Review

# Environmental influences on seminal plasma: Molecular and functional insights

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Abstract. Seminal plasma is a pivotal regulator of reproductive success that contributes to fertility and fecundity beyond its traditionally recognized function as a vehicle for spermatozoa. Rich in soluble and extracellular vesicle-encased signaling molecules, seminal plasma influences sperm integrity and function, whilst simultaneously driving profound physiological changes in the female reproductive tract. These functions are broadly conserved across vertebrate and invertebrate species and help to optimize fertilization and create an immunological environment that supports implantation and fetal development. Perturbation of seminal plasma composition or ablation of its effects can affect fertility, the progression of pregnancy and even the long-term health of offspring. Given these far-reaching effects, the responsiveness of seminal plasma composition to environmental exposures and influences has become an important focus of research. Studies across species using a variety of different physiological perturbations or environmental exposures have shown modification to the abundance and activities of soluble and extracellular vesicle-derived seminal plasma signaling molecules. Exposures to toxins, nutritional deficiency, metabolic disturbance, and infection-associated inflammation have each been shown to affect seminal plasma components with consequences for sperm function, female reproductive tract responses, embryo development, and offspring health. Collectively, these findings position seminal plasma, in addition to spermatozoa, as an important mediator of paternal environmental influences, offering a biological means through which males convey information on their physiological state to their mates and influence reproductive success across generations.
Key words: Environmental exposure, Seminal extracellular vesicles, Seminal plasma

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## Introduction

Seminal plasma is now recognized as a key regulator of reproductive success, through biological effects extending beyond its role as a carrier for spermatozoa. This complex mixture delivers not only gametes, but a diverse array of bioactive agents that interact with sperm cells and the female reproductive tract after intromission to induce molecular and cellular changes that influence the likelihood of conception and pregnancy, and have developmental programming effects on offspring [1, 2]. In the female, seminal plasma acts to promote reproductive success through complex interactions with the reproductive and immune systems [1]. Broadly speaking, the functions of seminal plasma are conserved across species, with comparable biological effects identified across invertebrate and vertebrate species; despite significant differences in reproductive strategies and reproductive tissue anatomy [1, 3, 4]. This evolutionarily conserved function raises an important question as to whether information conveyed in seminal plasma could transmit effects of paternal physiological state or environmental exposures to the female reproductive tract, and ultimately, affect the phenotype of the next generation. In this review, we summarize current understanding of how the paternal environment influences seminal plasma composition and the potential consequences of these changes for pregnancy and offspring across species.

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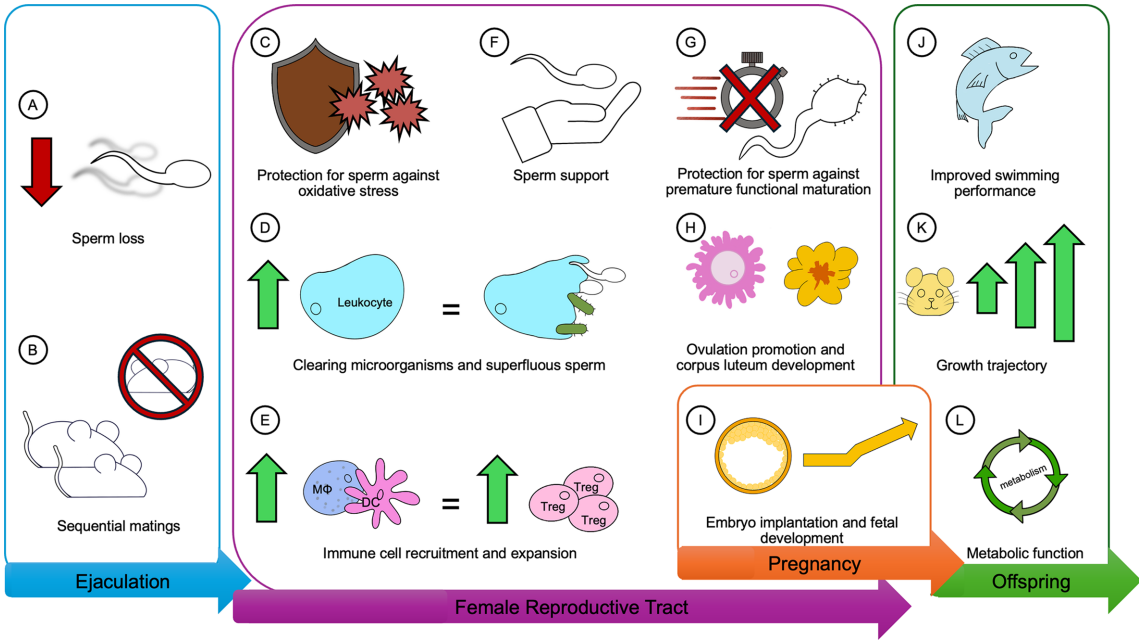


**Fig. 1.** Seminal plasma's role in reproduction: from ejaculation to offspring outcomes. Across species, there is compelling evidence that seminal plasma plays important functional roles at conception to support reproductive success. Following ejaculation, in humans the coagulation of seminal plasma limits sperm loss [8], while the presence of a copulatory plug in the mouse restricts sequential matings [2]. In the female reproductive tract, the seminal plasma of humans, cattle, dogs, and horses has been shown to support sperm survival through reducing the acidity of the microenvironment [1, 2, 7] and affording protection against oxidative stress [5, 9–11]. The seminal plasma of cattle, pigs, and humans has also been implicated in regulating functional changes in sperm motility, capacitation, and the acrosome reaction following semen deposition into the female reproductive tract [2, 5, 6, 12, 13]. Beyond actions on spermatozoa, seminal plasma exerts significant impact on female reproductive tract cells, driving inflammatory changes resulting in the recruitment of leukocytes, which are thought to aid in the clearance of microorganisms and superfluous sperm across multiple species [1, 3, 14, 36, 37]. Seminal plasma also influences ovarian function, promoting ovulation and development of the corpus luteum in alpacas, camel, horse, llamas, mouse, pig, and rabbit [2, 7, 31–34, 85]. Together, these changes aid in establishing a receptive uterine environment to support optimal embryo implantation and fetal development during pregnancy [1, 14, 36, 37], and even beyond, with documented impacts on offspring health. These include effects on offspring phenotype on flies [39] and improved swimming performance in fish [38], and regulation of offspring growth trajectory and metabolic function in mice [36].

## Physiological roles of seminal plasma in reproduction

When seminal fluid intromission at mating occurs, seminal plasma not only interacts with sperm cells to support their transit through the female reproductive tract to the site of fertilization, but also acts to shape the post-copulatory environment to promote reproductive success and maximize progeny fitness at an individual and population level [1]. These effects have important consequences and are especially pivotal in mating events that result in conception. The best characterized, and most conserved functions of seminal plasma concern its established role in modulating sperm viability and function during transit of spermatozoa to the site of fertilization [5]. In addition, signaling mediators within seminal plasma establish a post-copulatory immunological environment that, under usual circumstances, facilitates optimal embryonic and fetal development (Fig. 1) [1]. These responses are driven by soluble and extracellular vesicle-encased proteins, lipids, carbohydrates, and microRNAs that modulate sperm cell biology and provoke transcriptional responses and other physiological changes in female reproductive tract cells and tissues (Table 1) [5, 6].

One of the best characterized functions of seminal plasma is to promote the survival and function of spermatozoa as they navigate to the site of fertilization (Fig. 1) [5]. In insects, primates and rodents, these roles are initially supported by seminal plasma molecules that drive coagulation of the fluid at ejaculation (Table 1) [1, 2, 7]. In humans, the coagulum plays a dual role, firstly preventing sperm loss from the female reproductive tract and secondly, preventing premature acquisition of motility, capacitation and acrosome reaction in spermatozoa [8]. In mice, the coagulum is also thought to restrict sequential matings to increase the likelihood of siring offspring [2]. Beyond the coagulum, seminal plasma molecules support sperm survival, initially in humans through reducing the acidity of the female reproductive tract, but also in cattle, dog, horse, and human through delivering a rich array of antioxidants that protect spermatozoa against oxidative stress (Fig. 1) [5, 9–11].

In addition to these functions, seminal plasma from all studied mammalian species provides spermatozoa with signaling molecules that allow them to reach the oocyte and undergo fertilization. The molecules that contribute have varied actions, with some constraining motility, capacitation and the acrosome reaction, whilst others promote these functional changes (Fig. 1, Table 1) [2, 5, 6, 12, 13]. These findings highlight the complexity of spermatozoa and seminal plasma communication where seminal plasma is required to exert tight control over the activation of functional changes to spermatozoa to increase the likelihood of fertilization.

The second key conserved function of seminal plasma is to prepare the female reproductive tract for pregnancy (Fig. 1) [1, 3, 14]. This has primarily been characterized in mice, wherein seminal plasma drives inflammation in epithelial cells at the site of semen deposition and the recruitment of leukocytes including neutrophils [15, 16], which assist in clearing the uterine cavity of microorganisms

**Table 1.** The functional roles of major seminal plasma signaling factors in the reproductive physiology of representative species

| Seminal plasma influence on sperm function | | |
|---|---|---|
| *Biological functions* | *Signaling factors* | *Species* |
| Promotion of sperm capacitation | • CD38 | Human [83, 84] |
| | • BSPs | Alpaca, cattle, goat, horse, pig and sheep [64–66] |
| | • SEVs | Human, cattle, dog and horse [84, 93, 105–107] |
| Inhibition of sperm capacitation | • SEMG1/SVS2 | Human, mouse [53–56] |
| | • SERPINE2 | Mouse [58] |
| | • SPINK family members | Mouse [59, 60] |
| Sperm motility | • CD38 | Human [83, 84] |
| | • PGE | Human [74] |
| | • BSPs | Alpaca, cattle, goat, horse, pig and sheep [64–66] |
| | • SEVs | Human, cattle, dog and horse [84, 93, 105–107] |
| Coagulation | • SVS2 | Mouse [54, 55] |
| | • SEMG2 | Human [53, 56] |
| Seminal plasma influence on the female reproductive tract | | |
| *Biological functions* | *Signaling factors* | *Species* |
| Ovulation | • βNGF | Camel, llama and rabbit [34, 85, 86] |
| Post-mating immune alterations | • TGFB | Human, mouse, cattle and pig [67–70] |
| | • PGE | Human [72, 73] |
| | • Unidentified TLR ligands | Mouse and cattle [15, 16, 76] |
| | • SEVs | Human and cattle [6, 103, 104] |
| Maternal-fetal immune tolerance | • TGFB | Mouse [1, 71] |
| | • CD38 | Mouse [83, 84] |
| | • Unidentified TLR ligands | Mouse [77] |

and superfluous sperm cells introduced at mating. Similar female reproductive tract inflammatory responses to seminal plasma have been observed in cattle, dog, horse, human, pig, and rabbit [17–23]. In addition to neutrophils, recruitment of macrophages and dendritic cells into the mucosal surface of the cervix and uterus occurs, and these cells ultimately drive the expansion of the uterine population of tolerogenic regulatory T (Treg) cells [1, 3]. Gamma/delta$^{+}$ T cell recruitment into the uterus is another major element of the female immune response to seminal plasma in mice, although its significance in reproductive success remains to be fully investigated [24]. Notably, seminal plasma may interact directly with immune cells in the female reproductive tract to promote tolerance, with *in vitro* studies in humans showing effects of components of seminal plasma on the differentiation of tolerogenic dendritic cells, natural killer cells, and T cells (Fig. 1) [25–29]. Together, these immune mechanisms condition the female reproductive tract to support embryo implantation and fetal development [1, 14, 30]. Beyond these functions, it is of interest that in camel, cattle, horse, mouse, pig, and rabbit, seminal plasma compounds access the ovary to promote ovulation and/or corpus luteum development (Fig. 1) [2, 7, 31–35].

The beneficial effects of seminal plasma exposure extend beyond embryo implantation, with studies in model species demonstrating that seminal plasma contributes to shaping offspring health (Fig. 1). In rodent models, pregnancies sired in the absence of seminal plasma demonstrate that this fluid not only influences fertility, but offspring exhibit altered growth trajectories, disturbed metabolic function and altered behavior (Fig. 1) [36, 37]. Similarly, in European whitefish, neriid flies and *Drosophila*, seminal plasma appears to have consequences for offspring phenotype (Fig. 1) [38–40]. In humans, seminal plasma exposure around the time of embryo transfer improves clinical pregnancy rates in assisted reproductive technologies [41, 42]. Comparable benefits are also observed in livestock species, where seminal plasma exposure is associated with increased litter size in pigs [18, 43] and larger calf size in cattle [44].

## Bioactive factors in seminal plasma

In most mammals the primary source of seminal plasma is the seminal vesicles – poorly understood, androgen-dependent, male accessory glands [45] that provide critical signaling agents for fertility and fecundity [36, 46–51]. However, seminal vesicles are rudimentary or absent in canine and feline species [4], whilst in pigs, the bulbourethral glands are the most prominent accessory sex gland [4]. Due to this variation, the composition of seminal plasma substantially differs across species, reflecting unique reproductive physiology from one species to another [3]. The bioactive agents that bind to and exert influence on spermatozoa and female reproductive tract cells are present as soluble factors in seminal plasma as well as extracellular vesicle-encased bioactive molecules [5, 6]. Several of these signaling mediators are evolutionarily conserved, while others are unique to certain species.

## Soluble seminal plasma signaling molecules

In this section, we focus on the best-characterized seminal plasma signaling mediators that are relatively well conserved across species (Table 1). However, we acknowledge that there are additional mediators that influence both spermatozoa and female reproductive tract signaling and draw the reader's attention to extensive reviews of seminal plasma signaling mediators [1–3, 5, 52].

Focusing initially on the seminal plasma signaling mediators that influence the function of spermatozoa, components of the semen coagulum in humans and mice have been shown to regulate sperm motility and ensure the precise timing of capacitation and the acrosome

reaction (Table 1) [2, 5]. These include semenogelin 1 (or seminal vesicle secretory protein 2 in mouse) which is required to control sperm capacitation and protect spermatozoa from damage caused by uterine-derived cytotoxic factors [53–56]. Additional decapacitation factors include serine protease inhibitor 2 (SERPINE2), which is detected in donkey, horse, and mouse seminal plasma [57, 58], and members of the serine protease inhibitor kazal (SPINK) protein family in the mouse [59, 60]. In mice, SERPINE2 blocks protein tyrosine phosphorylation and inhibits sperm capacitation and while it is present on the surface of oviductal sperm cells, is lost prior to the onset of capacitation [58], while SPINK proteins that are bound to sperm cells in the uterus, but no longer present in oviductal sperm cells, prevent premature capacitation and the acrosome reaction through attenuation of SRC tyrosine kinase activity [59, 60]. In addition, seminal plasma motility inhibitor present in seminal plasma of cattle and human has been shown to transiently restrict sperm motility [61, 62], while an equivalent role in the mouse is undertaken by seminal vesicle autoantigen [63]. Among livestock species the best characterized seminal plasma sperm modulators are the binder of sperm (BSP) proteins. These are present in the seminal plasma of alpaca, cattle, goat, horse, pig, and sheep [64, 65] and bind to sperm cells, support sperm motility and viability, assist in forming sperm storage reservoirs and facilitate sperm capacitation [66].

In addition to seminal plasma molecules that influence sperm function, studies have also identified signaling mediators that influence the female reproductive tract response to mating (Table 1). A principal immune signaling mediator in seminal plasma is identified as transforming growth factor beta (TGFβ), which is detected across cattle, human, mouse, pig, and sheep [3]. In comprehensive studies in cattle, human, mice and pigs, TGFβ is activated from the latent form after intromission and binds to receptors on uterine and cervical epithelial cells to drive pro-inflammatory cytokine synthesis and secretion [67–70]. TGFβ has profound effects on immune cells, most notably promoting the development of tolerogenic dendritic cells and Treg cells [1], such that vaginal administration of TGFβ at the time of mating to abortion-prone mice increases Treg cell numbers and reduces spontaneous fetal loss [71]. Another highly conserved family of seminal plasma signaling agents are E-series prostaglandins, which are present in the seminal plasma of cattle, horse, human, and rhesus monkey, as well as fish, birds and invertebrates [1]. In humans, E-series prostaglandins have been shown to activate inflammatory cytokine and angiogenesis associated pathways in female reproductive tract cells [72, 73] and also have a dual role in regulating sperm motility (Table 1) [74]. Interestingly, in invertebrates prostaglandins simulate mating induced egg release [75]. Finally, there is extensive evidence that unidentified toll-like receptor (TLR) ligands are present in the seminal plasma of species and are key mediators of the female reproductive tract inflammatory response to seminal fluid. This is best characterized in cattle and mice, where sperm and seminal plasma TLR ligands increase inflammatory cytokine production by binding TLR2 and TLR4 respectively [15, 16, 76]. Studies using TLR4-deficient mice demonstrate the importance of these signals, showing that in their absence there is reduced induction of cytokines and expansion of regulatory T cells, with increased fetal loss and fetal growth restriction (Table 1) [77].

Beyond these well-characterized signaling molecules, numerous studies identify other potential seminal plasma signaling molecules in a variety of species. A range of cytokines have been documented in cattle, human, pig and rodent seminal plasma [78–81]. These are presumed to exert effects on the female immune environment [1] and may also directly influence sperm function - for example, cattle interleukin (IL)-10 and human IL8 levels in seminal plasma correlate with sperm motility [78, 82]. Similarly, ADP-ribosyl cyclase 1 (CD38) is present in both human and mouse seminal plasma where they have dual roles influencing both sperm function and the female immune response. CD38, for example, influences sperm capacitation and motility and drives the expansion of Treg cells (Table 1) [83, 84]. Interestingly, in induced ovulator species such as camel, llama and rabbit, seminal plasma nerve growth factor beta subunit (βNGF) induces ovulation following mating (Table 1) [34, 85, 86]. In cattle, which are spontaneous ovulators, seminal plasma βNGF influences corpus luteum size and progesterone release and may also play a role in conceptus development and reduce early pregnancy loss [87]. Strikingly, the effects of βNGF extend beyond this, with studies demonstrating that human and cattle βNGF affects semen quality following cryopreservation [88, 89].

## Seminal extracellular vesicle derived signaling molecules

An emerging mechanism by which seminal plasma delivers bioactive factors to the female reproductive tract and spermatozoa is via seminal extracellular vesicles (SEVs) (Table 1). SEVs are highly heterogeneous, nanosized, membrane-bound particles released by tissues across the male reproductive tract [6] in a variety of mammalian species including buffalo [90], cat [91], cattle [92], dog [93], donkey [94], horse [95], human [96], mice [97], pig [98], and sheep [99]. SEVs have also been detected in the seminal plasma of chickens [100], *Drosophila* [101], and fish [102], demonstrating the evolutionary conservation of these EVs and their potential importance in influencing conception. Specific functions attributed to SEVs include supporting spermatozoa as they transit through the female reproductive tract, and modulating the immune environment within the female reproductive tract through effects on cytokine secretion and immune cell function (Fig. 2) [6, 103, 104].

By encapsulating their cargo within a protective lipid bilayer, EV-encased molecules such as nucleic acids, proteins, lipids, and metabolites are shielded from degradation or modification during intercellular transit. Of the different types of cargo carried by EVs, the most well characterized are proteins. Candidate SEV molecules shown to influence sperm function include calcium signaling molecules such as CD38, which in humans is transferred from SEVs to spermatozoa and supports progesterone-induced sperm motility and capacitation [84, 105]. Beyond humans, SEV proteins including clusterin, T-complex protein 1, and members of the peroxiredoxin, ATPase and glycolysis-associated protein families are conserved across cattle, dog, horse and human SEVs, and are associated with a range of sperm functions including motility, capacitation and the acrosome reaction [93, 106, 107]. These likely do not represent the sole SEV proteins that influence sperm function as proteomics analyses in human have identified a broad range of SEV proteins with links to signaling pathways and functions that contribute to sperm fertilization capacity. These include SEV proteins associated with transforming protein RHOA, protein kinase A, protein ubiquitination, and various cytoskeletal signaling pathways [108].

SEVs also have potent immune regulatory roles. In humans, proteomic studies have identified that SEVs carry important immune-regulatory molecules such as CD38, semenogelin, TLR4 ligands (including beta defensin, high mobility group box, and heat shock proteins), TGFβ, and vacuolar-type $H^+$-ATPase family members [108–110], all of which have been implicated as signaling agents within seminal plasma [1]. Notably, vacuolar-type $H^+$-ATPase is

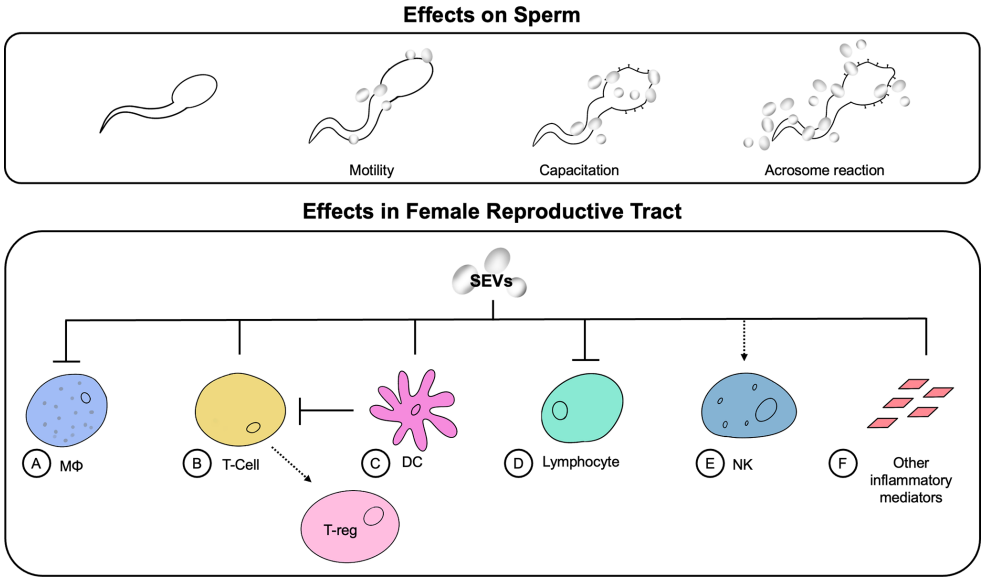


**Fig. 2.** Impact of seminal extracellular vesicles on spermatozoa and the female reproductive tract at conception. A mechanism by which seminal plasma delivers bioactive factors to the female reproductive tract and spermatozoa is via seminal extracellular vesicles (SEVs). Studies in human, cattle, dog, and horse have shown that SEVs carry cargo with the capacity to influence functional changes to sperm that promote motility, capacitation, and acrosome reaction [6, 93, 105–107]. In the female reproductive tract, SEVs aid in the induction and modulation of the immune environment. Early *in vitro* studies in humans demonstrated the capacity of SEVs to inhibit macrophage (MΦ) phagocytosis, while T-cells were shown to be directly modified by SEVs by promoting their differentiation into T-reg cells or indirectly by dendritic cells inhibiting T-cells. Simultaneously, SEVs have been shown to inhibit lymphocyte proliferation, and modify natural killer cells (NK) function [6]. Additionally, in cattle and humans, SEVs have been shown to induce the production of cytokines and other inflammatory mediators in female reproductive tract cells [6, 103, 104].

carried by both human [108] and horse [93] SEVs and is linked to the establishment of an inflammatory response prior to implantation in pregnancy [111], while human SEVs contain CD38, that as discussed above promotes the differentiation of CD4+ T cells into Treg cells [83]. Other potential SEV signaling agents that are conserved across species are galectin-3 and its ligand galectin-3 binding protein, that are detected in horse, dog, cattle, and human SEVs [93, 108] and have capacity to modulate the female immune response [112]. Given the range of proteins present in SEVs with known immune regulatory functions [93, 108] and the likelihood that other as yet unidentified signaling molecules exist, there is a need for comprehensive studies that explore the function of specific SEV cargo in modulation of the female reproductive tract immune environment.

## Environmental effects on seminal plasma composition and function

A growing body of evidence supports the paradigm that parental life history and experience can influence biological traits in subsequent generations. In males, acquired traits and environmental exposures can impair fertility and influence offspring health [113]. While sperm-borne genetic and epigenetic alterations are widely regarded as the primary mechanism for transmitting paternal information, seminal plasma also plays a pivotal role [1, 113, 114]. As the physiological influence of seminal plasma on the female reproductive tract becomes increasingly clear [1], research is now focused on how paternal physiological status and environmental exposures modulate seminal plasma composition and signaling activity.

An altered composition of seminal plasma in response to environmental exposures would reasonably act to transmit information about male partner physiological status and environmental experience to the female reproductive tract [1, 45, 52, 115–119]. These modifications would then allow fine-tuning of the female reproductive environment through a two-way communication system where males provide signals to boost paternity success and females interpret these cues. When seminal plasma composition reflects a favourable physiological state, these signals can provide beneficial effects and ultimately promote offspring with traits better suited for the prevailing environmental conditions. Conversely, when seminal plasma composition is perturbed, these signals may be maladaptive, constraining fertility, impairing embryo development, and even diminishing long-term offspring health. Importantly, seminal plasma signals enable females to preferentially select sperm cells and adjust female investment in pregnancy, in a form of cryptic female choice that ensures maternal investment provides the highest likelihood of producing viable, healthy progeny [1, 120, 121].

## Sensitivity of the male reproductive tract to environmental exposures

There is emerging information demonstrating that the male reproductive tract organs contributing to seminal plasma are sensitive to environmental influences [1, 45, 52, 115–119]. In particular, the seminal vesicle has been shown to be responsive to several forms of environmental perturbations by rapidly modulating protein production [114]. Following bacterial or viral infection, seminal vesicle epithelial cells mount innate immune responses [122], while chronic stress [123], diabetes [124], diet [125], endocrine disrupting compounds [126–128], and reproductive toxicants [129, 130] can all cause disruption in seminal vesicle tissue structure and/or function. For example, chronic stress in rats driven by cage restraint and forced swimming for a period of 60 days increases the expression of heat-shock protein 70, and caspase 3 and 9 proteins in seminal vesicle tissue as well as a reduction in seminal vesicle epithelial cell

height and secretory capacity [123].

Similarly, prostate function is influenced by a variety of environmental perturbations including air pollution [131], microbial dysbiosis [132], smoking status [133], stress [134], and diet [135, 136], with the majority of studies focused on understanding how these exposures may be associated with prostate cancer risk. For example, smoking status in men was associated with smaller prostate size, and an increased risk of acute prostate inflammation compared to both former smokers and individuals who had never smoked [133]. Changes to the prostate are not just limited to humans—studies across species show that inflammation of the prostate is a common response to a variety of different etiologies [137]. Less is known about the bulbourethral gland, but studies in diverse species including African straw-colored fruit bat and white-tailed deer show seasonal variations in bulbourethral gland size [138, 139] and histological appearance [139]. Similarly, in pigs, diets including hydrolysable tannins thought to improve meat odor, reduce bulbourethral gland size [140], while in koalas, the bulbourethral gland is susceptible to chlamydia infection with inflammation severity increasing alongside infection burden [141].

In addition to effects on accessory glands, accumulating evidence shows that paternal exposures influence the epididymis and testes and thereby impact embryo development and offspring health [142, 143]. Such effects may arise from direct actions on sperm development and function, but also could be influenced through factors secreted by these organs into seminal plasma [2]. Studies from numerous species have shown that diet, obesity, stress, smoking, and environmental toxin exposure during germ cell development can reprogram the sperm epigenome through mechanisms including DNA methylation changes, histone modifications, and altered small RNA profiles [126, 144–146]. These changes affect sperm quality and fertilization potential, influence early embryo development, and can lead to long-term health consequences in offspring. Whether these changes are specifically due to impacts on the testes, or downstream effects on the epididymis and its secretome, is challenging to unravel.

While numerous studies demonstrate that environmental perturbations can directly affect both testicular [147–150] and epididymal [149, 151–153] function, comparison between these tissues indicate that offspring health is influenced predominantly by epididymal exposures [153, 154]. Supporting this, studies specifically designed to explore the impacts of environmental exposures on spermatozoa during epididymal transit show that elevated ambient temperature, dietary perturbations, and reproductive toxicant exposure all alter sperm small non-coding RNA (sncRNA) profiles and exert profound influences over embryo development, fetal outcomes, and offspring health [152–158]. For example, in mice sub-chronic elevation in ambient temperature leads to altered sperm sncRNA profile, which contributed to pronounced changes in embryo gene expression, accelerated early embryo development, and disrupted fetal development [155]. Changes include dysregulation of embryonic genes associated with “abnormal placental morphology”, linked to elevated sperm sncRNAs, such as *miR-127-3p* [155], a regulator of fetal capillary development within the labyrinth zone during placentation [159]. Taken together, these studies clearly demonstrate that environmental exposures affect male reproductive tract organs, but they have not assessed whether the consequences may in part be mediated by modifications to the secretome that culminate in altered seminal plasma composition and function.

## Environmental effects on soluble seminal plasma signaling mediators

Compelling studies in many species indicate that changes to the composition and function of seminal plasma act to influence fertilization, implantation, and pregnancy outcomes [36, 49, 113, 114]. These findings point clearly to seminal plasma being a mediator, along with spermatozoa, of effects of paternal perturbations on reproduction and development. A series of studies by Watkins and colleagues has demonstrated that low-protein diet programs offspring health through both sperm-mediated and seminal plasma-mediated pathways. Using mouse models, low-protein diet was shown to alter the sperm epigenome and blunt the capacity of seminal plasma to drive uterine immunological and vascular signaling activation, with both sperm cells and seminal plasma shown to independently influence offspring health [47]. More recently, studies have revealed that these effects extend to offspring bone health [160], lipid metabolism [161], and vascular function [162] (Fig. 3). Additionally, paternal circadian rhythm disruption induced by night-restricted feeding in mice has been shown to program offspring metabolic health. It was proposed that the effects of circadian disruption were driven by loss of rhythmicity in seminal plasma corticosterone secretion leading to dysregulated female reproductive tract corticosterone signaling at conception [163] (Fig. 3). Other markers of stress in humans may similarly influence reproductive outcomes, as elevated seminal plasma IL18 in male partners has been linked to a higher likelihood of pregnancy failure during IVF cycles [164] (Fig. 3).

Amongst the most compelling evidence for environmental modulation of seminal plasma composition and function are studies investigating the impact of dietary perturbations. In mice, paternal high-fat diet has been shown to accelerate embryo development and negatively impact metabolic health in offspring through sperm-mediated pathways [165, 166], but these exposure regimens also dysregulate seminal vesicle fluid composition through changes in metabolites and proteins associated with immune system and endocrine function [166–168]. This includes reduced abundance of TGFβ and other seminal vesicle cytokines, resulting in impaired Treg cell expansion [167] (Fig. 3). Interestingly, changes in seminal vesicle fluid composition are also seen in low-protein diet interventions in mice, with increased expression of SPINK1 linked to modification of sperm function, and decreased expression of cystatin-C, a protein with well-established immune regulatory roles observed in seminal vesicle fluid [166, 169] (Fig. 3).

In humans, body mass index (BMI) is associated with elevated IL6 and tumor necrosis factor (TNF) levels in seminal plasma [170], while in cattle, nutritional stress and adiposity alter the seminal plasma cytokines interferon-gamma (IFNγ), macrophage inflammatory protein 1 alpha (MIP1α), and TNF [171]. Other forms of paternal dietary modification can dysregulate seminal plasma composition and function. For example, dietary supplementation of fatty acids, or essential amino acids in rams has been shown to alter seminal plasma composition, including increased abundance of the immune mediators, galectin and complement factor H, as well as increased abundance of sperm protein 17 and acrosin, which have established roles in capacitation and interactions with the zona pellucida [172–174].

Beyond dietary challenges, inflammation has emerged as a key factor driving seminal plasma composition and function. In men, seminal plasma cytokine expression appears to be highly sensitive to environmental exposures and lifestyle factors [175, 176], likely resulting from pro-inflammatory effects. For example, COVID-19

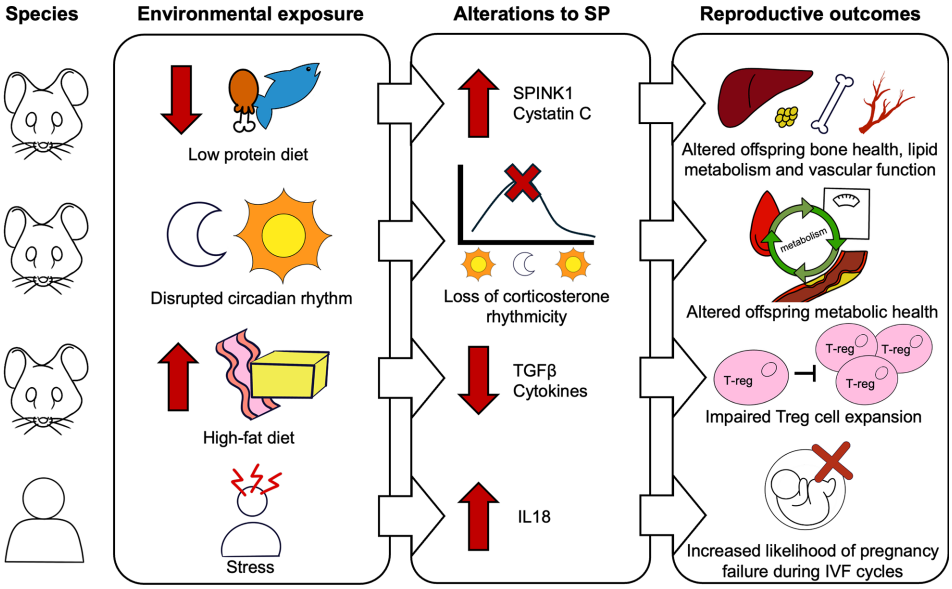


**Fig. 3.** Environmental perturbations reshape seminal plasma composition and influence reproductive and offspring health outcomes. Across species, diverse paternal environmental exposures elicit changes in soluble seminal plasma (SP) signaling mediators. In this figure, those studies that have explored not only alterations to SP, but also the consequences of those alterations are presented. These include low-protein diet [160–162, 166, 169], circadian rhythm disruption [163], high-fat diet [167], and chronic stress [164], which all elicit changes in SP which are correlated to impacts on fertility, the female reproductive tract environment, and offspring health. Together, these studies illustrate that SP responds dynamically to the paternal environment and acts as a mediator of environmentally induced effects on fertility and offspring development.

infection, chronic pelvic pain syndrome, prostatic hyperplasia, and urinary tract infections all cause changes to the composition of human seminal plasma [177–180]. Dysregulated proteins including cytokines TNF, IL1α, and IL8, TLR4 ligands such as proteins S100A8, S100A9, and heat-shock proteins, as well as CD38, all have potential to influence the female reproductive tract immune response and/or sperm viability and function [1, 177–180]. In rats, induction of inflammation via an experimental autoimmune orchitis model lead to significant upregulation of the immune modulatory protein calprotectin in seminal plasma [181]. In livestock, infectious and inflammatory diseases trigger changes in seminal plasma composition. In cattle, mycoplasma infection alters the amino acid content of seminal plasma [182], while in goats, viral infection alters the composition of seminal plasma, with increased immune-related proteins, including cathepsins [183]. Importantly, infection-induced changes to seminal plasma have been shown to have functional consequences, with HIV-infection altering the endometrial epithelial and stromal fibroblast response to seminal plasma [104]. Elevated IFNγ in men with reproductive tract infection appears to be a mediator of this effect, by impairing TGFβ-induced granulocyte-macrophage colony-stimulating factor (GM-CSF) synthesis in mouse and human female reproductive tract epithelial cells [176, 184].

In addition to these comprehensively assessed environmental conditions, there are other perturbations that disrupt homeostasis in the male reproductive tract leading to altered seminal plasma composition and function. Consistent with their androgen-dependent status, testosterone promotes glucose uptake in seminal vesicle epithelial cells, resulting in increased synthesis of fatty acids, including oleic acid whose presence in seminal plasma supports ejaculated spermatozoa in carrying out active metabolism [185]. Notably, heat stress in cattle, chicken, and sheep, has been shown to modify seminal plasma composition, including BSP homologs, which are associated with optimal sperm function [186–188]. In humans, heat stress causes dysregulation of seminal plasma antioxidant levels [189], while in the giant panda, heat stress induced by cryptorchidism alters seminal plasma proteins associated with cellular metabolism [190].

Social and behavioral factors can also affect seminal plasma composition. In mice, the seminal vesicles have the capacity to rapidly modulate protein production as an adaptive response to sperm competition [114], leading to alterations to seminal vesicle fluid protein profile [191, 192]. Consistent with this, studies of sperm competition in chinook salmon, an externally fertilizing fish, show that seminal plasma exerts different effects on sperm velocity depending on the dominance status of the male, such that increases in sperm velocity increase the proportion of offspring sired [193].

Taken together, these studies highlight the exquisite sensitivity of male accessory gland secretion to regulatory control and reveal robust effects of a range of different environmental stressors on seminal plasma composition and function through altered protein, metabolite, and signaling profiles. This plasticity in seminal plasma affects sperm quality, the female reproductive tract immune environment, and fertilization potential, and likely also programs offspring phenotype with consequences for life-long health, acting alongside sperm epigenetic changes. Such findings position seminal plasma molecules as functional modulators and potential biomarkers of environmental stress – and also supports the interpretation that, because of its differential effect on female reproductive investment, seminal plasma can be considered a ‘pheromone’ in the classical meaning of this term [194].

## Environmental effects on seminal extracellular vesicles

Studies assessing SEV response to environmental exposures are limited, and to our knowledge, none have examined effects on offspring. However, there is extensive evidence that SEV cargo is altered in infertile men which highlights the dynamic and responsive nature of SEVs to changes in the male reproductive tract [6]. SEV

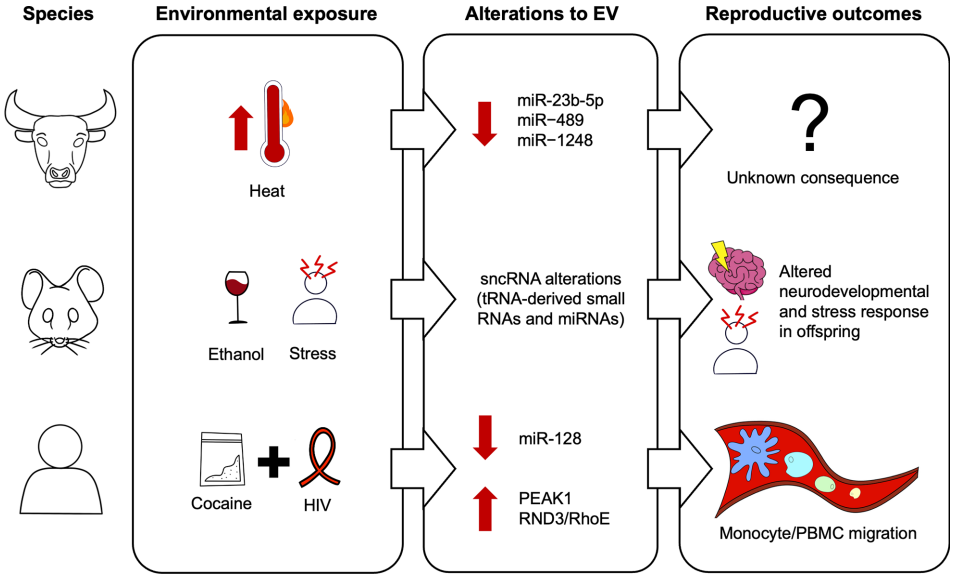


**Fig. 4.** Environmental perturbations alter seminal extracellular vesicle composition with implications for reproductive and offspring outcomes. A range of paternal environmental exposures elicit changes in the composition of seminal extracellular vesicles (SEVs) released from the male reproductive tract. In this figure, we highlight the small number of studies that have examined how SEV or other male reproductive tract EV cargo is altered in response to exposures such as heat stress (SEVs [198]), ethanol (Epididymosomes [218, 223]) or psychological stress (Epididymosomes [220]), and combined cocaine use and HIV infection (SEVs [199]), and the downstream consequences of these alterations if studied. Together, these studies demonstrate that EVs, like seminal plasma, respond dynamically to the paternal environment and may act as key vectors through which environmentally induced signals influence fertility, immune function, and offspring development.

composition is altered in cattle [195] and chickens [100] with contrasting fertility, while supplementation of SEVs from fertile cattle with spermatozoa from infertile cattle improves IVF outcomes [196]. Further supporting the beneficial functions of SEVs are studies in humans, which show that SEVs isolated from normozoospermic, but not from asthenozoospermic donors can improve sperm motility, potentially through the delivery of cysteine-rich secretory protein 1 from SEVs to spermatozoa [197]. In Egyptian buffalo, the size and composition of SEVs varies seasonally, with winter associated with higher quality spermatozoa. Changes in SEV cargo observed are associated with reduced apoptotic signaling, enhanced antioxidant capacity, and an increased ability to control epigenetic modifications to spermatozoa [90].

Further evidence for environmental influences on SEV composition has been documented in mice, where age modifies SEV cargo and function. In this study, SEVs from aged (12–18-month-old) males were shown to be larger and capable of enhancing the maturation of dendritic cells compared to equivalent SEVs from young (12–14-week-old) males [97]. Since dendritic cell maturation is a key step in shaping immune tolerance in the female reproductive tract [1], this finding suggests that age-related changes in SEVs may influence immune adaptation to sperm antigens and subsequent reproductive outcomes. Interestingly, supplementation of 'young' SEVs to seminal plasma from old mice acted to improve implantation rate [97], highlighting the importance of SEVs in pregnancy success. In cattle, transient scrotal heat stress led to alterations in the SEV miRNA profile, with differentially regulated miRNA associated with cell proliferation, differentiation, and regeneration, including reduced expression of *miR-23b-5p*, *miR-489*, and *miR-1248* [198] (Fig. 4). In humans, cocaine use concomitant with HIV infection alters the SEV proteome and sncRNAome, leading to a rapid and more directional haptotactic migration pattern in monocytes and peripheral blood mononuclear cells (PBMCs) [199] (Fig. 4). Importantly, studies in rats have shown that paternal cocaine use confers sex-dependent effects on offspring health [200, 201]. How SEVs convey these changes to the female reproductive tract to exert consequences for fertility, is poorly understood.

As EVs reflect the physiological or pathological state of the parent cell of origin, further insight into the impact of the paternal environment on SEV composition and function can be acquired through studies of male reproductive tract EVs. It is well-established that environmental stressors that impact EV-secreting cells also can influence the local EV population [202]. Such influences extend beyond alterations to the contents of EVs, with a strong body of evidence showing that EVs produced by 'stressed' cells can confer phenotypic and functional changes in recipient 'stress naïve' cells [202–204]. Thus, EVs secreted by the male reproductive tract may transfer 'stress' signals from the parent cell to spermatozoa that influence fertility and fecundity prior to fertilization [106]. 'Stressed' EVs may also influence fertility through their accumulation within seminal plasma, to in turn exert effects on spermatozoa and potentially female reproductive tract cells [6, 108].

As described above, SEVs are highly heterogeneous and likely arise from diverse male cellular origins, reflecting the male reproductive tract organs that contribute to seminal plasma [108, 205–207]. However, little is known about the sensitivity of seminal vesicle EVs to the environment [208–210], and to our knowledge no studies have examined bulbourethral gland EVs. In contrast, prostatic EVs are far better characterized. In studies of prostate cancer, they have been shown to be responsible for the transfer of metastatic traits and chemoresistance, and regulate cell phenotypic plasticity through the induction of stem-like state, epithelial-to-mesenchymal transition, and neuroendocrine differentiation [211]. Additionally, recent studies have shown that distinct EV protein signatures correspond to known prostate cancer molecular subtypes [212] highlighting that changes in the cargo of prostatic EVs are associated with pathology.

Similarly, testicular EVs are responsive to environmental stress with studies in sheep showing viral infection alters the abundance of EV microRNAs associated with immune system regulation [213]. Sertoli cells, which are essential for normal testis and germ cell development produce EVs sensitive to environmental conditions. Sertoli cell EVs carry cargo including Inhibin A and B, that have altered abundance in porcine prepuberal Sertoli cells following testosterone and follicle stimulating hormone treatment [214]. Additionally, hypoxia stimulates EV release in Sertoli cells and alters microRNA (miRNA) abundance [215]. Amongst the altered miRNA, increased *miR-210-3p* plays a protective role under hypoxic stress where it regulates cell survival, proliferation, inflammation, and metabolism [215].

The interaction between spermatozoa and EVs encountered during their passage through the epididymis has been more comprehensively studied than testicular EVs [216]. Akin to other EV populations, epididymosomes have been shown to be sensitive to the paternal environment. This adaptability allows EVs to help align spermatozoa epigenetically with the father's environment, which may subsequently influence offspring health [217]. Several studies in mice using challenges such as alcohol [218], dietary perturbation [157], endocrine disrupting compounds [219], reproductive toxicants [152], and stress [220–222], have consistently shown alterations to epididymosome composition, most notably to small non-coding RNAs, occur in response to environmental stressors. To demonstrate that changes in epididymosome content have functional effects, a few studies have incubated epididymosomes from stressed cells with naïve spermatozoa. Remarkably, offspring conceived from these sperm cells show altered neurodevelopment and stress responses [220, 223] (Fig. 4).

Collectively, these studies provide evidence that SEVs have the capacity to respond dynamically to the paternal environment with implications for fertility and offspring health, both directly through effects on spermatozoa and indirectly through effects on the female reproductive tract. However, there remains an imperative for studies to systematically assess how specific environmental exposures shape SEV composition and the range of consequences these changes may have for offspring.

## Conclusions

Although reproductive strategies and physiology vary between species, there is now compelling evidence for consistent effects of seminal plasma on the reproductive process – both through modulating sperm survival and developmental potential, and by mediating communication with the female reproductive tract. Substantial evidence shows that these effects of seminal plasma influence the capacity of the female reproductive tract to support pregnancy and influence offspring health, depending on the quality and strength of seminal plasma signals. Emerging research indicates that the composition of seminal plasma is highly dynamic and responsive to the paternal environment. Factors such as diet, infection, heat stress, chemical exposures, and stress can all modify seminal plasma composition through effects on the relative abundance of a range of secreted factors, particularly those contained within SEVs produced by the seminal vesicle, prostate, and other male reproductive tract organs. Through impacts on spermatozoa and on immune responses and other biological consequences in the female reproductive tract, these alterations affect events at conception and ultimately influence implantation, placental development, fetal growth, and offspring health. The plasticity of seminal plasma and its consequences are best understood in rodent models, but effects on fertility due to disruptions to seminal plasma likely occur across species, with similar functional impacts.

Future research should comprehensively explore the impact of relevant environmental exposures on seminal plasma composition and function in a range of species. Advances in 'omics technologies enable comprehensive profiling of seminal plasma and the extracellular vesicles carried within, offering powerful tools to identify conserved signaling mediators and to understand the consequences of their dysregulation. Leveraging these approaches could reveal common molecular signatures of environmental perturbations and is expected uncover conserved signaling pathways across species, as has been demonstrated in spermatozoa [224]. Such efforts will not only advance our understanding of how the paternal environment shapes conception and development but also inform interventions to improve fertility and the health of future generations across human, livestock and endangered species.

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