevents microbes from entering the uterus. Investigation showed that the expression level of MUC-1 was increased in the human endometrial epithelial cells treated with the semen of healthy men compared to oligoasthenoteratozoospermia ones [58].

Exposure of endometrial epithelial cells to seminal plasma increased the expression of VEGF, EGF, FGF-1, and FGF-2. These genes are involved in endometrial angiogenesis and tissue proliferation, leading to successful implantation [17, 42, 59, 60]. An increased expression of VEGF and FGF-1 was observed in the oviduct of seminal plasma-treated gilts [61]. A study using HeLa cervical adenocarcinoma cells investigated the role of seminal plasma in regulating neoplastic cervical epithelial cell growth and tumorigenesis [62]. They showed that seminal plasma-induced cytokine production, VEGF-A expression, and cell proliferation by induction of the inflammatory PTGS pathway [62]. HB-EGF belongs to the EGF family of growth factors. This gene plays a role in preparing the uterus for endometrial receptivity. Seminal plasma enhances HB-EGF upregulation, preparing the uterus for implantation [3].

The expression of this growth factor associated with VEGF, FGF-2, EGF, LIF, LIF-R, HOXA10, MUC1, and CSF increased in mice after seminal plasma exposure compared to vasectomized mice [3]. GM-CSF is continuously released by the epithelial cells that line the uterine endometrial stroma and make up the endometrial glands, with the highest production occurring during ovulation [63, 64]. Seminal plasma exposure significantly enhances GM-CSF expression in the female reproductive tract, particularly in the uterus [16, 35, 65, 66]. This enhancement is critical for a successful pregnancy and the prevention of sexually transmitted diseases. The TGF-β components of seminal plasma are proposed as a potent stimulator for GM-CSF expression in uterine epithelial cells. Comparable amounts of recombinant TGF-β1 stimulated GM-CSF release in cultures of uterine epithelial cells from estrous mice and, when instilled into the uterine lumen, caused an increase in GM-CSF content and an infiltration of leukocytes into the endometrium similar to the post-mating response [67].

IL-1β, IL-6, IL-17A, IL-8, and TGF-β1 are inflammatory cytokines important for embryo implantation during pregnancy. These cytokines are expressed by uterine epithelial cells after seminal plasma exposure [68-71]. A dose- and time-dependent induction by seminal plasma of IL8, IL6, CSF-2 and CCL-2 mRNA expression in ectocervical epithelial (Ect1) cells was verified by quantitative RT-PCR [36]. Seminal plasma components, especially PGE-2, are considered the primary stimulator of IL-8 release from human cervical explant [72].

Modulation of miRNA expression

MicroRNAs are small, non-coding RNAs with significant regulatory functions in biological processes, such as modulating the immunological environment. After fertilization, miRNAs perform essential roles in pregnancy, with numerous miRNAs being associated with endometrial receptivity (miR-30 family, miR-494, and miR-923) [73], implantation (miR-101 and miR-199a) [74], placental function (miR-17-92, miR-371-) [75], and labor (miR-223, miR-3, and iR-200) [76]. The exposure of the female reproductive tract to different seminal plasma fractions resulted in the differential expression of several miRNAs, with the most significant changes observed in the media of uterine explants incubated with seminal plasma from the post-sperm-rich fraction. Seminal plasma exposure primarily affected the miRNAs miR-34b, miR-205, miR-4776-3p, and miR-574-5p [77]. Seminal plasma also causes an increase of various immune-regulatory miRNAs in the female reproductive tract in patterns that correlate with the activation of tolerogenic DCs (tDCs) and Tregs. Interaction with seminal plasma induces two crucial miRNAs associated with immunological tolerance, including miR-223 and miR-146a [78]. Bioinformatics analysis identified that predicted target genes of dysregulated miRNAs, mainly miR-34b, miR-205, miR-4776-3p, and miR-574-5p, were involved in several immune-related pathways, such as Th1 and Th2 cell differentiation, cytokine-cytokine receptor interaction, T cell receptor signaling pathway, TGF-β signaling pathway and pathways involved in cellular processes, such as PI3K-Akt signaling pathway, focal adhesion, cell adhesion molecules, MAPK signaling pathway, and Wnt signaling pathway [77].

Enhancement of maternal immune tolerance

Seminal plasma plays a central role in establishing maternal-fetal immune tolerance by modulating populations of uterine natural killer (uNK) cells, Tregs, dendritic cells, macrophages, and neutrophils (**Figure 3**).

Uterine natural killer cells: uNK cells are an immune subset located in the uterus. uNK cells have distinct tissue-specific characteristics compared to their peripheral blood and lymphoid organ counterparts. These cells are abundant in the secretory endometrium and decidua, especially during early pregnancy, accounting for 70% of leukocytes. uNK cells protect the host from pathogen invasion and contribute to a series of physiological processes that affect successful pregnancy, including uterine spiral artery remodeling, fetal development, and immunity tolerance [79]. Seminal plasma significantly influences uNK cells, which facilitate immunological tolerance during pregnancy. Some studies have documented the impact of seminal plasma exposure on the populations of uNK cells in the human reproductive tract [36, 80]. The number of $CD56^+$ uNK cells in the uterine endometrium of women is higher [80], as are the $CD57^+$ NK cells in the

ectocervix after unprotected sexual intercourse [36]. uNK cells are less cytotoxic than peripheral ones, and their cytotoxic activity is downregulated during preimplantation. Some in vitro studies have shown the suppressive effects of seminal plasma exposure on the cytotoxicity mediated by NK cells [81]. PGE and polyamines in seminal plasma are responsible for such an inhibitory effect on the lytic activity of NK cells [82, 83].

T cells: A key component of the female reaction to seminal plasma is the production of an adequate T-cell reaction to paternal antigens. To have a successful pregnancy, the T cell response must promote the expansion of immune-suppressive Tregs, identified by the transcription factor Foxp3. Different Th cells exert various effects in the context of pregnancy. Th1 is needed to induce an inflammatory response that facilitates embryo implantation, while Th2 is necessary for pregnancy maintenance. Besides these, Tregs play essential roles in inducing and mediating a tolerogenic state during pregnancy [84, 85]. The modulation of this T cell response by seminal plasma during fertilization has been thoroughly investigated in human and animal models [86-88].

Seminal plasma is rich in immune-regulatory substances that contribute to its capacity to stimulate the production of Tregs, including TGF-β and PGE-related molecules, specifically 19OH-PGE1 and 19OH-PGE2 [89, 90]. They have been linked to the generation of Tregs by enhancing the development of naïve $CD4^+$ $CD25^-$ T cells into suppressor T cells that express Foxp3 [91]. Remarkably, the concentration of TGFβ in seminal plasma is one of the highest recorded in biological fluids, reaching around 500 μg/mL in human semen. Male accessory glands, such as the seminal vesicle and prostate, mainly produce it [90]. Investigations have shown that the administration of TGFβ from an external source increases the number of Tregs in the vagina and decreases the occurrence of fetal loss in the abortion-prone CBA/J × DBA/2J mouse model [92]. Robertson et al. examined male seminal fluid's role in female tolerance induction to fetus using paternal tumor cell grafts and by delayed-type hypersensitivity (DTH) challenge on Day 3.5 postpartum [7]. They found that exposure to seminal fluid inhibited rejection of paternal tumor cells through decreased type 1 immunity. The efficacy of this effect is particular to antigens, as seminal plasma from males with different MHC is less effective at establishing tolerance. They also showed that mating with intact males suppressed the DTH response to paternal alloantigens in an MHC-specific fashion. At the same time, excision of the seminal vesicle glands diminished the tolerance-inducing activity of seminal fluid. In addition, they detected an increase in $CD4^+CD25^+$ cells expressing Foxp3 in the para-aortic lymph nodes, draining the uterus of mice after mating with intact males. The increase in $CD4^+CD25^+$ cells was abrogated when males were vasectomized, or seminal vesicles were excised. Collectively, these data provide evidence that exposure to seminal fluid at mating promotes a state of functional tolerance to paternal alloantigens that may facilitate maternal acceptance of the conceptus at implantation, and the effects of seminal fluid are likely to be mediated by expansion of the Tregs pool and modulation of type 1 immunity [7].

Further studies have demonstrated that Treg cells' activation and expansion directly result from seminal plasma exposure during mating (**Figure 3**). Initially, it was discovered that mating results in the expansion of T cells in the para-aortic lymph nodes that receive drainage from the uterus. Subsequently, it was shown that many reactive lymphocytes that responded were Treg cells. By the 3.5th day after sexual intercourse, the number of Tregs increases by approximately two times compared to the estrus cycle in mice. This increase is due to the enhancement of their recruitment from the circulation into the implantation site by the effect of CCL19 [7, 93].

The development of Tregs following mating necessitates DCs transporting antigens to the lymph nodes, which drain the uterus. DCs prompt naïve T cells to proliferate and acquire a Treg phenotype [94]. Tolerogenic DCs form paternal antigen-specific Tregs during pregnancy [95, 96].

T cells with a regulatory phenotype can emerge due to interactions with other immune cells. Neutrophils can activate pro-angiogenic Tregs by transporting pro-apoptotic proteins [97]. In addition, Tregs interact with mast cells to generate a pro-angiogenic phenotype [98]. This

phenomenon is clearly shown in the CBA/J × DBA/2J model, where the transfer of Tregs increases mast cells. These mast cells promote T cell-mediated tolerance by producing IL-9 and TGF-β [99].

In vitro studies have also shown that seminal plasma can directly influence the differentiation of DCs into a tolerogenic phenotype characterized by increased production of IL-10 and TGF-β [72, 100, 101] and the differential activation of Tregs [86, 101]. Our previous research has demonstrated that exposure to seminal plasma can stimulate the expression of IL-10 and TGF-β, as well as the expansion of Tregs, which collectively contribute to improving IVF outcomes in couples with unexplained infertility [102-104].

Dendritic cells: DCs are renowned for their ability to shape the adaptive immune response by presenting antigens and guiding T cells to adopt specific immune functions. Additionally, they can interact with non-immune cells and play a vital role in forming the uterine lining and preparing the uterus for embryo implantation. These cells are present in the non-pregnant endometrium of both humans and rodents and accumulate in the uterus before implantation, persisting throughout the entire pregnancy [105, 106]. Rodents, pigs, and human seminal plasma are essential in recruiting DCs [35, 66, 107, 108]. DCs in the uterus take paternal alloantigens in seminal plasma and transport them to lymph nodes via the uterine lymphatic system. Once in the lymph nodes, the cells present the antigen and stimulate T cells that mediate immunological tolerance towards the paternal alloantigens expressed by the implanting embryo [94]. Human monocytes exposed to highly diluted seminal plasma differentiated to DCs that did not express CD1a but displayed higher levels of CD14, known as tolerogenic DCs [107]. The inhibitory effect of seminal plasma on DCs is presumably induced by specific prostaglandins, including PGE-I, 19-OH-PGE-I, and PGE-2, found in seminal plasma at high concentrations [107]. It is impossible for them to fully develop following exposure to lipopolysaccharides (LPS), TNF-α, CD40L, Pam2CSK4 (TLR2/6 agonist), or Pam3CSK4 (TLR1/2 agonist). Upon activation, they produced low levels of the inflammatory cytokines IL-12p70, IL-1β, TNF-α, and IL-6 but showed a significant capacity for producing IL-10 and TGF-β [107, 109]. Seminal plasma proteins, such as clusterin, stimulate DCs' ability to induce $CD25^{+}FoxpF3^{+}CD4^{+}$ T lymphocyte expansion via DC-SIGN (a C-type lectin receptor selectively expressed on DCs) [110]. Additionally, the immunomodulatory properties of seminal plasma may assist spermatozoa to circumvent the attack of DCs in the female reproductive tract, thereby promoting successful fertilization [111].

Macrophages: Macrophages at the maternal-fetal interface play a critical role in fetal tolerance, priming of cervical tissues, parturition, postpartum tissue repair, and displaying self-renewal capacity [112]. Macrophages efficiently capture and transport antigens from seminal plasma to draining lymph nodes. It leads to the activation of immune responses against paternal MHC and other antigens found in semen. Macrophages release enzymes and signaling molecules that alter the luminal epithelial glycocalyx and stromal extracellular matrix composition. This modification supports embryo attachment and promotes trophoblast invasion during the initial stages of placental development [14]. Seminal plasma increases the expression of pro-inflammatory cytokines, such as IL-8, IL-1β, MCP-1, and GM-CSF, in cervical epithelial cells, which can promote the recruitment and activation of macrophages in the female genital tract [60, 113]. Exposure to seminal plasma in mice increases the number of macrophages in the corpora lutea. These cells are crucial in remodeling activities to maintain steroidogenic function [114]. Studies have demonstrated a clear correlation between administering seminal plasma in pigs during ovulation and increased numbers of corpus luteum macrophages, enhanced steroid production, and heightened levels of progesterone in the bloodstream [115]. Researchers gave gilts a mixture of seminal plasma through a transcervical catheter. They found that when seminal plasma interacts with uterine cells, it raises GM-CSF, IL-6, and MCP-1 levels and helps white blood cells move around [116]. The inflammatory cells that invade the endometrium seem to remain and undergo differentiation in the tissue for several days, while the luminal neutrophil response is resolved within 24 hours. This process increases locally activated macrophage and dendritic cell populations throughout preimplantation [116].

Neutrophils: After mating, the initial influx of neutrophils in the female reproductive tract plays a crucial role in regulating the immune response. These neutrophils, abundant during the early post-mating inflammatory response, exhibit multifaceted immune functions. Their primary capabilities include effectively eliminating pathogens and tissue debris, which enables them to clear excess sperm and seminal plasma, thereby preventing the spread of sexually transmitted infections [4]. The constituents of seminal plasma actively contribute to the transit and viability of spermatozoa in the female reproductive tract [117]. In vitro studies have reported that seminal plasma can reduce neutrophil function, which may benefit sperm survival and fertility [118].

The interactions between seminal plasma and neutrophils may enhance the adaptive immune response to antigens in seminal plasma. Neutrophils, which can function as antigen-presenting cells, can influence the antigen-presenting milieu by promoting the growth of Tregs, thereby modifying the immune response [97, 119].

Song and his colleagues discovered that after insemination in mice, neutrophils move and gather around the uterine epithelium, accompanied by a rise in IL-17A levels [70]. Inhibiting IL-17A decreased the quantity of neutrophils in the uterus by reducing the chemokines CXCL1, CXCL2, and CXCL5. They discovered that seminal plasma can stimulate γδ T cells to produce IL-17A.

Assisted reproductive technologies

Seminal plasma is vital in ART because it strengthens the reproductive environment's quality and increases the likelihood of successful implantation and conception. Studies have shown that seminal plasma exposure can improve the chances of successful pregnancy in women undergoing IVF and intracytoplasmic sperm injection (ICSI). A meta-analysis of seven randomized controlled studies found that using seminal plasma as an auxiliary measure during IVF significantly increased clinical pregnancy rates (CPR) [120]. An analysis combining data from eight randomized controlled studies found that intracervical seminal plasma application during oocyte collection significantly affected CRP. These findings indicate that localized seminal plasma administration at the cervix can improve IVF effectiveness by creating a more favorable environment for embryo implantation [121]. Only a few randomized controlled studies provide the available data on birth outcomes. These trials showed a slight rise in live birth rates, but this increase was not statistically significant in all meta-analyses. This highlights the need for more comprehensive and well-designed research to understand better the influence of seminal plasma on IVF success rates and birth outcomes [120, 121]. Researchers have found that seminal plasma components like proteins and cytokines most effectively improve IVF success. Key proteins linked to successful IVF outcomes include A2LD1, ATP1B3, FBXO2, PTGDS, clusterin, and NPC2 [122-124]. These proteins contribute to sperm maturation, capacitation, antioxidative defense, and immune modulation (**Table 2**).

Seminal plasma contains cytokines such as IL-1β, IL-6, IL-8, LIF, IL-18, TGF-β1, and IL-11. These are released by various immunocompetent cell subsets and are thought to affect sperm cell function and the reproductive process [127, 128]. Some studies assessed the relationship between seminal plasma cytokines and fertilization rates in men attending an IVF program. IL-11 is part of an exclusive group of genes that are essential for implantations and was found in significant levels in the seminal plasma of men with successful IVF [129]. Elevated levels of proinflammatory cytokines IL-1β, IL-6, IL-8, and TNF-α in seminal plasma may impair implantation and pregnancy establishment in couples who underwent IVF treatment [21]. A study indicates that an excess of seminal IL-18 negatively affects IVF and ICSI outcomes, which could potentially be mitigated by the TGF-β1 content found in seminal plasma [130].

Variability in seminal plasma composition driven by age, metabolic disorders, infections, or lifestyle habits (e.g., smoking, diet, physical activity) can significantly impact its immunological and molecular profile. Studies have shown that aging and obesity, for example, may alter the levels of key cytokines, prostaglandins, and antioxidant proteins, potentially impairing sperm function and endometrial immune responses [4, 131-133]. These alterations could serve as biomarkers for male repro-

Table 2. Seminal plasma proteins associated with IVF outcomes, their functions, and expression patterns

Protein	Function/Role in Reproduction	Expression Level in IVF Outcome
A2LD1	γ-glutamyl amine acyltransferase; may degrade crosslinked proteins in oocyte/granulosa cells	↑ Upregulated in successful IVF [122]
ATP1B3	Maintains ion gradients critical for sperm motility and function	↑ Upregulated in successful IVF [122]
FBXO2	E3 ubiquitin ligase; regulates protein turnover and impacts sperm quality	↑ Upregulated in successful IVF [122, 125]
PTGDS	Converts PGH2 to PGD2; linked to sperm maturation and motility	↑ Positively correlated with better IVF outcomes [124]
DJ-1	Antioxidant; protects sperm from oxidative damage, maintains motility	↓ Downregulated in asthenozoospermia [126]
Clusterin	Chaperone; involved in sperm maturation, motility, and capacitation	↑ Higher in successful IVF [123]
NPC2	Cholesterol transport; maintains sperm membrane integrity and protects against oxidative stress	↑ Higher in successful IVF [123]
PSA	Facilitates semen liquefaction; correlated with improved sperm quality	↑ Higher in successful IVF [127]

A2LD1: γ-glutamyl amine acyltransferase; ATP1B3: ATPase Na^+/K^+ transporting subunit beta 3; FBXO2: F-box only protein 2; PTGDS: Prostaglandin D2 Synthase; NPC2: Niemann-Pick C2 protein; PSA: Prostate-Specific Antigen.

ductive health or predictors of ART outcomes [28]. Furthermore, therapeutic strategies targeting seminal plasma composition, such as dietary interventions, antioxidant therapy, or modulation of exosomal content, warrant further investigation as adjunctive approaches to improve fertility outcomes.

Pregnancy disorders

Studies have demonstrated that seminal plasma exposure during the preconception period, in addition to its immunomodulating properties, reduces the risk of certain pregnancy disorders, such as preeclampsia. According to the results of some studies, limited exposure to the conceiving partner's seminal plasma increases the risk of developing preeclampsia [134, 135]. Women diagnosed with preeclampsia exhibit a decreased number of Tregs [136]. The protective effect of seminal plasma exposure is partner-specific. Multiparous women conceiving with a new partner (different from previous pregnancies) have an increased risk of preeclampsia compared to conceiving with the same partner, a phenomenon called primipaternity [137, 138]. In assisted reproduction using donor sperm or surgically obtained sperm (no seminal plasma exposure), the incidence of preeclampsia is higher compared to the use of the partner's ejaculated sperm containing seminal plasma [139, 140]. Therefore, it appears that repeated preconception exposure to the conceiving partner's seminal plasma is crucial for priming maternal immune tolerance to paternal antigens and reducing the risk of preeclampsia, a pregnancy disorder associated with impaired maternal-fetal tolerance.

The impaired immunomodulatory effects of seminal plasma may play a role in recurrent spontaneous abortion (RSA) or unexplained recurrent pregnancy loss (URPL) [101]. These problems may contribute to the underlying pathophysiology and higher risk of recurrent pregnancy losses (RPL). Decreased female Treg function was shown after stimulation with the seminal plasma of RPL males compared to control males [101]. Metabolomic analysis revealed differences in seminal plasma and sperm cell metabolites and pathways related to oxidative stress, nucleic acid synthesis, and hormone metabolism in men from URPL couples compared to fertile controls [141]. Cluster analysis showed that men with RPL had a less favorable expression pattern for pro-inflammatory cytokines (IL-1α, IL-1β, IL-6, IL-8, IL-12, IL-18, and TNF-α) [142].

Future directions

Advancing our understanding of seminal plasma's immunological and molecular functions opens new avenues for clinical translation. Identification of key seminal plasma components such as exosomal miRNAs, immunoregulatory cytokines (e.g., TGF-β, GM-CSF), and fertility-associated proteins may support the

development of novel biomarkers to predict ART success or diagnose subfertility. Additionally, therapeutic modulation of the female immune response through seminal plasma supplementation, exosome-based therapy, or cytokine mimetics could improve endometrial receptivity and implantation rates. Future research should explore these possibilities in well-designed clinical trials to integrate seminal plasma-based tools into personalized reproductive medicine protocols.

Conclusion

The growing body of evidence reviewed here highlights the crucial role of seminal plasma in priming the female reproductive tract and optimizing the endometrial environment for successful embryo implantation and healthy pregnancy. Seminal plasma benefits through a multifaceted molecular interaction with the endometrium. Seminal plasma upregulates key genes that make the endometrium more receptive. These genes include LIF, LIFR, MUC1, VEGF, EGF, and FGF2. These genes enhance endometrial-embryo communication, fostering a supportive environment for implantation. Seminal plasma controls the female reproductive tract's immune responses and inflammatory pathways. It helps the mother accept the semi-allogenic embryo and mitigates immune rejection by increasing Tregs. These findings suggest that exposure to seminal plasma during embryo transfer or oocyte retrieval may improve ART success rates, such as IVF. However, it is crucial to note that abnormal seminal plasma composition is associated with some pregnancy disorders. Further research is warranted to elucidate the complex molecular mechanisms that control the interaction between seminal plasma and the endometrium and to find the best ways to use seminal plasma or its parts in assisted reproductive settings. Nonetheless, the current understanding of this crucial dialogue highlights the importance of maintaining a healthy seminal plasma composition for optimal reproductive success.

Disclosure of conflict of interest

None.

Address correspondence to: Zahra Kanannejad, Allergy Research Center, Mohammad Rasool Allah Research Tower, 6rd Floor, Khalili Street, Mollasadra Street, Shiraz, Iran. E-mail: zkanannejad@gmail.com

References

[1] Al-Maini M, Jeyalingam T, Brown P, Lee JJ, Li L, Su J, Gladman DD and Fortin PR. A hot spot for systemic lupus erythematosus, but not for psoriatic arthritis, identified by spatial analysis suggests an interaction between ethnicity and place of residence. Arthritis Rheum 2013; 65: 1579-85.

[2] Medawar PB. Some immunological and endocrinological problems raised by the evolution of viviparity in vertebrates. Symposia of the Society for Experimental Biology 1953.

[3] Ajdary M, Zandieh Z, Amjadi FS, Keyhanfar F, Mehdizadeh M and Aflatoonian R. Interaction of sperm with endometrium can regulate genes involved in endometrial receptivity pathway in mice: an experimental study. Int J Reprod Biomed 2020; 18: 815-24.

[4] Schjenken JE and Robertson SA. The female response to seminal fluid. Physiol Rev 2020; 100: 1077-117.

[5] Shen Q, Wu X, Chen J, He C, Wang Z, Zhou B and Zhang H. Immune regulation of seminal plasma on the endometrial microenvironment: physiological and pathological conditions. Int J Mol Sci 2023; 24: 14639.

[6] Palacio JR and Martínez P. Contribution of seminal plasma to the female immune regulation in embryo implantation. Adv Neuroimmune Biol 2011; 2: 23-30.

[7] Robertson SA, Guerin LR, Bromfield JJ, Branson KM, Ahlström AC and Care AS. Seminal fluid drives expansion of the CD4+CD25+ T regulatory cell pool and induces tolerance to paternal alloantigens in mice. Biol Reprod 2009; 80: 1036-45.

[8] Meuleman T, Snaterse G, van Beelen E, Anholts JDH, Pilgram GSK, van der Westerlaken LAJ, Eikmans M and Claas FHJ. The immunomodulating effect of seminal plasma on T cells. J Reprod Immunol 2015; 110: 109-16.

[9] Furuya Y, Akashi T and Fuse H. Soluble Fas and interleukin-6 and interleukin-8 levels in seminal plasma of infertile men. Arch Androl 2003; 49: 449-52.

[10] Matalliotakis IM, Cakmak H, Fragouli Y, Kourtis A, Arici A and Huszar G. Increased IL-18 levels in seminal plasma of infertile men with genital tract infections. Am J Reprod Immunol 2006; 55: 428-33.

[11] Sanocka D, Jedrzejczak P, Szumała-Kaękol A, Frączek M and Kurpisz M. Male genital tract inflammation: the role of selected interleukins in regulation of pro-oxidant and antioxidant enzymatic substances in seminal plasma. J Androl 2003; 24: 448-55.

[12] Kocak I, Dündar M, Yenisey C, Serter M and Günaydin G. Pro-inflammatory cytokine re-

sponse of the fluid contents of spermatoceles and epididymal cysts. Andrologia 2002; 34: 112-5.
[13] Ahmadi H, Csabai T, Gorgey E, Rashidiani S, Parhizkar F and Aghebati-Maleki L. Composition and effects of seminal plasma in the female reproductive tracts on implantation of human embryos. Biomed Pharmacother 2022; 151: 113065.
[14] Robertson SA. Seminal plasma and male factor signalling in the female reproductive tract. Cell Tissue Res 2005; 322: 43-52.
[15] Bromfield JJ, Schjenken JE, Chin PY, Care AS, Jasper MJ and Robertson SA. Maternal tract factors contribute to paternal seminal fluid impact on metabolic phenotype in offspring. Proc Natl Acad Sci U S A 2014; 111: 2200-5.
[16] Sharkey DJ, Macpherson AM, Tremellen KP, Mottershead DG, Gilchrist RB and Robertson SA. TGF-β mediates proinflammatory seminal fluid signaling in human cervical epithelial cells. J Immunol 2012; 189: 1024-35.
[17] Gutsche S, von Wolff M, Strowitzki T and Thaler CJ. Seminal plasma induces mRNA expression of IL-1beta, IL-6 and LIF in endometrial epithelial cells in vitro. Mol Hum Reprod 2003; 9: 785-91.
[18] Wang W, Sung N, Gilman-Sachs A and Kwak-Kim J. T Helper (Th) cell profiles in pregnancy and recurrent pregnancy losses: Th1/Th2/Th9/Th17/Th22/Tfh cells. Front Immunol 2020; 11: 2025.
[19] Hedger MP and Meinhardt A. Cytokines and the immune-testicular axis. J Reprod Immunol 2003; 58: 1-26.
[20] Sharkey DJ, Schjenken JE, Mottershead DG and Robertson SA. Seminal fluid factors regulate activin A and follistatin synthesis in female cervical epithelial cells. Mol Cell Endocrinol 2015; 417: 178-90.
[21] Arefieva AS, Babayan AA, Kalinina EA and Nikolaeva MA. Cytokine profile of seminal plasma and effectiveness of assisted reproductive technology programs. RJol 2021; 24: 391-8.
[22] Soucek K, Slabáková E, Ovesná P, Malenovská A, Kozubík A and Hampl A. Growth/differentiation factor-15 is an abundant cytokine in human seminal plasma. Hum Reprod 2010; 25: 2962-71.
[23] Sharkey DJ and Robertson SA. Seminal fluid and the female immune response - an update on the male contribution to pregnancy beyond fertilisation. J Reprod Immunol 2023; 159: 104018.
[24] George AF, Jang KS, Nyegaard M, Neidleman J, Spitzer TL, Xie G, Chen JC, Herzig E, Laustsen A, Marques de Menezes EG, Houshdaran S, Pilcher CD, Norris PJ, Jakobsen MR, Greene WC, Giudice LC and Roan NR. 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. Hum Reprod 2020; 35: 617-40.
[25] Joseph T, Zalenskaya IA, Sawyer LC, Chandra N and Doncel GF. Seminal plasma induces prostaglandin-endoperoxide synthase (PTGS) 2 expression in immortalized human vaginal cells: involvement of semen prostaglandin E2 in PTGS2 upregulation. Biol Reprod 2013; 88: 13.
[26] Larsen MH, Bzorek M, Pass MB, Larsen LG, Nielsen MW, Svendsen SG, Lindhard A and Hviid TV. Human leukocyte antigen-G in the male reproductive system and in seminal plasma. Mol Hum Reprod 2011; 17: 727-38.
[27] Pilatz A, Hudemann C, Wolf J, Halefeld I, Paradowska-Dogan A, Schuppe HC, Hossain H, Jiang Q, Schultheiss D, Renz H, Weidner W, Wagenlehner F and Linn T. Metabolic syndrome and the seminal cytokine network in morbidly obese males. Andrology 2017; 5: 23-30.
[28] Candenas L and Chianese R. Exosome composition and seminal plasma proteome: a promising source of biomarkers of male infertility. Int J Mol Sci 2020; 21: 7022.
[29] Shen Y, You Y, Zhu K, Fang C, Chang D and Yu X. Exosomes in the field of reproduction: a scientometric study and visualization analysis. Front Pharmacol 2022; 13: 1001652.
[30] Paktinat S, Esfandyari S, Karamian A, Koochaki A, Asadirad A, Ghaffari Novin M, Mohammadi-Yeganeh S, Salehpour S, Hashemi SM and Nazarian H. Conditioned medium derived from seminal extracellular vesicles-exposed endometrial stromal cells induces inflammatory cytokine secretion by macrophages. Eur J Obstet Gynecol Reprod Biol 2021; 262: 174-81.
[31] Paktinat S, Hashemi SM, Ghaffari Novin M, Mohammadi-Yeganeh S, Salehpour S, Karamian A and Nazarian H. Seminal exosomes induce interleukin-6 and interleukin-8 secretion by human endometrial stromal cells. Eur J Obstet Gynecol Reprod Biol 2019; 235: 71-6.
[32] Wang D, Jueraitetibaike K, Tang T, Wang Y, Jing J, Xue T, Ma J, Cao S, Lin Y, Li X, Ma R, Chen X and Yao B. Seminal plasma and seminal plasma exosomes of aged male mice affect early embryo implantation via immunomodulation. Front Immunol 2021; 12: 723409.
[33] Perumal P. Seminal plasma proteins. Nature Precedings 2012.
[34] Lovell JW and Getty R. Fate of semen in the uterus of the sow: histologic study of endometrium during the 27 hours after natural service. Am J Vet Res 1968; 29: 609-25.
[35] O'Leary S, Jasper MJ, Warnes GM, Armstrong DT and Robertson SA. Seminal plasma regu-

lates endometrial cytokine expression, leukocyte recruitment and embryo development in the pig. Reproduction 2004; 128: 237-47.
[36] Sharkey DJ, Tremellen KP, Jasper MJ, Gemzell-Danielsson K and Robertson SA. Seminal fluid induces leukocyte recruitment and cytokine and chemokine mRNA expression in the human cervix after coitus. J Immunol 2012; 188: 2445-54.
[37] Ochsenkühn R, Toth B, Nieschlag E, Artman E, Friese K and Thaler CJ. Seminal plasma stimulates cytokine production in endometrial epithelial cell cultures independently of the presence of leucocytes. Andrologia 2008; 40: 364-9.
[38] Ma X, Pan Q, Feng Y, Choudhury BP, Ma Q, Gagneux P and Ma F. Sialylation facilitates the maturation of mammalian sperm and affects its survival in female uterus. Biol Reprod 2016; 94: 123.
[39] Suarez SS and Pacey AA. Sperm transport in the female reproductive tract. Hum Reprod Update 2005; 12: 23-37.
[40] Marey MA, Ma D, Yoshino H, Elesh IF, Zinnah MA, Fiorenza MF, Moriyasu S and Miyamoto A. Sperm induce proinflammatory responses in the uterus and peripheral blood immune cells of artificially inseminated cows. J Reprod Dev 2023; 69: 95-102.
[41] Robertson SA, Sjöblom C, Jasper MJ, Norman RJ and Seamark RF. Granulocyte-macrophage colony-stimulating factor promotes glucose transport and blastomere viability in murine preimplantation embryos. Biol Reprod 2001; 64: 1206-15.
[42] Mateo-Otero Y, Sánchez JM, Recuero S, Bagés-Arnal S, McDonald M, Kenny DA, Yeste M, Lonergan P and Fernandez-Fuertes B. Effect of exposure to seminal plasma through natural mating in cattle on conceptus length and gene expression. Front Cell Dev Biol 2020; 8: 341.
[43] Brusentsev EY, Kizilova E, Igonina T, Ranneva S and Amstislavsky SY. Effects of insulin-like growth factor 1 on the in vitro development of mouse embryos after cryopreservation. Russ J Dev Biol 2021; 52: 120-4.
[44] Neyroud AS, Chiechio R, Yefimova M, Lo Faro MJ, Dejucq-Rainsford N, Jaillard S, Even-Hernandez P, Marchi V and Ravel C. Extra-cellular vesicles of the male genital tract: new actors in male fertility? Basic Clin Androl 2021; 31: 25.
[45] Rodriguez-Martinez H, Martinez EA, Calvete JJ, Peña Vega FJ and Roca J. Seminal plasma: relevant for fertility? Int J Mol Sci 2021; 22: 4368.
[46] Xie Y, Xu Z, Wu C, Zhou C, Zhang X, Gu T, Yang J, Yang H, Zheng E, Xu Z, Cai G, Li Z, Liu D, Wu Z and Hong L. Extracellular vesicle-encapsulated miR-21-5p in seminal plasma prevents sperm capacitation via vinculin inhibition. Theriogenology 2022; 193: 103-13.
[47] Barranco I, Tvarijonaviciute A, Perez-Patiño C, Alkmin DV, Ceron JJ, Martinez EA, Rodriguez-Martinez H and Roca J. The activity of paraoxonase type 1 (PON-1) in boar seminal plasma and its relationship with sperm quality, functionality, and in vivo fertility. Andrology 2015; 3: 315-20.
[48] Piccinni MP, Raghupathy R, Saito S and Szekeres-Bartho J. Cytokines, hormones and cellular regulatory mechanisms favoring successful reproduction. Front Immunol 2021; 12: 717808.
[49] Gutsche S, von Wolff M, Strowitzki T and Thaler CJ. Seminal plasma induces mRNA expression of IL-1β, IL-6 and LIF in endometrial epithelial cells in vitro. Mol Hum Reprod 2003; 9: 785-91.
[50] Moharrami T, Ai J, Ebrahimi-Barough S, Nouri M, Ziadi M, Pashaiefar H, Yazarlou F, Ahmadvand M, Najafi S and Modarressi MH. Influence of follicular fluid and seminal plasma on the expression of endometrial receptivity genes in endometrial cells. Cell J 2021; 22: 457-66.
[51] Wang H, Lin Y, Chen R, Zhu Y, Wang H, Li S, Yu L, Zhang K, Liu Y, Jing T and Sun F. Human seminal extracellular vesicles enhance endometrial receptivity through leukemia inhibitory factor. Endocrinology 2024; 165: bqae035.
[52] Özcan C, Özdamar Ö, Gökbayrak ME, Doğer E, Çakıroğlu Y and Çine N. HOXA-10 gene expression in ectopic and eutopic endometrium tissues: does it differ between fertile and infertile women with endometriosis? Eur J Obstet Gynecol Reprod Biol 2019; 233: 43-8.
[53] Moharrami T, Ai J, Ebrahimi-Barough S, Nouri M, Ziadi M, Pashaiefar H, Yazarlou F, Ahmadvand M, Najafi S and Modarressi MH. Influence of follicular fluid and seminal plasma on the expression of endometrial receptivity genes in endometrial cells. Cell J 2020; 22: 457-466.
[54] Berger C, Boggavarapu NR, Menezes J, Lalitkumar PG and Gemzell-Danielsson K. Effects of ulipristal acetate on human embryo attachment and endometrial cell gene expression in an in vitro co-culture system. Hum Reprod 2015; 30: 800-11.
[55] Gholipour H, Amjadi FS, Zandieh Z, Mehdizadeh M, Ajdary M, Delbandi AA, Akbari Sene A, Aflatoonian R and Bakhtiyari M. Investigation of the effect of seminal plasma exosomes from the normal and oligoasthenoteratospermic males in the implantation process. Rep Biochem Mol Biol 2023; 12: 294-305.
[56] Raheem KA, Marei WFA, Campbell BK and Fouladi-Nashta AA. In vivo and in vitro studies of MUC1 regulation in sheep endometrium. Theriogenology 2016; 85: 1635-43.
[57] Jasper MJ, Care AS, Sullivan B, Ingman WV, Aplin JD and Robertson SA. Macrophage-derived LIF and IL1B regulate alpha(1,2)fucosyltrans-

ferase 2 (Fut2) expression in mouse uterine epithelial cells during early pregnancy. Biol Reprod 2011; 84: 179-88.
[58] Gholipour H, Amjadi FS, Zandieh Z, Mehdizadeh M, Ajdary M, Delbandi AA, Akbari Sene A, Aflatoonian R and Bakhtiyari M. Investigation of the effect of seminal plasma exosomes from the normal and oligoasthenoteratospermic males in the implantation process. Rep Biochem Mol Biol 2023; 12: 294-305.
[59] Muller M, Sales KJ, Katz AA and Jabbour HN. Seminal plasma promotes the expression of tumorigenic and angiogenic genes in cervical adenocarcinoma cells via the E-series prostanoid 4 receptor. Endocrinology 2006; 147: 3356-65.
[60] Rametse CL, Adefuye AO, Olivier AJ, Curry L, Gamieldien H, Burgers WA, Lewis DA, Williamson AL, Katz AA and Passmore JS. Inflammatory cytokine profiles of semen influence cytokine responses of cervicovaginal epithelial cells. Front Immunol 2018; 9: 2721.
[61] Krawczynski K and Kaczmarek MM. Does seminal plasma affect angiogenesis in the porcine oviduct? Reprod Biol 2012; 12: 347-54.
[62] Sutherland JR, Sales KJ, Jabbour HN and Katz AA. Seminal plasma enhances cervical adenocarcinoma cell proliferation and tumour growth in vivo. PLoS One 2012; 7: e33848.
[63] Robertson SA. GM-CSF regulation of embryo development and pregnancy. Cytokine Growth Factor Rev 2007; 18: 287-98.
[64] Robertson SA, Chin PY, Femia JG and Brown HM. Embryotoxic cytokines-potential roles in embryo loss and fetal programming. J Reprod Immunol 2018; 125: 80-8.
[65] Robertson SA, O'Connell AC, Hudson SN and Seamark RF. Granulocyte-macrophage colony-stimulating factor (GM-CSF) targets myeloid leukocytes in the uterus during the post-mating inflammatory response in mice. J Reprod Immunol 2000; 46: 131-54.
[66] Sharkey DJ, Macpherson AM, Tremellen KP and Robertson SA. Seminal plasma differentially regulates inflammatory cytokine gene expression in human cervical and vaginal epithelial cells. Mol Hum Reprod 2007; 13: 491-501.
[67] Parks SE, Geng T and Monsivais D. Endometrial TGFβ signaling fosters early pregnancy development by remodeling the fetomaternal interface. Am J Reprod Immunol 2023; 90: e13789.
[68] Ibrahim L, Rizo J, Fontes P, Lamb G and Bromfield J. Seminal plasma modulates expression of endometrial inflammatory meditators in the bovine. Biol Reprod 2019; 100: 660-671.
[69] Hidalgo AI, Ulloa-Leal C, Gajardo G, López G, Carretta D, Burgos RA and Ratto M. Ovulation induced by intrauterine seminal plasma increases total protein, PGE2, IL-8, and IL-1β in uterine fluid of llamas (Lama glama). Animals (Basel) 2023; 13: 554.
[70] Song ZH, Li ZY, Li DD, Fang WN, Liu HY, Yang DD, Meng CY, Yang Y and Peng JP. Seminal plasma induces inflammation in the uterus through the γδ T/IL-17 pathway. Sci Rep 2016; 6: 25118.
[71] Palm F, Walter I, Budik S, Kolodziejek J, Nowotny N and Aurich C. Influence of different semen extenders and seminal plasma on PMN migration and on expression of IL-1beta, IL-6, TNF-alpha and COX-2 mRNA in the equine endometrium. Theriogenology 2008; 70: 843-51.
[72] Denison FC, Grant VE, Calder AA and Kelly RW. Seminal plasma components stimulate interleukin-8 and interleukin-10 release. Mol Hum Reprod 1999; 5: 220-6.
[73] Altmäe S, Martinez-Conejero JA, Esteban FJ, Ruiz-Alonso M, Stavreus-Evers A, Horcajadas JA and Salumets A. MicroRNAs miR-30b, miR-30d, and miR-494 regulate human endometrial receptivity. Reprod Sci 2013; 20: 308-17.
[74] Chakrabarty A, Tranguch S, Daikoku T, Jensen K, Furneaux H and Dey SK. MicroRNA regulation of cyclooxygenase-2 during embryo implantation. Proc Natl Acad Sci U S A 2007; 104: 15144-9.
[75] Bidarimath M, Khalaj K, Wessels JM and Tayade C. MicroRNAs, immune cells and pregnancy. Cell Mol Immunol 2014; 11: 538-47.
[76] Hassan SS, Romero R, Pineles B, Tarca AL, Montenegro D, Erez O, Mittal P, Kusanovic JP, Mazaki-Tovi S, Espinoza J, Nhan-Chang CL, Draghici S and Kim CJ. MicroRNA expression profiling of the human uterine cervix after term labor and delivery. Am J Obstet Gynecol 2010; 202: 80, e1-8.
[77] Barranco I, Padilla L, Martinez CA, Alvarez-Rodriguez M, Parrilla I, Lucas X, Ferreira-Dias G, Yeste M, Rodriguez-Martinez H and Roca J. Seminal plasma modulates miRNA expression by sow genital tract lining explants. Biomolecules 2020; 10: 933.
[78] Schjenken J and Robertson S. Induction of endogenous miR223 expression by sperm in the female reproductive tract following mating in mice. Am J Reprod Immunol 2013; 70: 18-9.
[79] Xie M, Li Y, Meng YZ, Xu P, Yang YG, Dong S, He J and Hu Z. Uterine natural killer cells: a rising star in human pregnancy regulation. Front Immunol 2022; 13: 918550.
[80] Kimura H, Fukui A, Fujii S, Yamaguchi E, Kasai G and Mizunuma H. Timed sexual intercourse facilitates the recruitment of uterine CD56(bright) natural killer cells in women with infertility. Am J Reprod Immunol 2009; 62: 118-24.

[81] Mayoral Andrade G, Vásquez Martínez G, Pérez-Campos Mayoral L, Hernández-Huerta MT, Zenteno E, Pérez-Campos Mayoral E, Martínez Cruz M, Martínez Cruz R, Matias-Cervantes CA, Meraz Cruz N, Romero Díaz C, Cruz-Parada E and Pérez-Campos E. Molecules and prostaglandins related to embryo tolerance. Front Immunol 2020; 11: 555414.

[82] Ablin RJ, Bartkus JM and Polgár J. Effect of human seminal plasma on the lytic activity of natural killer cells and presumptive identification of participant macromolecules. Am J Reprod Immunol 1990; 24: 15-21.

[83] Tarter TH, Cunningham-Rundles S and Koide SS. Suppression of natural killer cell activity by human seminal plasma in vitro: identification of 19-OH-PGE as the suppressor factor. J Immunol 1986; 136: 2862-7.

[84] Moldenhauer LM, Diener KR, Hayball JD and Robertson SA. An immunogenic phenotype in paternal antigen-specific CD8(+) T cells at embryo implantation elicits later fetal loss in mice. Immunol Cell Biol 2017; 95: 705-15.

[85] Moldenhauer LM, Schjenken JE, Hope CM, Green ES, Zhang B, Eldi P, Hayball JD, Barry SC and Robertson SA. Thymus-derived regulatory T cells exhibit Foxp3 epigenetic modification and phenotype attenuation after mating in mice. J Immunol 2019; 203: 647-57.

[86] Balandya E, Wieland-Alter W, Sanders K and Lahey T. Human seminal plasma fosters CD4(+) regulatory T-cell phenotype and transforming growth factor-β1 expression. Am J Reprod Immunol 2012; 68: 322-30.

[87] Saito S, Shima T, Nakashima A, Inada K and Yoshino O. Role of paternal antigen-specific treg cells in successful implantation. Am J Reprod Immunol 2016; 75: 310-6.

[88] Robertson SA, Prins JR, Sharkey DJ and Moldenhauer LM. Seminal fluid and the generation of regulatory T cells for embryo implantation. Am J Reprod Immunol 2013; 69: 315-30.

[89] Kelly RW and Critchley HO. Immunomodulation by human seminal plasma: a benefit for spermatozoon and pathogen? Hum Reprod 1997; 12: 2200-7.

[90] Robertson SA, Ingman WV, O'Leary S, Sharkey DJ and Tremellen KP. Transforming growth factor beta--a mediator of immune deviation in seminal plasma. J Reprod Immunol 2002; 57: 109-28.

[91] Chen W, Jin W, Hardegen N, Lei KJ, Li L, Marinos N, McGrady G and Wahl SM. Conversion of peripheral CD4+CD25- naive T cells to CD4+CD25+ regulatory T cells by TGF-beta induction of transcription factor Foxp3. J Exp Med 2003; 198: 1875-86.

[92] Clark DA, Fernandes J and Banwatt D. Prevention of spontaneous abortion in the CBA x DBA/2 mouse model by intravaginal TGF-beta and local recruitment of CD4+8+ FOXP3+ cells. Am J Reprod Immunol 2008; 59: 525-34.

[93] Guerin LR, Moldenhauer LM, Prins JR, Bromfield JJ, Hayball JD and Robertson SA. Seminal fluid regulates accumulation of FOXP3+ regulatory T cells in the preimplantation mouse uterus through expanding the FOXP3+ cell pool and CCL19-mediated recruitment. Biol Reprod 2011; 85: 397-408.

[94] Moldenhauer LM, Diener KR, Thring DM, Brown MP, Hayball JD and Robertson SA. Cross-presentation of male seminal fluid antigens elicits T cell activation to initiate the female immune response to pregnancy. J Immunol 2009; 182: 8080-93.

[95] Shima T, Nakashima A, Yasuda I, Ushijima A, Inada K, Tsuda S, Yoshino O, Tomura M and Saito S. Uterine CD11c+ cells induce the development of paternal antigen-specific Tregs via seminal plasma priming. J Reprod Immunol 2020; 141: 103165.

[96] Shima T, Inada K, Nakashima A, Ushijima A, Ito M, Yoshino O and Saito S. Paternal antigen-specific proliferating regulatory T cells are increased in uterine-draining lymph nodes just before implantation and in pregnant uterus just after implantation by seminal plasma-priming in allogeneic mouse pregnancy. J Reprod Immunol 2015; 108: 72-82.

[97] Nadkarni S, Smith J, Sferruzzi-Perri AN, Ledwozyw A, Kishore M, Haas R, Mauro C, Williams DJ, Farsky SH, Marelli-Berg FM and Perretti M. Neutrophils induce proangiogenic T cells with a regulatory phenotype in pregnancy. Proc Natl Acad Sci U S A 2016; 113: E8415-E24.

[98] Woidacki K, Meyer N, Schumacher A, Goldschmidt A, Maurer M and Zenclussen AC. Transfer of regulatory T cells into abortion-prone mice promotes the expansion of uterine mast cells and normalizes early pregnancy angiogenesis. Sci Rep 2015; 5: 13938.

[99] Zhang W, Wu K, He W, Gao Y, Huang W, Lin X, Cai L, Fang Z, Zhou Q, Luo Z, Chen ZK and Zhou H. Transforming growth factor beta 1 plays an important role in inducing CD4(+) CD25(+)forhead box P3(+) regulatory T cells by mast cells. Clin Exp Immunol 2010; 161: 490-6.

[100] Meuleman T, Snaterse G, van Beelen E, Anholts JD, Pilgram GS, van der Westerlaken LA, Eikmans M and Claas FH. The immunomodulating effect of seminal plasma on T cells. J Reprod Immunol 2015; 110: 109-16.

[101] du Fossé NA, Lashley EELO, Anholts JDH, van Beelen E, le Cessie S, van Lith JMM, Eikmans M and van der Hoorn MLP. Impaired immunomodulatory effects of seminal plasma may

play a role in unexplained recurrent pregnancy loss: results of an in vitro study. J Reprod Immunol 2022; 151: 103500.
[102] Kanannejad Z, Jahromi BN and Gharesi-Fard B. Seminal plasma and CD4(+) T-cell cytokine profiles in the in vitro fertilization success. J Res Med Sci 2020; 25: 26.
[103] Azad M, Keshtgar S, Jahromi BN, Kanannejad Z and Gharesi-Fard B. T helper cell subsets and related cytokines in infertile women undergoing in vitro fertilization before and after seminal plasma exposure. Clin Exp Reprod Med 2017; 44: 214-23.
[104] Kanannejad Z, Namavar Jahromi B and Gharesi-Fard B. T cell subsets profiling in unexplained infertile women with successful and unsuccessful in vitro fertilization outcome: focus on the effect of seminal plasma. Iran J Allergy Asthma Immunol 2019; 18: 163-72.
[105] Blois SM, Alba Soto CD, Tometten M, Klapp BF, Margni RA and Arck PC. Lineage, maturity, and phenotype of uterine murine dendritic cells throughout gestation indicate a protective role in maintaining pregnancy. Biol Reprod 2004; 70: 1018-23.
[106] Kämmerer U. Antigen-presenting cells in the decidua. In: Markert UR, ed. Immunology of Pregnancy: S.Karger AG; 2005.
[107] Remes Lenicov F, Rodriguez Rodrigues C, Sabatté J, Cabrini M, Jancic C, Ostrowski M, Merlotti A, Gonzalez H, Alonso A, Pasqualini RA, Davio C, Geffner J and Ceballos A. Semen promotes the differentiation of tolerogenic dendritic cells. J Immunol 2012; 189: 4777-86.
[108] Iijima N, Linehan MM, Saeland S and Iwasaki A. Vaginal epithelial dendritic cells renew from bone marrow precursors. Proc Natl Acad Sci U S A 2007; 104: 19061-6.
[109] Merlotti A, Ruiz MJ, Díaz FE, Dantas E, Varese A, Duette G, Pereyra P, Glenda E, Lenicov FR and Geffner J. Seminal plasma modulates dendritic cell function favoring the generation of CD25+/FOXP3+ T-cells. AIDS Res Hum Retroviruses 2014; 30: A174.
[110] Merlotti A, Dantas E, Remes Lenicov F, Ceballos A, Jancic C, Varese A, Rubione J, Stover S, Geffner J and Sabatté J. Fucosylated clusterin in semen promotes the uptake of stress-damaged proteins by dendritic cells via DC-SIGN. Hum Reprod 2015; 30: 1545-56.
[111] Rennemeier C, Schwab M, Lermann U, Albert C, Kämmerer U, Frambach T, Morschhäuser J, Dietl J and Staib P. Seminal plasma protects human spermatozoa and pathogenic yeasts from capture by dendritic cells. Hum Reprod 2011; 26: 987-99.
[112] True H, Blanton M, Sureshchandra S and Messaoudi I. Monocytes and macrophages in pregnancy: the good, the bad, and the ugly. Immunol Rev 2022; 308: 77-92.
[113] Bischof R, Lee C, Brandon M and Meeusen E. Inflammatory response in the pig uterus induced by seminal plasma. J Reprod Immunol 1994; 26: 131-46.
[114] Gangnuss S, Sutton-McDowall ML, Robertson SA and Armstrong DT. Seminal plasma regulates corpora lutea macrophage populations during early pregnancy in mice. Biol Reprod 2004; 71: 1135-41.
[115] O'Leary S, Jasper MJ, Robertson SA and Armstrong DT. Seminal plasma regulates ovarian progesterone production, leukocyte recruitment and follicular cell responses in the pig. Reproduction 2006; 132: 147-58.
[116] Rozeboom KJ, Troedsson MHT, Molitor TW and Crabo BG. The effect of spermatozoa and seminal plasma on leukocyte migration into the uterus of gilts. J Anim Sci 1999; 77: 2201-6.
[117] Troedsson MH, Desvousges A, Alghamdi AS, Dahms B, Dow CA, Hayna J, Valesco R, Collahan PT, Macpherson ML, Pozor M and Buhi WC. Components in seminal plasma regulating sperm transport and elimination. Anim Reprod Sci 2005; 89: 171-86.
[118] Alghamdi AS, Foster DN and Troedsson MHT. Equine seminal plasma reduces sperm binding to polymorphonuclear neutrophils (PMNs) and improves the fertility of fresh semen inseminated into inflamed uteri. Reproduction 2004; 127: 593-600.
[119] Gosselin EJ, Wardwell K, Rigby WF and Guyre PM. Induction of MHC class II on human polymorphonuclear neutrophils by granulocyte/macrophage colony-stimulating factor, IFN-gamma, and IL-3. J Immunol 1993; 151: 1482-90.
[120] Crawford G, Ray A, Gudi A, Shah A and Homburg R. The role of seminal plasma for improved outcomes during in vitro fertilization treatment: review of the literature and meta-analysis. Hum Reprod Update 2014; 21: 275-84.
[121] Saccone G, Di Spiezio Sardo A, Ciardulli A, Caissutti C, Spinelli M, Surbek D and von Wolff M. Effectiveness of seminal plasma in in vitro fertilisation treatment: a systematic review and meta-analysis. BJOG 2019; 126: 220-5.
[122] Zhu Y, Wu Y, Jin K, Lu H, Liu F, Guo Y, Yan F, Shi W, Liu Y, Cao X, Hu H, Zhu H, Guo X, Sha J, Li Z and Zhou Z. Differential proteomic profiling in human spermatozoa that did or did not result in pregnancy via IVF and AID. Proteomics Clin Appl 2013; 7: 850-8.
[123] Kanannejad Z and Gharesi-Fard B. Difference in the seminal plasma protein expression in unexplained infertile men with successful and unsuccessful in vitro fertilisation outcome. Andrologia 2019; 51: e13158.
[124] Diamandis EP, Arnett WP, Foussias G, Pappas H, Ghandi S, Melegos DN, Mullen B, Yu H, Srig-

ley J and Jarvi K. Seminal plasma biochemical markers and their association with semen analysis findings. Urology 1999; 53: 596-603.
[125] Aitken RJ and Baker MA. The role of genetics and oxidative stress in the etiology of male infertility-a unifying hypothesis? Front Endocrinol (Lausanne) 2020; 11: 581838.
[126] Wang J, Wang J, Zhang HR, Shi HJ, Ma D, Zhao HX, Lin B and Li RS. Proteomic analysis of seminal plasma from asthenozoospermia patients reveals proteins that affect oxidative stress responses and semen quality. Asian J Androl 2009; 11: 484-91.
[127] van den Berg JS, Molina NM, Altmäe S, Arends B and Steba GS. A systematic review identifying seminal plasma biomarkers and their predictive ability on IVF and ICSI outcomes. Reprod Biomed Online 2024; 48: 103622.
[128] Nawroth F and von Wolff M. Seminal plasma activity to improve implantation in in vitro fertilization-How can it be used in daily practice? Front Endocrinol (Lausanne) 2018; 9: 208.
[129] Seshadri S, Bates M, Vince G and Lewis Jones DI. Cytokine expression in the seminal plasma and its effects on fertilisation rates in an IVF cycle. Andrologia 2011; 43: 378-86.
[130] Nikolaeva M, Babayan A, Stepanova E, Arefieva A, Dontsova T, Smolnikova V, Kalinina E, Krechetova L, Pavlovich S and Sukhikh G. The link between seminal cytokine interleukin 18, female circulating regulatory T cells, and IVF/ICSI success. Reprod Sci 2019; 26: 1034-44.
[131] Hanafy S, Mostafa T, Abd-Elhameed H, Rashed L and Akl EM. Seminal endoglin in infertile men with varicocele, a cohort study. EJDV 2024; 44: 90-4.
[132] MacDonald A, Herbison G, Showell M and Farquhar C. The impact of body mass index on semen parameters and reproductive hormones in human males: a systematic review with meta-analysis. Hum Reprod Update 2010; 16: 293-311.
[133] Khosrowbeygi A and Zarghami N. Levels of oxidative stress biomarkers in seminal plasma and their relationship with seminal parameters. BMC Clin Pathol 2007; 7: 1-6.
[134] Dekker GA, Robillard PY and Hulsey TC. Immune maladaptation in the etiology of preeclampsia: a review of corroborative epidemiologic studies. Obstet Gynecol Surv 1998; 53: 377-82.
[135] Klonoff-Cohen HS, Savitz DA, Cefalo RC and McCann MF. An epidemiologic study of contraception and preeclampsia. JAMA 1989; 262: 3143-7.
[136] Robertson SA, Bromfield JJ and Tremellen KP. Seminal 'priming' for protection from pre-eclampsia-a unifying hypothesis. J Reprod Immunol 2003; 59: 253-65.
[137] Robillard PY, Hulsey TC, Alexander GR, Keenan A, de Caunes F and Papiernik E. Paternity patterns and risk of preeclampsia in the last pregnancy in multiparae. J Reprod Immunol 1993; 24: 1-12.
[138] Robillard PY, Hulsey TC, Périanin J, Janky E, Miri EH and Papiernik E. Association of pregnancy-induced hypertension with duration of sexual cohabitation before conception. Lancet 1994; 344: 973-5.
[139] Kyrou D, Kolibianakis EM, Devroey P and Fatemi HM. Is the use of donor sperm associated with a higher incidence of preeclampsia in women who achieve pregnancy after intrauterine insemination? Fertil Steril 2010; 93: 1124-7.
[140] Wang JX, Knottnerus AM, Schuit G, Norman RJ, Chan A and Dekker GA. Surgically obtained sperm, and risk of gestational hypertension and pre-eclampsia. Lancet 2002; 359: 673-4.
[141] Zhang X, Wang H, Feng T, Yang J, Huang Q, Lu C, Guan Y, Sun R, Chen M and Qian Y. The relationship between semen factors and unexplained recurrent spontaneous abortion. Clin Chim Acta 2020; 510: 605-12.
[142] du Fossé NA, Lashley E, van Beelen E, Meuleman T, le Cessie S, van Lith JMM, Eikmans M and van der Hoorn MLP. Identification of distinct seminal plasma cytokine profiles associated with male age and lifestyle characteristics in unexplained recurrent pregnancy loss. J Reprod Immunol 2021; 147: 103349.