# The influence of seminal plasma on offspring development and health

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## Abstract

The concept that a father's wellbeing at the time of conception influences the development and long-term health of his offspring is now well established. However, the mechanisms underlying the paternal programming of offspring health are not fully defined. While sperm-mediated effects on offspring development have been investigated in detail, the significance of seminal plasma has been over-looked. Typically, the seminal plasma is viewed as a simple medium, with a main role to transport sperm into the female reproductive tract at the time of conception. However, a more sophisticated role for seminal plasma in the modulation of the maternal periconception cell-signalling, inflammatory and immunological physiology is emerging. Seminal plasma comprises a complex mix of nutrients, proteins, signalling molecules and cell-free genetic material which all interact with the endometrium to regulate gene expression, vascular remodelling, leukocyte recruitment and the priming of regulatory T cells (Tregs). These seminal plasma effects on the maternal periconception environment all act to facilitate uterine remodelling, embryo implantation and fetal development. Evidence is now emerging that poor paternal lifestyle factors such as diet, can modify these essential uterine responses, altering fetal development and ultimately long-term offspring health. The use of animal models has enhanced our understanding of the effects of seminal plasma on maternal uterine physiology, embryo development and offspring health. However, further studies are needed to define the interaction between seminal plasma components and female reproductive tissues in humans. Such studies will be central in providing better information and infertility treatments to intending parents.



**Keywords**

Seminal plasma; paternal health; preimplantation embryo; developmental programming; uterine responses.

## Introduction

In 1989, David Barker published a study linking impaired growth in utero with blood pressure at the age of 10 and increased adult mortality risk for cardiovascular disease in humans [1]. In the decades that have followed, a wealth of human epidemiological data and animal model studies have established that the quality and quantity of a mothers diet during pregnancy can influence the development, growth and long-term cardiovascular and metabolic health of her offspring [2]. Out of this large body of multidisciplinary data, the Developmental Origins of Health and Disease (DOHaD) concept [3] has been developed to understand how environmental conditions experienced during gamete maturation, embryo development and fetal growth can affect offspring long-term health. Underlying much of the research supporting the DOHaD concept has been the use and development of a range of animal models [4]. These have focused typically on aspects of maternal undernutrition during specific stages of gestation and have been fundamental in furthering our understanding of the underlying mechanisms programming offspring health. However, as many Western societies are burdened by the health consequences of obesity and diabetes, the focus of many DOHaD studies has now shifted towards models of over-nutrition [5]. Here, many studies also demonstrate significant changes in reproductive fitness, fetal growth and offspring health in response to excessive nutrition. Therefore, it seems the case that an imbalance (both over or under) in either global parental nutritional, or in individual macro/micro nutrients, all exert a range of programming effects on offspring health [6].

While the link between maternal well-being and offspring health has been investigated in detail, the role a father has in directing the development of his offspring has been largely overlooked. However, in recent years, a new focus has emerged on the importance of paternal health at the time of conception for semen quality, post-fertilisation development and offspring health [7]. Mirroring maternal programming studies, a range of paternal dietary manipulations and exposure to environmental toxicants have all been shown to impact on various aspects of offspring health [8].

Again, animal models have been central to linking paternal well-being with offspring development. For example, in mice, paternal obesity alters placental function [9], offspring metabolic health [10] and even breast cancer risk [11]. Furthermore, factors such as induction of paternal stress have also been shown to impact on offspring hepatic function in mice [12].

While many studies have explored the impact of paternal health on sperm quality and epigenetic status, the role of the seminal plasma has been largely overlooked. This is in part due to the assumption that the primary role of the seminal plasma is simply to transport the sperm into the female reproductive tract at conception. However, it is now well established that the seminal plasma promotes a range of signalling, inflammatory and gene expression changes within the female reproductive trace, which are essential for successful pregnancy establishment and maintenance [13] (Fig. 1). Therefore, in this review, we will outline current data on paternal programming, the role seminal plasma plays in linking paternal lifestyle with offspring health and the molecular and signalling mechanisms by which seminal plasma influences post-fertilisation development.

## 1. Establishing a father's role in the programming of offspring health

Some of the most supportive evidence that our health as adults is influenced by the maternal environment in which we developed has come from large, diverse epidemiological cohort studies [14]. There is now compelling evidence from similar such data sets to support a link between a father's wellbeing and the development and health of his children. Data from the UK Biobank Study [15] revealed children from diabetic fathers were on average 45 g lighter at birth than children from non-diabetic fathers and were at increased risk of developing type-2 diabetes themselves. Similarly, paternal BMI at conception has been shown to associate positively with offspring BMI at both 11 years of age and at 45 years [16]. Recently, using the Utah population Database, Anderson and colleagues identified links between weight at birth and male fertility, where offspring of men with poor semen quality (reduced concentration, total count and motility) were over 150 g lighter at birth

than those from fertile men [17]. However, no long-term impact on offspring BMI was observed. Potentially the most widely-known epidemiological support comes from the Overkalix cohort from northern Sweden. Analysis of the records revealed an inverse correlation between a grandfather's access to nutrition during their pre-teen growth (between 9 and 12 years of age) and the life span of their grandsons [18], with the reduction in life span being driven by increased rates of cardio-metabolic mortality [19].

To date, much of the work investigating the paternal mechanisms of offspring programming have been conducted in rodents. One of the first observations showed that feeding male mice a low protein diet elevated expression levels of genes central to cholesterol and lipid synthesis within fetal offspring livers [20]. Using a similar mouse paternal low protein diet model, we have shown that adult offspring glucose tolerance, adiposity, inflammatory status and cardiovascular function are all impaired in response to poor paternal diet at the time of conception [21]. Furthermore, we identified significant changes in preimplantation embryonic metabolic gene expression, placental function and epigenetic status and fetal growth [22]. Separate studies have also shown that feeding rodents diets high in fat [10, 23, 24], low in folate [25] or paternal fasting [26] all compromise offspring metabolic health and homeostasis. Together, these studies demonstrate that poor paternal well-being at the time of conception impacts significantly on a range of reproductive and developmental mechanisms which all affect the long-term ill-health of the offspring.

The field of paternal programming of offspring health has benefited significantly both from the substantial body of maternal environmental studies, and the rapid development of new sequencing platforms and analytical approaches. Using different Next Generation Sequencing platforms, studies have shown that sperm from rodents fed diets high in fat [27], low in folate [25] or low in protein [20] display altered epigenetic status. In male mice fed a low protein diet, we identified genome-wide DNA hypomethylation in sperm correlating with significant changes in testicular regulators of DNA

methylation and 1-carbon metabolism [28]. Interestingly, we observed that the pathway most enriched for DNA hypomethylation was calcium signalling, a pathway central in insulin signalling and regulation of cardiovascular control. Separately, studies have also identified changes in DNA methylation [29], histone variants [30] and RNA transcripts [31] profiles in sperm from infertile men. Further evidence for the importance of sperm epigenetic status comes from the observations that the injection of sperm-derived total RNA from high fat diet fed male mice into control zygotes programed offspring metabolic ill-health [32]. Subsequently, studies have highlighted the role of sperm small non-coding RNAs (sncRNA) such as transfer RNA-derived small RNAs (tsRNA) [33] as well as their epigenetic modifications [34] as the molecular mediators in the transfer of paternally acquired information. However, the negative consequences of paternal undernutrition for offspring metabolic health can be reversed by supplementing male mice with vitamins and antioxidants [35]. Furthermore, in obese mice, a low-moderate exercise regimen prevents the programming of offspring blood lipid, glucose and insulin levels when compared to non-exercised males [36]. These, studies indicate plasticity within the underlying mechanisms of paternal programming rather than a permanent change to spermatogonial stem cells. As such, the full process by which paternal diet programs offspring health may involve more than just a sperm-mediated genetic/epigenetic mechanism. Indeed, observations in cattle that seminal plasma from highly fertile sires can improve the fertilisation capacity of sperm from lower fertile sires [37], or that in golden hamsters, the removal of the accessory sex glands decreases embryo development and implantation capacity [38] demonstrate a role for seminal plasma in directing male fertility and post-fertilisation development.

## 2. The role of seminal plasma in programming offspring development

In some species, such as humans and cattle, where artificial insemination with washed sperm is successful, seminal plasma is not essential for fertilisation and pregnancy establishment. However, the use and development of mouse models has highlighted the significance of seminal plasma for post-fertilisation development, fetal growth and offspring health, separate to any influence of

fundamental male reproductive fitness. Bromfield et al., [39] demonstrated that removal of the seminal plasma at the time of conception impacts significantly on embryo development, fetal growth and adult offspring metabolic and cardiovascular health. Using embryo transfer, the authors also examined the window of sensitivity of embryos to the programming effects of seminal plasma [39]. Here, embryos were transferred from females mated with intact males into females mated with males devoid of seminal plasma. Offspring from such transfers displayed increased adiposity in adulthood, indicating the non-seminal plasma-primed uterine environment, and not a sperm-specific factor, programmed offspring adiposity [39].

Our own studies have shown that in mice, the reproductive tract environment of females is modified significantly in response to semen from males fed a low protein diet [28]. At day 3.5 of gestation, uteri from females mated with low protein diet fed males displayed significantly reduced levels of TNF, IL-1β, IFN-γ, MIP-1α, and CSF3 (formerly G-CSF). Additionally, we observed reduced uterine expression of several prostaglandin synthesis genes and genes associated with regulatory T cell (Tregs) mediated responses such as *Cd3e, Foxp3* and *H2-Ab1*. Analysis of blastocysts taken from these same females revealed significantly decreased expression of multiple genes within the central metabolic regulatory AMPK pathway [22]. In adulthood, offspring of low protein diet fed males displayed increased adiposity, hypotension, cardio-vascular dysfunction and poor glucose tolerance responses [21]. These data suggest that seminal plasma from sub-optimally fed males causes a blunting of the normal uterine inflammatory and cell signalling environment during the development of the preimplantation embryo. Ultimately, by modulating the developmental trajectory of the embryo, subsequent fetal growth and adult health become compromised. Similar changes in uterine phenotype and offspring development have been observed in response to maternal low protein diet fed exclusively during preimplantation development [40-43]. Interestingly, comparisons between maternal and paternal periconceptional low protein diet on the magnitude of offspring programming revealed similar size effects between parents [2].

To test the hypothesis that seminal plasma may have a direct influence on offspring health, we modified our existing mouse low protein diet model to separate the programming effects of the sperm from those of the seminal plasma. To achieve this, we combined artificial insemination with vasectomised male mating [28]. Using this approach, we generated offspring derived from low protein diet sperm, but in the presence of seminal plasma from normal protein diet fed males. We also generated offspring from normal protein diet sperm, but in the presence of low protein diet seminal plasma, as well as the respective controls (either normal protein diet sperm and seminal plasma or low protein diet sperm and seminal plasma). We observed that all offspring derived from low protein sperm and/or seminal plasma became heavier and remained heavier than offspring derived only from normal protein diet semen. In addition, offspring derived from low protein sperm and/or seminal plasma displayed glucose intolerance, altered gut bacterial profiles and perturbed hepatic gene expression symptomatic of non-alcoholic fatty liver disease [28]. Interestingly, offspring which were derived from control diet sperm and low protein diet seminal plasma, or vice versa, tended to display the biggest changes in growth and hepatic gene expression. We propose that the sperm passes on genetic/epigenetic information to the embryo programming patterns of metabolism. Separately, the seminal plasma modulates the metabolic, immunological and signalling molecule environment of the maternal reproductive tract. When the sperm and seminal plasma are from the same dietary origin, the seminal plasma-specific programming of the uterus is matched to the sperm-specific programming of the embryo and appropriate post-fertilisation development occurs. However, if the uterine environment is not primed appropriately for the programmed embryo, a mismatch occurs resulting in greater impact on offspring ill-health.

The use of our mouse model allows us to begin to identify the sperm- and seminal plasma-specific programming effects on offspring health and well-being. However, in a human or domestic animal setting, it is unlikely that any single female will be exposed to sperm and seminal plasma from two

separate males at any one time. However, our observations may still be of relevance in situations where an embryo is transferred back to a uterine environment that has not been primed adequately by seminal plasma. Significant improvements in pregnancy rates for women undergoing IVF have been reported following exposure to seminal plasma around the time of ovum pick-up or embryo transfer [44, 45]. Furthermore, studies have shown increased rates of pregnancy in couples who either had unprotected intercourse close to the administration of human chorionic gonadotropin [46] or in women who experiencing recurrent miscarriage and are given seminal plasma pessaries [47]. In addition, there is intriguing evidence linking a couples' duration of sexual cohabitation with a reduction in the risk of developing pregnancy pathologies. Data from epidemiological studies indicates a positive association between a woman's unprotected exposure to her partner's seminal plasma and the reduction in risk of her developing preeclampsia [48, 49]. Furthermore, it seems that while the first pregnancy with any given father is at increased risk for preeclampsia [50], cumulative exposure, either orally or vaginally, to the fathers' seminal antigens counteract this risk [51]. As preeclampsia is associated with intra-uterine growth restriction, elevated postnatal BMI and increased cardiovascular disease risk in offspring [52], a fathers' semen, or lack of exposure to it, may play a significant role in the health of his offspring.

## 3. The importance of seminal plasma for male fertility

Typically, seminal plasma is viewed as simple medium that transports and supports the sperm within the female reproductive tract. However, the fact that seminal plasma can modulate both sperm-egg interaction [53] and the surrounding maternal reproductive tract responses [13] indicates the important role it has in regulating male reproduction. Therefore, gaining a better understanding of the interaction between seminal plasma factors and sperm quality and function may provide new insight and strategies in the treatment of infertility.

In most mammalian species, seminal plasma is derived from secretions of the seminal vesicles, prostate, testis and epididymis and bulbourethral and periurethral glands [54]. The combination of fractions from differing glands means the seminal plasma is a complex mixture of different molecules including fructose (the main energy source for sperm), lipids, proteins, cell free DNA, RNA and micro RNAs and inorganic ions such as zinc, copper and selenium [55].

Due to the comparative accessibility of semen, there has been growing interest in identifying seminal plasma markers of poor male fertility including varicocele [56], infertility linked to oxidative damage [57], and general infertility [58]. Reduced levels of proteins such as prostaglandin-D synthase (PGDS) [59] while elevated levels of proteins including galectin-3-binding protein (LGALS3BP), prostatic acid phosphatase (PAP) and prolactin-inducible protein (PIP) have been reported in seminal plasma of azoospermic men [60] when compared to control samples. Following the analysis of seminal plasma from men of proven fertility, a panel of proteins important for male fertility including Semenogelin I and II, olfactory receptor 5R1, human cationic antimicrobial protein (hCAP18) and lactoferrin have been identified [61]. Semenogelins act to prevent premature sperm capacitation [62], with elevated levels being observed in azoospermic men [63]. hCAP18 plays a key role in male innate immunity [64], while downregulation of proteins such as DJ-1 results in elevated levels of oxidative stress in semen of asthenozoospermic men [65].

Of current interest in many fields of biological research is the characterisation of exosomes and their content. In human seminal plasma, the main contributors are the epididymis and prostate, making up approximately 3% of the protein content of seminal plasma [66]. Studies have shown that epididymal exosomes (epididymosomes) are not present within the ejaculate, suggesting they interact with the sperm during their transit and maturation within the epididymis [67]. Epididymosomes contain proteins, microRNAs, tRNA-derived small RNAs (tsRNAs) and fluid and can interact either with sperm or the surrounding epithelial cells. Recent analysis of mouse epididymosome microRNA

content identified >350microRNAs, with approximately 60% of them detected within the sperm [68]. Interestingly, two microRNAs, miR-191 and miR-210, shown to be in epididymosome trafficked between the epididymal Principal cells and sperm [68, 69], have also been identified in the follicular fluid surrounding the oocyte [70]. These observations indicate parental regulation of microRNA delivery to the developing embryo and [71] which could be influenced by parental environment and lifestyle. Indeed, feeding male mice a high fat 'Western diet' results in differential profiles of microRNAs within their sperm which can influence the metabolic phenotype of their offspring [32]. Furthermore, studies have shown that human seminal exosomes contain an array of tsRNAs which may act to regulate the immunomodulatory function of the maternal reproductive tract [72]. However, the precise role of seminal extracellular vesicles in regulating male fertility, and the degree to which they are regulated by environmental factors, remains to be determined fully.

## 4. The impact of seminal plasma on the female reproductive tract

Currently, the best described models of the interplay between seminal plasma and the maternal reproductive tract are the mouse and human. While seminal plasma reaches the upper parts of the reproductive tract in mice, in women seminal plasma predominantly interacts with the cervix following intercourse. In women, seminal plasma components such as prostaglandins, cytokines and peptides may also be transported from the vagina to the uterus via counter-current blood and lymphatic systems [73]. However, in both species, deposition of semen into the female reproductive tract results in an acute inflammatory and immunological response [74].

In female mice mated to males devoid of seminal plasma [39], or in women who's partner has used a condom [74], these inflammatory and immunological changes are not observed, indicating the source of these maternal responses resides within the seminal plasma. In mice, studies have shown that in response to seminal plasma deposition, significant changes in the expression profile of

mRNAs, micro RNAs and non-coding RNAs are observed in the surface epithelium of the endometrium [75]. Many of these genes have been shown to be involved in the regulation of the immune system [75] and within hours of exposure to seminal plasma, the maternal reproductive tract tissues are infiltrated by granulocytes, dendritic cells and macrophages [76]. The role of these cells is to clear up cellular debris from within the seminal plasma, as well as to pass on paternal major histocompatibility antigens to regulatory T cells (Tregs) [77]. As the embryo displays the same paternal antigens as are present within the seminal plasma, it is essential that the Tregs response to these antigens is sufficiently supressed to allow implantation of the semiallogenic embryo into the maternal uterine tissue [78]. Tregs are critical both for early pregnancy establishment, through supporting trophoblast invasion and uterine artery remodelling [78], as well as ensuring the pregnancy is maintained into late gestation [79]. Within the seminal plasma, studies in both human and rodent seminal plasma have identified the cytokine transforming growth factor beta (TGFβ) as a principal factor in the initiation of the maternal immunological responses [80, 81]. Interestingly, seminal plasma derived TGFβ has been show to bind onto the surface of human sperm resulting in its transport past the cervix and allowing it to interact with the endometrium [82]. Seminal plasma also results in the production of factors such as colony stimulating factor-2 (CSF2) [75], leukemia inhibitory factor (LIF) and interleukin 6 (IL-6) [83] by the maternal reproductive tract. Interestingly, factors such as CSF2, LIF and IL6 have all been shown to be important for promoting embryo development in both the mouse and human [84].

While the significance of seminal plasma for the modulation of the maternal reproductive environment in humans and mice is well recognised, the influence of seminal plasma in large animals is less well defined [85]. Similar to mice and men, differences in fertility between stud males has been attributed to the quality of their sperm while the significance of the seminal plasma has been overlooked. As a consequence, and mirroring human assisted reproductive technologies, the management of reproduction in many domestic animal species is conducted in a comparatively

seminal plasma free environment. Furthermore, generated embryos are often transferred into a non-seminal plasma primed uterine environment. However, in recent years, there has been growing interest in the role of seminal plasma in managed reproduction within commercially important agricultural species. In ruminants, seminal plasma contains proteins which bind to sperm and which can both stimulate and inhibit sperm function [86]. Additionally, varying compositions of bovine seminal plasma have been shown to affect aspects of sperm quality including motility and chromatin integrity [87, 88], while analysis of seminal plasma composition between bulls of high fertility and bulls of low fertility have identified differences in the profiles of specific proteins [89, 90]. In the cow, seminal plasma has also been shown to play a role in pregnancy outcomes. Odhiambo et al., observed that in heifers exposed to seminal plasma around the time of artificial insemination, pregnancy rates were increased by a non-significant 13.9% [91]. Interestingly, the authors also observed that the administration of both seminal plasma and the cytokine TGFβ, known to regulate maternal uterine immunological responses in mice, to dairy cows increased pregnancy outcomes by 10% [91].

In the pig, unlike other mammalian species, seminal plasma is deposited directly into the uterus at the time of ejaculation. However, similar to other species, exposure of the porcine uterus to seminal plasma results in the production of a cytokines and chemokines by the endometrial tissues and resident leukocytes [92]. Infusion of seminal plasma into the porcine uterus results in elevated levels of macrophages, major histocompatibility complex class II activated macrophages and dendritic cells 34 hours later, and which are maintained for up to 9 days after infusion [93]. Seminal plasma has also been shown to improve porcine sperm survival and motility when compared with standard commercial semen extenders [94]. Furthermore, increased numbers of embryos are recovered from gilts when infused with seminal plasma at the time of artificial insemination [93, 95]. Recently, seminal plasma has also been shown to influence the tissue orchestration of cell signalling and gene expression profiles between the uterus and ovary in the pig [96]. Together, these studies show that in

the pig, seminal plasma not only influences the sperm and uterine tissues, but also acts to influence ovarian function, which would all ultimately impact on the development of the embryo.

In sheep, similar patterns of cervical and uterine macrophage infiltration following mating with fertile rams to those observed in mice have been reported [97]. However, unlike other mammalian species, uterine responses to seminal plasma in the sheep are dependent upon which stage of estrous cycle the ewe is in. Exposure to seminal plasma or sperm while in estrous results in endometrial inflammatory responses and increased neutrophil levels, while no such responses occur following exposure during diestrous [97]. These cycle stage-specific responses may be a reflection of the seasonal changes in ram seminal plasma [98], a factor which may be influential in the outcomes of seasonal breeding in sheep.

## 5. Future perspectives

The concept that a father's health and wellbeing at the time of conception may affect the development and long-term health of his offspring is still being established. The use of animal models is helping to drive forward our understanding of the mechanisms linking paternal health, reproductive fitness and post-fertilisation development. Typically, the focus of many paternal programming studies have centred on sperm quality and the impact changes in sperm epigenetic status can have on offspring health. However, recent studies also highlight the significant role seminal plasma has in modulating the maternal reproductive tissues at conception. It is becoming increasingly clear that seminal plasma modifies the cell signalling, vascular and nutrient environment of the maternal reproductive tract during preimplantation embryo development. Furthermore, studies now show that these essential maternal responses can be modulated by paternal lifestyle factors such as diet. From the significant body of maternal dietary studies, it is now well established that modification of the maternal uterine environment during periconception development has long-term effects on offspring cardio-metabolic

health. Our own research is revealing that a father may influence the development and long-term health of his offspring through both sperm- and seminal plasmas-specific mechanisms [28].

Going forward, it is essential that a greater insight into the interactions between seminal plasma and maternal reproductive tissues in women is needed. In addition, studies into the impacts of male lifestyle characteristics such as BMI, smoking, air pollution and age on seminal plasma composition and how these factors influence the full range of maternal responses are needed. Furthermore, greater understanding of the importance of seminal plasma for priming the uterine environment ahead of pregnancy and its role in unexplained infertility and pregnancy complications is needed. Increased awareness and advice on how a male contributes to both his own reproductive fitness and that of his partner, as well as influencing the health of his offspring will have significant benefits to the long-term wellbeing of society.

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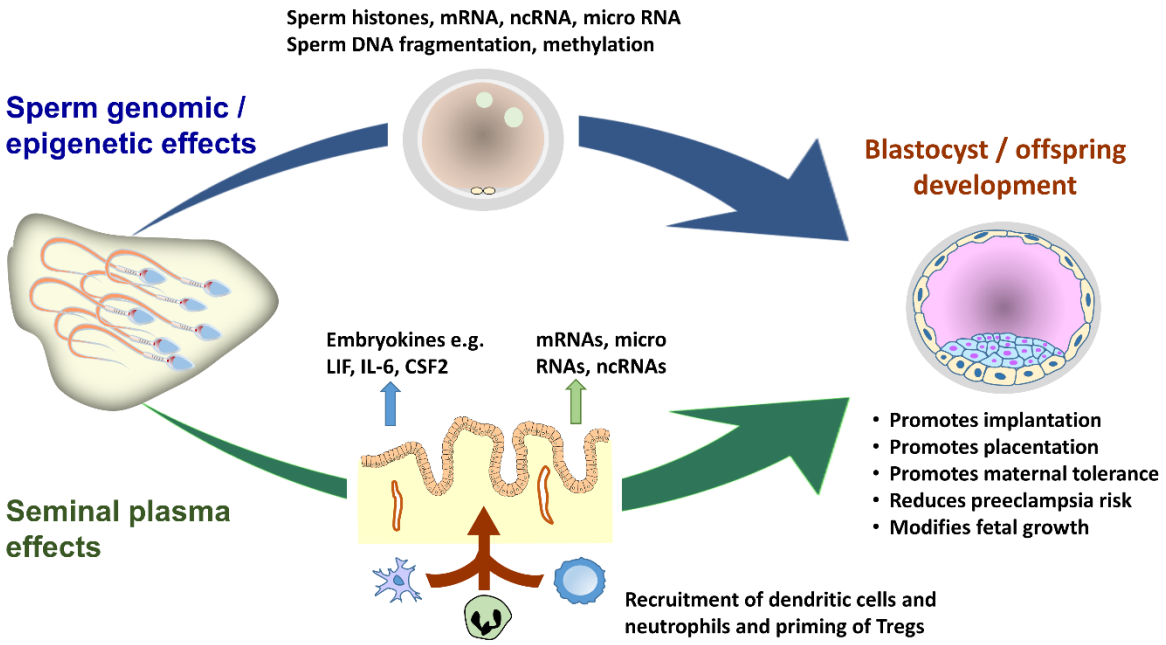


**Figure 1:** Schematic diagram of the known influences semen has on mammalian periconception development and the maternal uterine environment. Sperm epigenetic status influences early embryo development via the transfer of sperm-specific histones, RNA populations (e.g. mRNA, micro RNA) and aspects of DNA integrity at conception. These all influence gene expression and embryo developmental patterns during the earliest stages of development. Separately, seminal plasma influences the maternal reproductive environment through the upregulation in production of embryokines, chemokines and cytokines from oviductal and uterine tissues. In addition, seminal plasma stimulates the recruitment of dendritic cells and neutrophils into the uterine tissues as well as the priming of regulatory T cells (Tregs). These all act to remodel the uterine vasculature, clear cellular debris and dampen maternal immunological responses to paternal antigens, essential for embryo implantation and fetal development. In combination, both sperm-specific and seminal plasma-specific mechanisms can affect the development of the preimplantation embryo, maternal reproductive environment, pregnancy establishment, fetal/maternal health during pregnancy and ultimately, the long-term health of the offspring.