

The influence of seminal plasma on offspring development and health

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24 **Abstract**

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

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45

46 **Keywords**

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

49

50 **Introduction**

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

69

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

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

80

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

90

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

92 Some of the most supportive evidence that our health as adults is influenced by the maternal
93 environment in which we developed has come from large, diverse epidemiological cohort studies
94 [14]. There is now compelling evidence from similar such data sets to support a link between a
95 father's wellbeing and the development and health of his children. Data from the UK Biobank Study
96 [15] revealed children from diabetic fathers were on average 45 g lighter at birth than children from
97 non-diabetic fathers and were at increased risk of developing type-2 diabetes themselves. Similarly,
98 paternal BMI at conception has been shown to associate positively with offspring BMI at both 11
99 years of age and at 45 years [16]. Recently, using the Utah population Database, Anderson and
100 colleagues identified links between weight at birth and male fertility, where offspring of men with
101 poor semen quality (reduced concentration, total count and motility) were over 150 g lighter at birth

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

108

109 To date, much of the work investigating the paternal mechanisms of offspring programming have
110 been conducted in rodents. One of the first observations showed that feeding male mice a low protein
111 diet elevated expression levels of genes central to cholesterol and lipid synthesis within fetal offspring
112 livers [20]. Using a similar mouse paternal low protein diet model, we have shown that adult offspring
113 glucose tolerance, adiposity, inflammatory status and cardiovascular function are all impaired in
114 response to poor paternal diet at the time of conception [21]. Furthermore, we identified significant
115 changes in preimplantation embryonic metabolic gene expression, placental function and epigenetic
116 status and fetal growth [22]. Separate studies have also shown that feeding rodents diets high in fat
117 [10, 23, 24], low in folate [25] or paternal fasting [26] all compromise offspring metabolic health and
118 homeostasis. Together, these studies demonstrate that poor paternal well-being at the time of
119 conception impacts significantly on a range of reproductive and developmental mechanisms which
120 all affect the long-term ill-health of the offspring.

121

122 The field of paternal programming of offspring health has benefited significantly both from the
123 substantial body of maternal environmental studies, and the rapid development of new sequencing
124 platforms and analytical approaches. Using different Next Generation Sequencing platforms, studies
125 have shown that sperm from rodents fed diets high in fat [27], low in folate [25] or low in protein
126 [20] display altered epigenetic status. In male mice fed a low protein diet, we identified genome-wide
127 DNA hypomethylation in sperm correlating with significant changes in testicular regulators of DNA

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

148 149 **2. The role of seminal plasma in programming offspring development**

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

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

162

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

180

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

202

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

206 separate males at any one time. However, our observations may still be of relevance in situations
207 where an embryo is transferred back to a uterine environment that has not been primed adequately by
208 seminal plasma. Significant improvements in pregnancy rates for women undergoing IVF have been
209 reported following exposure to seminal plasma around the time of ovum pick-up or embryo transfer
210 [44, 45]. Furthermore, studies have shown increased rates of pregnancy in couples who either had
211 unprotected intercourse close to the administration of human chorionic gonadotropin [46] or in
212 women who experiencing recurrent miscarriage and are given seminal plasma pessaries [47]. In
213 addition, there is intriguing evidence linking a couples' duration of sexual cohabitation with a
214 reduction in the risk of developing pregnancy pathologies. Data from epidemiological studies
215 indicates a positive association between a woman's unprotected exposure to her partner's seminal
216 plasma and the reduction in risk of her developing preeclampsia [48, 49]. Furthermore, it seems that
217 while the first pregnancy with any given father is at increased risk for preeclampsia [50], cumulative
218 exposure, either orally or vaginally, to the fathers' seminal antigens counteract this risk [51]. As
219 preeclampsia is associated with intra-uterine growth restriction, elevated postnatal BMI and increased
220 cardiovascular disease risk in offspring [52], a fathers' semen, or lack of exposure to it, may play a
221 significant role in the health of his offspring.

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223

224 **3. The importance of seminal plasma for male fertility**

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

231

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

237

238 Due to the comparative accessibility of semen, there has been growing interest in identifying seminal
239 plasma markers of poor male fertility including varicocele [56], infertility linked to oxidative damage
240 [57], and general infertility [58]. Reduced levels of proteins such as prostaglandin-D synthase (PGDS)
241 [59] while elevated levels of proteins including galectin-3-binding protein (LGALS3BP), prostatic
242 acid phosphatase (PAP) and prolactin-inducible protein (PIP) have been reported in seminal plasma
243 of azoospermic men [60] when compared to control samples. Following the analysis of seminal
244 plasma from men of proven fertility, a panel of proteins important for male fertility including
245 Semenogelin I and II, olfactory receptor 5R1, human cationic antimicrobial protein (hCAP18) and
246 lactoferrin have been identified [61]. Semenogelins act to prevent premature sperm capacitation [62],
247 with elevated levels being observed in azoospermic men [63]. hCAP18 plays a key role in male innate
248 immunity [64], while downregulation of proteins such as DJ-1 results in elevated levels of oxidative
249 stress in semen of asthenozoospermic men [65].

250

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

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

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270

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

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

279

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

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

303

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

310 seminal plasma free environment. Furthermore, generated embryos are often transferred into a non-
311 seminal plasma primed uterine environment. However, in recent years, there has been growing
312 interest in the role of seminal plasma in managed reproduction within commercially important
313 agricultural species. In ruminants, seminal plasma contains proteins which bind to sperm and which
314 can both stimulate and inhibit sperm function [86]. Additionally, varying compositions of bovine
315 seminal plasma have been shown to affect aspects of sperm quality including motility and chromatin
316 integrity [87, 88], while analysis of seminal plasma composition between bulls of high fertility and
317 bulls of low fertility have identified differences in the profiles of specific proteins [89, 90]. In the
318 cow, seminal plasma has also been shown to play a role in pregnancy outcomes. Odhiambo et al.,
319 observed that in heifers exposed to seminal plasma around the time of artificial insemination,
320 pregnancy rates were increased by a non-significant 13.9% [91]. Interestingly, the authors also
321 observed that the administration of both seminal plasma and the cytokine TGF β , known to regulate
322 maternal uterine immunological responses in mice, to dairy cows increased pregnancy outcomes by
323 10% [91].

324

325 In the pig, unlike other mammalian species, seminal plasma is deposited directly into the uterus at the
326 time of ejaculation. However, similar to other species, exposure of the porcine uterus to seminal
327 plasma results in the production of a cytokines and chemokines by the endometrial tissues and
328 resident leukocytes [92]. Infusion of seminal plasma into the porcine uterus results in elevated levels
329 of macrophages, major histocompatibility complex class II activated macrophages and dendritic cells
330 34 hours later, and which are maintained for up to 9 days after infusion [93]. Seminal plasma has also
331 been shown to improve porcine sperm survival and motility when compared with standard
332 commercial semen extenders [94]. Furthermore, increased numbers of embryos are recovered from
333 gilts when infused with seminal plasma at the time of artificial insemination [93, 95]. Recently,
334 seminal plasma has also been shown to influence the tissue orchestration of cell signalling and gene
335 expression profiles between the uterus and ovary in the pig [96]. Together, these studies show that in

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

338

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

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348

349 **5. Future perspectives**

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

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

364

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

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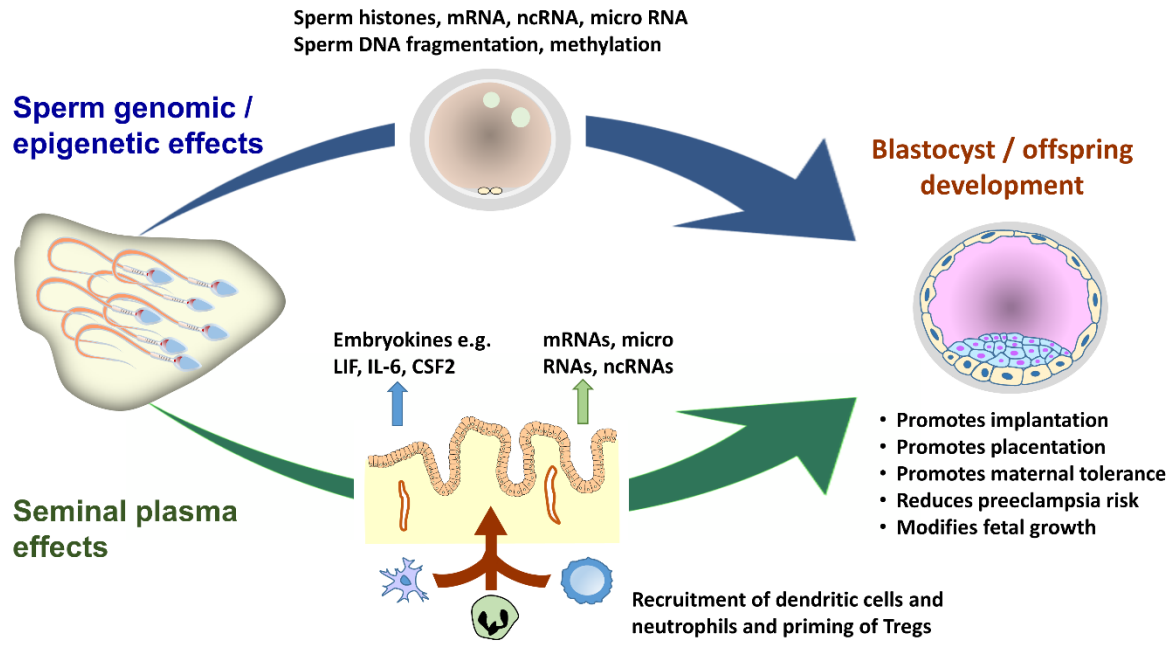


Figure 1: Schematic diagram of the known influences semen has on mammalian periconception development and the maternal uterine environment. Sperm epigenetic status influences early embryo development via the transfer of sperm-specific histones, RNA populations (e.g. mRNA, micro RNA) and aspects of DNA 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.