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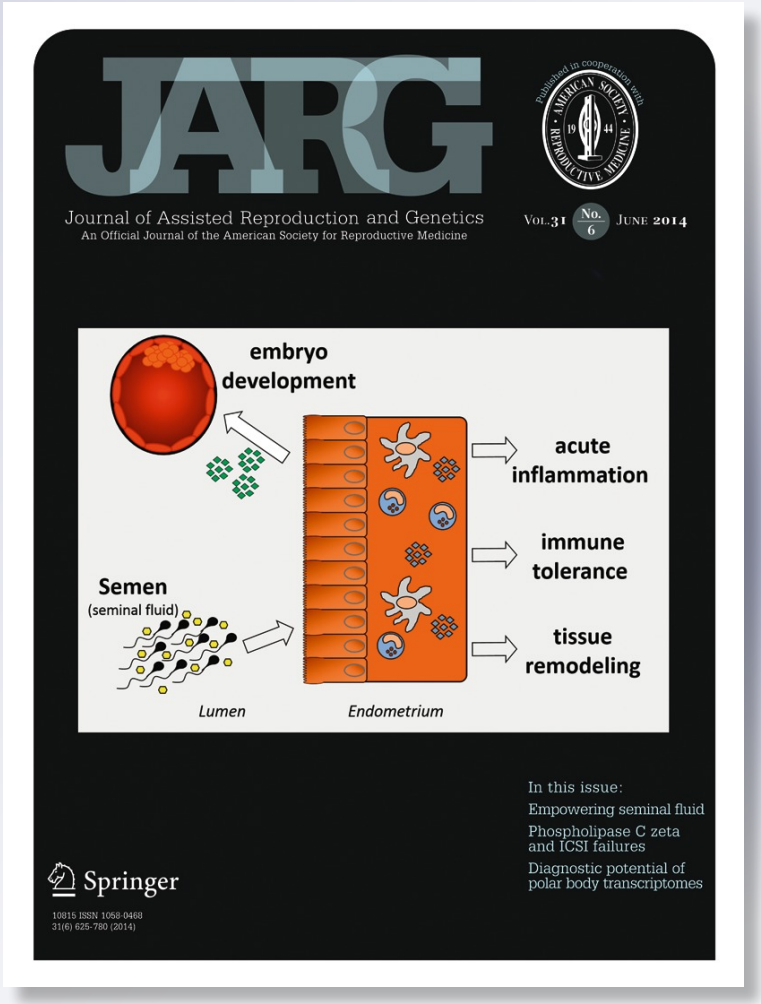

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REVIEW

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Abstract The influence of seminal plasma on the cytokine and immune uterine environment is well characterised in mice and humans, while the effects of disruption to uterine seminal plasma exposure on pregnancy and offspring health is becoming more clearly understood. The cellular and molecular environment of the uterus during the pre- and peri-implantation period of early pregnancy is critical for implantation success and optimal foetal and placental development. Perturbations to this environment not only have consequences for the success of pregnancy and neonatal health and viability, but can also drive adverse health outcomes in the offspring after birth, particularly the development of metabolic disorders such as obesity, hypertension and insulin resistance. It is now reported that an absence of seminal plasma at conception in mice promotes increased fat accumulation, altered metabolism and hypertension in offspring. The evidence reviewed here demonstrates that seminal plasma is not simply a transport medium for sperm, but acts also as a key regulator of the female tract environment providing optimal support for the developing embryo and benefiting future health of offspring.

Keywords Seminal fluid · Programming · Inflammation · Fertility

Introduction

The process of insemination is no longer viewed simply as the delivery of sperm into the female reproductive tract [1]. Although this might be the primary purpose of insemination, there is now evidence that semen can act directly on tissues in the female reproductive tract to elicit accessory functions which in turn may influence implantation, development of the pre-implantation embryo and future health of the offspring. Over the past decade specific compounds which can exert biological activities in female tract cells have been identified within seminal plasma. However, it is clear that whole semen is not an absolute requirement for a viable pregnancy outcome, as shown by the advent of embryo transfer and artificial insemination. Thus it appears that seminal factors act primarily to optimise the likelihood of successful pregnancy. This has been supported by studies showing the addition of seminal plasma or seminal factors to assisted reproductive procedures can markedly improve pregnancy success in mice, rats, hamsters, sheep and humans [2–6].

Studies using mouse models have demonstrated the importance of cytokines present in semen. In particular, seminal transforming growth factor-beta (TGFβ) [7] has been described to interact with uterine epithelial cells to induce the expression of an array of pro-inflammatory cytokines, resulting in a classic inflammatory response that culminates in an influx of leukocytes into the endometrial tissues [8]. This inflammatory response to semen and the associated change in the cytokine environment has been hypothesised to mediate several downstream effects in the female reproductive tract [9]. More recently these studies have been recapitulated in the human, particularly the cervix following intercourse [10–12]. Recently we have reported that pregnancies initiated in the absence of seminal plasma in mice give rise to progeny with altered metabolic profiles, obesity and hypertension due in part to perturbations in the peri-conceptional environment and oviduct expression of embryotrophic cytokines [13].

The inflammatory changes induced at insemination may be linked with the immune changes necessary to accommodate pregnancy. Introduction of allogeneic material into a host is usually met with a rapid rejection of the tissue by the host

Capsule Seminal fluid exposure promotes healthy pregnancy outcomes.

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immune system. The survival of a semi-allogeneic conceptus within its mother is the exception to this general rule. The process of embryo survival through implantation and pregnancy is thought to be mediated by maternal immune suppression or immune deviation, a process where the cytokine environment can direct the quality of an immune response to achieve functional immune tolerance. The events leading to these immune changes in pregnancy are unknown, but are hypothesised to be initiated at insemination, when the maternal immune system is first exposed to paternal transplantation antigens, some of which are shared by the conceptus. Thus, insemination may comprise a 'priming' event leading to the maternal immune tolerance required for the survival of the semi-allogeneic conceptus [14, 9].

The inflammatory events known to occur at insemination may also have subsequent effects on processes important in embryo development, implantation and trophoblast invasion. The substantial changes in the cytokine environment of the oviduct and uterus, as a consequence of seminal plasma exposure, may also contribute to enhancing pre-implantation embryo development and facilitating the changes in both the uterine epithelium and stroma necessary for embryo attachment and implantation. These early steps in establishing pregnancy are crucial to the ongoing success of a pregnancy.

Here we summarise the current understanding of the events of early pregnancy and discuss their possible modulation by uterine exposure to seminal factors. Many of the processes occurring in early pregnancy appear to be affected by cytokines or leukocytes activated by seminal factor signalling in the female tract (Fig. 1). As a consequence, disruption of seminal exposure may have negative effects on events occurring in early pregnancy, resulting in detrimental outcomes for both the pregnancy and offspring.

Early origins of adult disease and foetal programming

Increasingly, perturbations in the in utero environment have been linked with altered metabolic status and increased risk of disease in adult life. Since the late 1980s a clear association between low birth weight in humans and the development of adult hypertension has been defined by David Barker and his colleagues [15]. Since these initial studies a series of epidemiological studies have shown associations between low birth weight and the onset of adult diseases including hypertension and extending to obesity, type II diabetes mellitus, heart disease, kidney disease and the insulin resistance syndrome (reviewed in [16]). The relationship between birth weight and the development of adult disease has been termed the "foetal origins of adult disease". Foetal growth potential is controlled at many levels; however one very critical factor is that of the in utero maternal environment. Maternal feed restriction, through experimental approaches or food shortage, like that of the Dutch famine during World War II, has been correlated with low birth weight and subsequent changes in endocrine, metabolic and reproductive parameters in these offspring later in life, as well as predisposition to certain cancers [17–26]. It is hypothesised that these changes in endocrine and metabolic parameters are in essence programming the offspring for the development of endocrine associated adult diseases.

The molecular mechanisms underpinning foetal programming are not clearly defined. However, recently it is become more evident that epigenetic regulation of the genome may be playing some role [27]. At the very early stages of embryonic development epigenetic modification of the conceptus can be modulated by endogenous, environmental and dietary factors. Mitochondrial abnormalities have also been suggested as mechanisms affecting foetal programming, as suggested by studies investigating mitochondrial abnormalities arising due to in vitro embryo culture [28, 29]. Now it has been shown the offspring of rats fed on a high fat diet not only have impaired glucose homeostasis, but also have a decreased mitochondrial number accompanied by a decrease in the expression of mitochondrial specific genes [29].

The prenatal programming of endocrine axes is also a keg regulator of the future health and metabolic status of subsequent progeny. The hypothalamic/pituitary/adrenal (HPA), somatotropic and insulin axes are all thought to contribute to the differential regulation of key endocrine regulators of metabolism that can influence the metabolic status of an individual. These highly regulated, tissue specific endocrine regulators are known to be influenced by programming mechanisms to exert differential development of the foetus [30–32]. More recently a direct contribution of the father has been shown to influence the metabolism of offspring. Male rats fed a high fat diet give rise to female offspring with β-cell dysfunction [33], while our own studies provide evidence that male mice devoid of seminal plasma give rise to male offspring with altered metabolic profiles and increased fat accumulation [13].

Pre-implantation embryo development

The pre-implantation embryo is extremely susceptible to environmental stressors such as reactive oxygen species, ammonium and metabolic substrate supply, therefore small perturbations in the oviductal/uterine environment in which the embryo develops can have a long term impact on the health and viability of the organism [34–36]. The progression from a single cell zygote to a differentiated, highly organised competent blastocyst is controlled both by maternal and embryonic factors.

Specific growth factors and cytokines expressed by the epithelium of the oviduct and uterus have been shown to be of critical importance in optimal embryonic development. The

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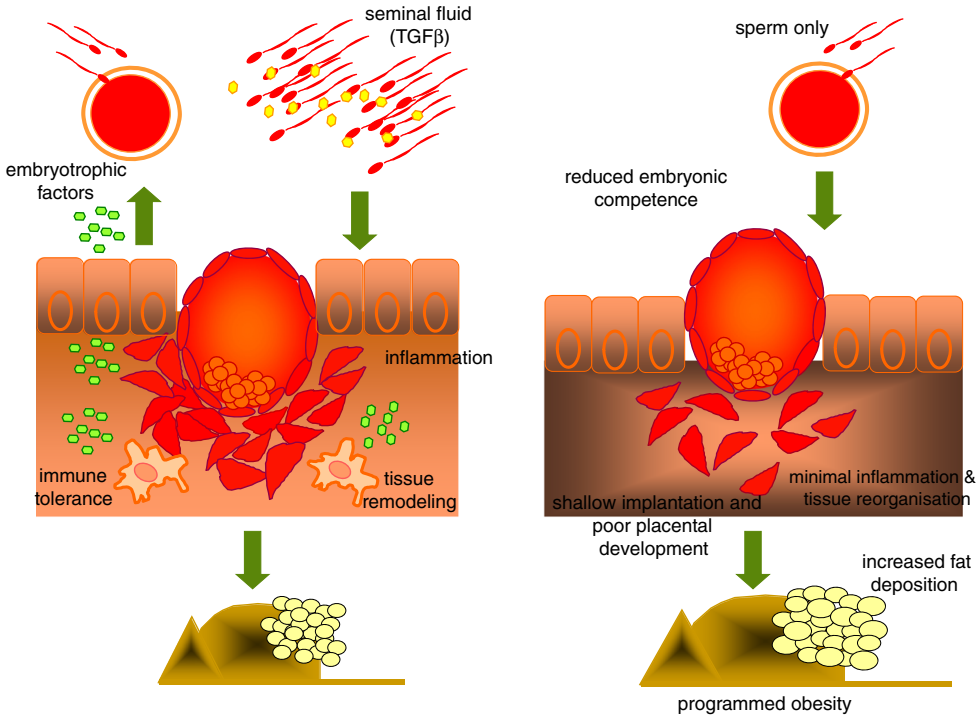

Fig. 1 Schematic representation of the early events following insemination. Seminal fluid components interact with the endometrial epithelium to produce embryotrophic factors to support embryonic development, and cytokines and chemokines to initiate an acute inflammatory reaction. Infiltration of leukocytes and antigen presenting cells follow to initiate the immune response for successful pregnancy establishment and tissue remodelling for embryo implantation. All of these events are critical to the establishment and maintenance of a healthy pregnancy and are initiated by exposure to seminal fluid. The right panel demonstrates our hypothesized series of events leading to altered pregnancy outcomes in the absence of seminal fluid. An absence of seminal fluid induced inflammation reduces the production of embryothrophic factors, immunological tolerance toward the conceptus, minimal tissue remodelling to facilitate implantation and placental development. These factors combined result in compromised foetal programming and development of adult metabolic syndrome

primary mechanism for the control of expression of these molecules is proposed to be that of ovarian steroid hormones [37]. More recently, regulation of these factors has also been attributed to male factors derived from semen [38, 39]. A wide range of molecules including granulocyte macrophage-colony stimulating factor (GM-CSF) [40], leukaemia inhibitory factor (LIF) [41], IL-6, TGFβ, TNFα [42], TGFα [43], insulin, insulin-like growth factor (IGF)-I and II [44], epidermal growth factor (EGF) [45], and heparin binding-epidermal growth factor-like growth factor (HB-EGF) [46] have all been identified as having potential roles in embryonic development, and are in part regulated in the oviductal epithelium by seminal plasma exposure. In female mice mated to males devoid of seminal plasma expression of embryotrophic factors in the oviduct is reduced while the pro-apoptotic factor Trail is increased. In addition embryos derived from these matings display perturbations in blastocyst formation which can be partially rescued using in vitro culture [13]. A definitive study by Sjoblom et al. has demonstrated that addition of GM-CSF into culture media can alleviate some of the detrimental effects of embryo culture on pregnancy outcomes, such as altered placental morphogenesis [47]. The addition of many these embryotrophic growth factors to in vitro embryo culture media is now being more closely investigated for their use in human assisted reproduction to allow closer mimicry of the in vivo environment.

Seminal plasma

Insemination

Insemination is the delivery of sperm into the female reproductive tract. Upon ejaculation men produce approximately 4 ml of semen that contains up to 600 million sperm. After coitus these sperm must then traverse the female tract to the oocyte where fertilisation can occur. Ejaculated semen contains a number of constituents, both cellular and acellular. Primarily, semen is regarded as a concentrated fluid of mature sperm. However, semen also contains a number of epithelial and myeloid cells derived from the testis and urogenital lining. The predominant constituent of semen is the seminal fluid termed seminal plasma. Seminal plasma is derived from the male accessory sex glands including the seminal vesicle

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glands, prostate, epididymis and bulbourethral (or Cowpers) gland. The fluid in which sperm are transported through the male urogenital tract and into the female reproductive tract is protein-rich and contains a number of compounds which assist in sustaining sperm viability. Seminal plasma is rich in fructose, which is the predominant metabolic substrate that facilitates the journey of sperm through the male urogenital tract across the cervix and into the oviduct. However, seminal fluid also contains a number of micronutrients and amino acids to aid in meeting the high metabolic requirements of the sperm. Seminal plasma is also a rich source of both oxidative and anti-oxidative agents. Sperm have been shown to be highly susceptible to oxidative DNA damage due to the small degree of buffering their diminished cytoplasm offers. Oxidative stress occurs due to the presence of hydroxyl radicals, superoxide anions and hydrogen peroxide present in either the ejaculate or the female reproductive tract fluids. In the event of sperm DNA damage, including that acquired from oxidative stress, pregnancy failure or pathologies can ensue due to embryonic loss [48, 49]. To counteract the detrimental effects of these oxidative agents seminal plasma is rich in powerful antioxidant agents such as catalase and superoxide dismutase [50]. Seminal plasma has a powerful buffering capacity required to counteract the harsh acidic environment of the female reproductive tract [51, 52].

Seminal plasma is rich in a number of active protein moieties. Various signalling molecules including many originally described for their immunological activities have been shown to be present in seminal plasma of both humans and rodents, including TGFβ, interferon-gamma (IFNγ), prostaglandin E_2 (PGE_2), tumour necrosis factor-alpha (TNFα) and members of the interleukin (IL) family of cytokines, including IL-1b, IL-6, IL-8, IL-10 and IL-12. TGFβ is produced predominately by the seminal vesicles and is present in ejaculated seminal plasma at concentration of approximately 200 ng/ml, substantially higher concentrations than that of blood plasma [9]. The seminal vesicles of men are also known to produce vast quantities of PGE_2 resulting in seminal plasma levels 100 000 times greater than those seen in tissues during an acute inflammatory responses [53]. It has recently become apparent the function of these molecules is to elicit strong molecular and cellular responses within the female reproductive tract after insemination.

For decades it has been proposed the sole purpose of seminal plasma has been as a transport medium for sperm to traverse the female reproductive tract. However, more recently accessory functions of seminal plasma during pregnancy establishment and progression have been described, specifically the modulation of the maternal immune response to pregnancy. The impact of seminal vesicle removal on fertility has been partially documented in the house mouse and golden hamster [54–56]. Peitz et al. have demonstrated that removal of the seminal vesicles severely diminishes the capacity of these mice to fertilise oocytes efficiently, therefore significantly reducing the pregnancy rate of mated females. Similarly male hamsters in which the accessory glands have been removed have been shown to have detrimental effects on embryonic development [4, 57, 58].

Post-insemination inflammation

Induction of pro-inflammatory cytokines is the first step in elicitation of a transient inflammatory response. The inflammatory response occurring at insemination can be attributed to factors within seminal plasma, as opposed to sperm. This conclusion is based in findings that show the lack of a uterine inflammatory response after mating mice with seminal vesicle deficient stud males [8], suggesting that the factors initiating this inflammatory cascade originate in the seminal vesicle, where the majority of seminal plasma is produced. The up-regulation of cytokines within the human cervix and murine uterus and has been specifically linked with the seminal plasma cytokine TGFβ [7, 11].

The inflammatory response initiated within the human cervix and murine uterus is very similar to a classical inflammatory response, for example seen after chemical insult or injury [59]. After uterine epithelial cells are exposed to seminal factors, the surge of pro-inflammatory cytokines and chemokines (as stated above) causes an infiltration of inflammatory leukocytes. In addition to neutrophils a large number of antigen presenting cells (APCs) are recruited into the uterine endometrium, including macrophages and dendritic cells (DCs) expressing high levels of MHC class II [60, 8]. This response has now been well characterised in other species including rabbit, horse, pig, and human [61–64, 12].

Immunological actions of seminal plasma

As previously stated seminal plasma itself has immune deviating properties, some of which may be more important than sperm protection alone. It has been known for several decades that seminal plasma from various species can directly affect the immunological functions of T cells, B cells, NK cells and macrophages in vitro [65–67]. While it does not directly influence the generation of tolerogenic lymphocytes, seminal fluid has been shown to impair complement dependent antibody cell lysis and cell mediated killing of pathogenic bacteria [68]. Anderson et al. tested the effects of seminal plasma on the extent of humoral responses to antigen challenge in mice and showed that all fractions of seminal plasma; prostate, seminal vesicle, and epididymis, were able to suppress both the primary and secondary humoral responses to venous administered washed sperm [69]. Kelly has also demonstrated that human seminal plasma creates a cytokine switch in blood lymphocytes in vitro, resulting in an up-regulation of IL-10

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and a down-regulation of IL-12, effectively creating an immunosuppressive environment [70].

More recently it has demonstrated that seminal plasma, predominately the bioactive factor TGFβ, has the capability of interacting with the female tract. Seminal fluids target the epithelial cell layer of the cervix and uterus, inducing the expression of pro-inflammatory cytokines such as GM-CSF, CSF-1 (colony stimulating factor 1), IL-1α, IL-6, IL-8, LIF, RANTES and MIP-1α [9]. The up-regulation of these cytokines by the epithelium has multiple consequences. These pro-inflammatory cytokines are responsible for establishing the post-insemination inflammatory response, while many of the cytokines are also potent immune-deviating signals which act to drive the establishment of a Th2 immune environment conducive to pregnancy success [71]. Other cytokines up-regulated by the epithelium of the female tract as a consequence of seminal plasma exposure are known to be potent embryotrophic molecules.

Studies in mice suggest that semen plays a role in the induction of systemic immune tolerance in early pregnancy. Females inseminated after uterine ligation become transiently tolerant to male transplantation antigens as measured by survival of paternal tumour challenge, suggesting that semen, as opposed to the embryo itself is a key requirement for inducing tolerance [9]. The cytokine environment at the site of antigen exposure is also a critical factor for the future development of tolerance, and seminal plasma elicits a cascade of events leading to the induction of a unique cytokine microenvironment with the uterine epithelium.

Antigenic characteristics of semen

Semen carries a multitude of paternal antigens expressed on the sperm itself, genital tract epithelial cells and seminal leukocytes some of which are also expressed by the conceptus [72, 73]. The antigens expressed on trophoblast cells and found in semen are limited, however there are a number of transplantation antigens found within semen, or expressed on the sperm itself. Mouse sperm has been shown to express both class I and class II MHC [74], as well as H-Y [75], all of which have the potential to interact with reactive lymphocytes, and are commonly expressed by the conceptus. In the case of human sperm, it remains controversial whether MHC antigens are expressed on the sperm surface [76–78]. However, it is evident that a number of leukocytes and epithelial cells are also present in the ejaculate, and these have been shown to express MHC antigens [73].

Whether APCs recruited after insemination can traffic from the uterus to the LN remains to be formally demonstrated. However, there is a small body of evidence to suggest this does occur. In the mid-1970s Beer and Billingham showed that the PALN of mice transiently enlarge after allogeneic insemination occurs, suggesting a cellular influx into the PALN [79]. Watson et al. showed that radio-labelled sperm not involved in the fertilisation process are phagocytosed by macrophages expressing high levels of class II MHC [80]. Watson also showed that these APCs could traffic to the MLN and spleen; however the draining LN of the uterus were not examined in this study. Parr et al. conducted similar studies using the introduction of FITC-conjugated proteins to trace the uptake of antigen within the vagina and uterus of mice [81]. Parr et al. studies indicated intravaginal administered proteins were later localised in dendritic and Langerhan-like cells within the vaginal epithelium and stroma, whereas labelled whole lymphocytes could be seen to pass across the epithelium and into maternal tissue after introduction into the murine uterine tract [82].

Lymphocyte activation following insemination

The studies mentioned above suggest the PALN and ileac LN as the draining LN of the uterus. It is therefore feasible to assume that DCs and macrophages exiting the uterus after insemination would arrive at these LN and perhaps become involved in lymphocyte activation. More recently it has been shown that the PALN increase in size is due to a cellular influx or proliferation, and that activation of T cells, B cells and NK cells occurs after insemination [83]. Alloreactive T cells have also been shown to increase in number within the PALN of mice in early pregnancy [84]. Although the precise phenotype of these activated lymphocytes is unknown, they are known to be recruited back into uterine tissues around the time of implantation, suggesting a role in the preparation of uterine immune environment for an ensuing pregnancy [83]. To further support the conclusion that maternal tolerance toward paternal antigen originates within these LN, O'Hearn demonstrated that PALN cells taken from allogeneic pregnant mice are specifically hypo-responsive toward paternal antigen, compared to those from virgin or syngeneically mated mice [85]. Suppression of alloreactive T cells taken from the PALN during pre-implantation and implantation stages of pregnancy has also been demonstrated, further supporting insemination as a possible start point for maternal T cell tolerance [86]. TGFβ producing suppressor cells have also been identified within the PALN during implantation [87]. Experiments conducted by Beer et al. [88] showed that the removal of the PALN before mating reduced the size of the feto-placental unit in mice, while splenectomy did not, consistent with the PALN being an important inductive site of maternal tolerance toward the semi-allogeneic conceptus. More recently the importance of antigen specific T-regulator lymphocytes (FoxP3+/CD25+) has become a focus in maintaining pregnancy. Initial studies depleting T-regulator lymphocytes showed a failure of pregnancy due to immune rejection of the conceptus [89]. Our

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studies have now shown that exposure to seminal plasma at insemination drives expansion of T-regulatory lymphocytes in the PALN and uterus [90].

Other mechanisms for the activation of alloreactive lymphocytes have been proposed, including interaction between lymphocytes and antigen in the peripheral circulation due to free trophoblast cells in blood [91]. A mechanism of trophoblast cells themselves activating alloreactive lymphocytes has also been proposed [92].

Tissue remodelling and seminal plasma

The myeloid immune cells recruited into the uterus after exposure to seminal plasma, predominately macrophages and neutrophils may have roles in regulation of epithelial and stromal remodelling during early pregnancy. These cells play a key role in the production of molecules critical for the breakdown and regeneration of specific ECM components and the generation of new blood vessels known to be required at the time of implantation.

Uterine macrophages and neutrophils produce a range of factors which contribute to ECM breakdown and rebuilding, namely MMPs and TIMPs. Neutrophils have been identified as the key source of MMP-9, a collagen specific protease during the peri-implantation period [93], while macrophages are known to produce a range of MMPs. A comprehensive study by Chow et al. [94] in the golden hamster showed that expression of molecules involved in ECM remodelling are controlled in a temporal and spatial manner and that seminal plasma is implicated in their regulation. VEGF, its receptors (VEGF-R1 and -R2) and MMP-2 expression in the uterus during the peri-implantation period were all up-regulated by seminal plasma exposure at the time of conception. Another study has further implicated seminal plasma exposure in regulating uterine artery remodelling in early mouse pregnancy, showing that uterine artery remodelling occurred comparably in mice mated with vasectomised studs or intact stud males [95].

The surface characteristics of epithelial cells are paramount for embryo attachment to occur successfully. One study has demonstrated that macrophages can contribute to the regulation of the embryo adhesive properties of epithelial cells in vitro [96]. This suggests a further important role for macrophages recruited into uterine tissues following seminal plasma exposure in events as early as embryo attachment.

Seminal plasma and pathologies of pregnancy

It is apparent that abnormal maternal immune responses, particularly insufficient immune tolerance are detrimental to pregnancy success. Immune disturbances can be most conclusively linked to implantation failure and trophoblast rejection in women [97], both of which are the basis of pregnancy pathologies such as pre-eclampsia and recurrent spontaneous abortion. There is good evidence that a strong Th1 response leading to detrimental cell-mediated immunity is deleterious to pregnancy outcome [98], where as a Th2 response resulting in a humoral immune response is seen as more favourable for a positive outcome [99]. The overall phenotype and proportion of lymphocytes is also thought to play a role in pathologies such as spontaneous abortion. For example, NK cells of the Th1 lineage are linked with foetal resorption in mice [98]. Interestingly, an aberrant immune response can be redirected; for example, foetal resorption in the abortion prone mouse model is significantly reduced by pre-immunisation of females with maternally matched class II MHC spleen cells [100].

Other immunological factors influencing pregnancy appear to be linked with semen exposure in a partner specific manner. Human studies show that both acute exposure to semen at the beginning of a pregnancy, as well as cumulative exposure over time, can protect against recurrent miscarriage and pre-eclampsia, in a partner specific manner [101]. Studies have also shown that semen exposure in women is advantageous to pregnancy outcome, the use of barrier contraception methods and the period of cohabitation between couples suggests that chronic semen exposure by an individual can be beneficial to subsequent pregnancies [102]. There is now a large body of evidence to suggest that preeclampsia has male factors, derived from semen, involved in its aetiology [103, 104].

Seminal plasma and assisted reproduction

Assisted reproductive techniques (ART), such as in vitro fertilisation (IVF), have become a widely utilised resource in the treatment of infertility in humans. Currently the consequences of such treatments on the health of offspring remain controversial. However, several studies now suggest that pregnancies derived from IVF/ICSI result in babies who are at an increased risks of cerebral palsy [105], premature birth [106, 107], low and very low birth weight [108], complications during delivery [109] and serious birth defects [110]. It is important however to note the controversy in the current literature, where opposing studies have found no association between the use of ART and various health outcome in children [111, 112]. The mechanisms by which these changes arise are as yet undefined; however epigenetic gene alterations of the placenta and foetus resulting from perturbations of the peri-conceptual environment are hypothesised to be significant factors [113].

Some applications of ART are relatively non-invasive and in part mimic natural conception, such as intra-uterine insemination. However, high tech approaches to ART are far more

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invasive and are dramatically different from the process of natural conception, particularly in regards to the handling of gametes and embryos. The circumstances involved in ART vary greatly from those of natural conception, including the utilisation of non-ejaculated sperm and forced fertilisation by intra-cytoplasmic sperm injection as well as the in vitro culture of embryos for extended periods of time. Another confounding factor in ART is the absence of cervical semen exposure both at the time of fertilisation and subsequent implantation.

Studies in animal models have begun to investigate the impact that semen exposure can have on altering the outcome of embryo transfer. Carp et al. demonstrated that mechanically induced pseudopregnant rats had a greater implantation rate after embryo transfer when exposed to semen at the time of implantation [114]. Artificial insemination in sheep has also been shown to benefit from cervical seminal plasma exposure, resulting in an increased percentage of pregnant ewes [6]. Removal of the accessories sex glands in the golden hamster has shown significant reductions in the expression of angiogenic and embryotrophic factors within the peri-implantation endometrium [94]. Our own studies have demonstrated the susceptibility to the very early embryo in generating offspring with metabolic perturbations. When in vivo derived 2-cell embryos are transferred to an oviduct not exposed to seminal plasma metabolic phenotypes develop in offspring, whereas in vivo derived blastocyst transferred to the same environment do not [13]. More recently this work has been carried over into the human ART program. It has been shown that semen exposure around the time of embryo transfer increases the rates of embryo implantation and possible subsequent foetal development [5, 115, 116]. Bellinge et al. has previously shown that seminal exposure as early as the time of oocyte retrieval can increase the incidence of pregnancy in women undergoing IVF [117]. However the effect is inconsistent as similar clinical trials found no relationship between high vaginal insemination at the time of oocyte pick up and pregnancy rates [118].

Summary

A large body of evidence now exists to suggest the importance of seminal exposure in driving multi factorial changes within the maternal uterus to establish an environment conducive to optimal embryo implantation and pregnancy outcome. Many of the processes known to be influenced by seminal exposure are critical in the processes of early embryonic development, implantation and trophoblast invasion. It has been clearly defined in the current literature that perturbation to these processes can have detrimental consequences in progeny not only during pregnancy but also after birth, with an increased risk of developmental and metabolic disorders. Although many studies have been conducted in animal models, epidemiological evidence exists suggesting an important role for seminal plasma exposure in the prevention of pregnancy related pathologies such as preeclampsia and spontaneous recurrent miscarriage. These are pathologies with unclear aetiologies; however both have links to the failure of the immune changes and other critical events occurring very early in pregnancy, at the time when seminal exposure is known to have its strongest influence in the maternal reproductive tract.

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