REPRODUCTION
SPECIAL REVIEW

REPRODUCTIVE TOXICOLOGY

Impacts of paternal environment and lifestyle on maternal health during pregnancy

Afsaneh Khoshkerdar, Ece Eryasar, Hannah L Morgan and Adam J Watkins

Division of Child Health, Obstetrics and Gynaecology, Faculty of Medicine, University of Nottingham, Nottingham, UK

Correspondence should be addressed to A J Watkins; Email: adam.watkins@nottingham.ac.uk

This paper forms part of a special section on Reproductive toxicology. The guest editors for this section were Dr Adam Watkins (The University of Nottingham, UK) and Dr Aileen Keating (Iowa State University, IA, USA)

Abstract

Pregnancy represents a time of dramatic physiological adaptation by the mother in which dramatic changes in maternal cardiovascular, metabolic and immune systems occur. These adaptations, initiated from the earliest stages of gestation, are crucial for the implantation and continued development of the embryo, the establishment of the placenta and the growth of the fetus. Impairments in the normal adaptation of the maternal cardiovascular, metabolic and immune systems underlie the aetiology of gestational disorders such as preeclampsia and gestational diabetes. Studies have shown that the development of such gestational complications not only affects the well-being of the mother but also the short- and long-term health of her offspring. While the connection between maternal lifestyle factors and the development of gestational disorders such as preeclampsia and gestational diabetes has been studied in detail, the link between a father's lifestyle and the well-being of the mother during pregnancy has received less attention. In this review, we will explore the evidence that a range of paternal factors, such as age and diet, at the time of conception can not only affect the development of his offspring, but also the well-being of the mother during pregnancy. In addition, we will examine the sperm- and seminal plasma-specific mechanisms that connect the health of the father with that of the mother and his offspring.

Reproduction (2021) **162** F101–F109

Introduction

During pregnancy, maternal physiology must undergo dramatic changes in order to support the growing metabolic needs of the developing fetus. These changes affect almost every biological system within the mother, resulting in significant adaptations in her cardiovascular, metabolic and immune functions (Soma-Pillay *et al.* 2016). Inadequate maternal adaptations during pregnancy can result in significantly impaired changes to uteroplacental blood flow, allocation and transport of nutrients via the placenta and the growth and development of the fetus.

It is now well appreciated that poor maternal health during pregnancy can have short- and long-term consequences for both the mother and her offspring (Christoforou & Sferruzzi-Perri 2020). Hypertensive and metabolic complications of pregnancy, such as gestational diabetes mellitus (GDM) and pre-eclampsia (PE), are amongst the most prevalent pregnancy complications, and can have significant detrimental effects on maternal and neonatal health. PE complicate between 2-8% of pregnancies globally (Duley 2009). However, hypertensive disorders of pregnancy linked to comorbidities, such as superimposed PE or gestational hypertension, were responsible for maternal mortality in 14% of pregnancies in 2013 (Say *et al.* 2014). Gestational diabetes currently affects approximately 10% of pregnancies, though its global prevalence is growing (Casagrande *et al.* 2018). Both PE and GDM are major causes of maternal and foetal mortality and can impact foetal growth, leading in severe cases to intra-uterine growth restriction in PE and foetal overgrowth in GDM (Brett *et al.* 2014, Dimasuay *et al.* 2016, Kingdom *et al.* 2018). This abnormal foetal growth is itself associated with neonatal cardiac dysfunction and developing long-term conditions including obesity, impaired glucose tolerance and diabetes as adults (Hanson & Gluckman 2008, Goffin *et al.* 2018, Nijs & Benhalima 2020). Further to this, there is evidence that a mother who has suffered from these disorders during pregnancy has an increased risk of developing hypertension, cardiovascular disease and/or metabolic disorders in adult life (Sattar & Greer 2002, Cunningham & LaMarca

ISSN 1470–1626 (paper) 1741–7899 (online)
https://doi.org/10.1530/REP-20-0605
Online version via https://rep.bioscientifica.com

2018). In this respect, pregnancy has been compared to a stress test for the maternal cardiovascular system, as it can reveal previously unknown pathology with lasting life-long consequences to any pathophysiological adaptations (Sattar & Greer 2002). The placenta has a crucial role in the development of these pregnancy complications as well as directing foetal development and growth (Sferruzzi-Perri & Camm 2016). Inappropriate establishment of the early placenta is a significant factor in the development of PE, and indeed, the only current 'cure' is the removal of this organ (Steegers *et al.* 2010). Interestingly, the research attention these disorders receive has often been associated with maternal health prior to and during pregnancy, and the role of placental-maternal interactions in the pathophysiology development. Yet the placenta is a bipaternal organ, with the contributions to its genetics from both the mother and father. Male imprinted genes are known to play key roles in implantation and placental development (Hemberger 2007). A well-studied example is the paternal expression of the insulin-like growth factor-2 (*IGF2*) gene that promotes the growth of the placenta, this is balanced by the maternal control of expression of the IGF2 receptor which reduces the bioavailability of IGF2 and thus regulates growth, demonstrating crucial interplay between both the mother and father in placental development (Constância *et al.* 2002). Similarly, placentas with a paternal-specific knock-out of the sodium-coupled amino acid transporter (Slc38a4) demonstrated reduced placental weight and hypoplasia alongside evidence of foetal growth restriction (Matoba *et al.* 2019). These findings outline the importance of male contributions to successful pregnancy and foetal growth, and highlights the potential for detrimental impacts on maternal wellbeing during gestation.

Over the past decade, there has been a growing interest in the role that a father may play in directing the *in utero* development of his offspring (Watkins *et al.* 2020). There is a growing body of animal data, supported by retrospective analysis of epidemiological data sets, that has identified significant associations between paternal lifestyle characteristics, semen quality, embryonic development, foetal and placental growth and offspring health (Watkins *et al.* 2020). However, whether the father's health also affects maternal responses to pregnancy has been relatively understudied. In this article, we will focus on the role the father may have in affecting the wellbeing of the mother during pregnancy. It is becoming increasingly apparent that the health of the father at the time of conception can impact significantly on the development and long-term health of his offspring, however, the impact on the wellbeing of the mother has received little attention. There is emerging evidence that the father can impact pregnancy outcomes and studies have highlighted connections between specific paternal factors and maternal responses to pregnancy (Schjenken & Robertson 2020). A recent retrospective cohort study has provided evidence that the likelihood of poor neonatal outcomes and maternal comorbidities increases as the fathers health worsens, due to age and diagnosed metabolic syndromes, including hypertension, hyperlipidemia, diabetes, and obesity (Kasman *et al.* 2020). The paternal contribution to the placenta is the most likely candidate for driving maternal pregnancy complication onset. The invasion of placentally-derived trophoblast cells, which express paternal alloantigens, into the maternal decidua and an associated spiral artery remodelling play a key role in the development of PE (Cartwright *et al.* 2010). There is also evidence of paternal-driven alterations to uterine vascular remodelling and immune cell populations observed shortly after conception in response to the deposition of semen in the female reproductive tract (Schjenken & Robertson 2020). These early uterine changes could impact on embryo implantation and the establishment of the early placenta. Indeed, studies in rodents have shown poor paternal diet affects the development and gene expression profile of the mature placenta (Lambrot *et al.* 2013, Binder *et al.* 2015*a*). Furthermore, profiles of foetal development, growth and viability have been reported in response to paternal factors such as diet (Fullston *et al.* 2013) and age (Frattarelli *et al.* 2008). Some studies have also identified paternal associations with the maternal risk for developing PE (Galaviz-Hernandez *et al.* 2018). In this article, we will briefly outline the normal maternal adaptations that occur during pregnancy, focusing predominantly on the cardiovascular, metabolic and immune systems, and the consequences that inappropriate adaptations can have for the health of the mother and her offspring. Following this, we will explore the evidence for the paternal effects on sperm quality and on maternal health during gestation and outline the potential mechanisms through which paternal factors may operate.

Maternal adaptations during pregnancy

Major physiological adaptations in almost all organ systems of the mother are required throughout gestation to allow for successful pregnancy and provide a suitable environment for the development and growth of the fetus. One of the very first changes that occurs even prior to pregnancy is the remodelling and decidualisation of the uterine environment, driven by actions of oestrogen and progesterone, which is essential to support the implanting embryo (Kim & Kim 2017). Upon conception decidual-associated early vascular remodelling occurs in the uterine spiral arteries. This involves the vacuolation of endothelial cells and some swelling of the vascular muscle cells driven by maternal immune cells within the decidua which prime the vasculature for a more robust placental trophoblast associated remodelling (Pijnenborg *et al.* 2006). Uterine natural killer (uNK) cells account for 70% of the immune cell population in the

uterine tissue (Robson *et al.* 2012), with dendritic cells, macrophages and cells of the adaptive immune system such as T regulatory cells (Tregs) making up the rest (Liu *et al.* 2017). These populations secret many angiogenic factors such as vascular endothelial growth factor (VEGF), placental growth factors (PlGF), angiopoietin (1 and 2) and transforming growth factor-beta (TGF-β) (Lash *et al.* 2010) Furthermore, the production of chemokines and cytokines such as granulocyte macrophage colony-stimulating factor (CSF2) from these immune cell populations can regulate the action of the invading trophoblast (Sferruzzi-Perri *et al.* 2009).

It is the invading trophoblasts that bring about the dramatic remodelling of uterine spiral arteries from highly coiled, muscular high resistance arteries to wide vessels with low resistance in order to increase blood flow to the placenta (Pijnenborg *et al.* 2006). These adaptations, along with placental mediated paracrine and endocrine signals throughout gestation lead to dramatic modifications to maternal cardiovascular and metabolic physiology. For example, significant increases in cardiac output can be detected in women by as early as the 8th week of pregnancy and increase by as much as 50% by 16–20 weeks gestation (Hunter & Robson 1992, Chapman *et al.* 1998). Underlying the maternal haemodynamic changes is a reduction in peripheral vasodilatation, driven by endothelial upregulation of nitric oxide synthase (Sanghavi & Rutherford 2014) resulting in a fall in systemic vascular resistance. Ultimately, these adaptations allow for increased uteroplacental blood flow while maintaining maternal blood pressure (Gallo *et al.* 2012). In hypertensive pregnancy complications such as PE, these cardiovascular alterations are perturbed and an abnormal systemic vasculature response to pregnancy is observed. This includes vasoconstriction and endothelial dysfunction which contribute to the increased vascular resistance and hypertension (Crews *et al.* 2000). One cause of this is evidenced to be impaired uteroplacental blood flow, thought to stem from an impairment in the spiral artery remodelling (Pijnenborg *et al.* 1991, Pijnenborg *et al.* 2006). Spiral arteries from pre-eclamptic patients have been found to have shallower remodelling (i.e. limited to decidua, not extending into the myometrium) retaining a contractile phenotype and do not show a pregnancy dependent increase in flow-mediated vasodilation (Brosens *et al.* 1972, Kublickiene *et al.* 1998, 2000, Lyall *et al.* 2013). Ultimately the impaired remodelling creates a hypoxic uterine environment leading to placental damage and an increase of antiangiogenic and pro-inflammatory factors, which are released into the circulation leading to systemic vascular dysfunction (Brennan *et al.* 2014, Li *et al.* 2014).

Going in hand with the pregnancy-associated changes in cardiovascular function are adaptations of maternal metabolism including weight gain, elevated fasting blood glucose levels, insulin resistance, glucose intolerance, low grade inflammation and changes in metabolic hormone levels. Normal pregnancy is characterised typically by an increased insulin resistance to supply sufficient carbohydrates to support foetal growth (Zeng *et al.* 2017). In contrast, glucose homeostasis is regulated by increasing insulin secretion through hypertrophy and hyperplasia of pancreatic β-cells (Ernst *et al.* 2011). In early pregnancy, there is a switch in maternal metabolism from a utilisation of glucose to lipids, allowing glucose to be diverted to the developing foetus (Zeng *et al.* 2017). Later in pregnancy, an accelerated breakdown of maternal adipose reserves occurs through the action of hormones such as leptin, helping to maintain high circulating levels of triglycerides, cholesterol and free fatty acids (Catalano *et al.* 2006). The placenta has been found to express nearly all known adiopokines which are produced by adipose cells, thus during pregnancy, there is a critical reliance on the placenta for appropriate physiological responses (Bowen *et al.* 2002). In cases of GDM, placental dysfunction is evident by increased lipid accumulation, inflammation and oxidative stress and it has altered transport capabilities (Jansson *et al.* 2009), specifically a dysregulated in expression of glucose, amino acid and fatty acid transporters (Brett *et al.* 2014). The fact that the placenta plays a prominent role in the development of aberrant responses to pregnancy means it is crucial to fully understand the paternal involvement.

Paternal environmental influences on maternal health in pregnancy

Influences of paternal age

An association between paternal age and an increased incidence of pregnancy complications in their partners has also been observed (Harlap *et al.* 2002, Khandwala *et al.* 2018). In men, being over 45 years of age has been linked to an increased risk of placental abruption and placental praevia, while being under 20 years old was linked to increased rates of maternal anaemia and PE (Alio *et al.* 2012). This association is supported by a separate study in which divergent categories of paternal age (<30 and > 60 years old) were both shown to increase the risk for PE in the mother (Hurley & DeFranco 2017). Advanced paternal age has also been shown to influence patterns of foetal and placental growth. A study examining singleton pregnancies between 1999 and 2009 in Norway discovered higher placental weight as well as higher placental to birth weight ratios from men over 50 than from men aged 20–24 years (Strom-Roum *et al.* 2013). Both increases and decreases in placental weight have been attributed as a risk factor for the development of PE, especially at term (Eskild *et al.* 2009). Furthermore, epidemiological and animal data have identified differential placental dynamics as a risk factor for long-term offspring cardiometabolic ill-health (Sferruzzi-Perri & Camm 2016). Underlying

the changes in placental growth may be alterations in the epigenetic status of the tissue. The KCNQ1OT1 imprinting control region, and the paternally expressed long ncRNA Kcnq1ot1 derived from it, are responsible for the regulation of several imprinted genes required for normal placental development in both humans and mice (Oh-McGinnis *et al.* 2010). In mice, advanced paternal age (approximately equivalent to 40–50 years in men) is associated with general DNA hypomethylation of this region in the developing placenta when compared to tissue derived from the same males at a younger age (Denomme *et al.* 2020). Interestingly, adverse effects on offspring well-being have also been reported in response to both young and older fathers (Auroux *et al.* 1998, Reichenberg *et al.* 2006).

Influences of paternal obesity

The association between maternal gestational obesity, pregnancy complications and elevated foetal growth is well established. However, studies have also shown that paternal obesity at the time of conception not only adversely affects his own reproductive health, but can also have a detrimental impact on foetal and placental development, which can influence maternal wellbeing during pregnancy. There is evidence from mouse models that paternal obesity impacts negatively on implantation rates and alters late gestation placental expression of genes involved in inflammation responses and key nutrient transporters, as well as influencing placental DNA methylation status (Mitchell *et al.* 2011, Binder *et al.* 2015*a*, Claycombe-Larson *et al.* 2020). Even though these studies found paternal obesity could alter both placental and foetal development, none made mention of the impact (if any) this poor paternal health had on the mother. Few studies have examined whether the father's poor health can impact the maternal physiological response to pregnancy with many focusing solely on the impact on offspring development. However, as several of the studies previously mentioned have found alterations in aspects of placental physiology, this is an area which crucially requires further study.

Assisted reproductive technologies (ART)

As mentioned previously, connections exist between paternal antigen exposure and incidences of PE. These associations have been corroborated from studies in the field of assisted reproductive technologies (ART) (Tandberg *et al.* 2015). The use of donor sperm in procedures such as *in vitro* fertilisation (IVF) has been associated with an increase in the incidence of PE when compared to women using their partner's sperm (Wang *et al.* 2002, Gonzalez-Comadran *et al.* 2014). The significance of sperm exposure is highlighted further by observations that the risk of PE was increased in women who, due to impaired sperm numbers and production, had never been exposed to their partner's sperm naturally, but who received embryos fertilised using sperm surgically retrieved from their partner's testes (Wang *et al.* 2002). A recent large meta-analysis supports the association between the use of donor sperm and an increased risk of gestational hypertension and reduced foetal growth, however, the number of studies is limited (Allen *et al.* 2020). Interestingly, there is data to suggest that the chances of becoming pregnant following procedures such as ART may also have a male influence. For women undergoing IVF, significant improvements in pregnancy rates have been reported following unprotected intercourse and exposure to seminal plasma around the time of oocyte collection or embryo transfer (Marconi *et al.* 1989, Tremellen *et al.* 2000, Crawford *et al.* 2015). Some forms of ART, such as intracytoplasmic sperm injection (ICSI), are associated with a lack of exposure to the seminal fluid. In rodents, the removal of the seminal vesicles in males, and thus the prevention of seminal plasma exposure in the maternal reproductive tract, results in significant impairments in embryo development and poor adult offspring cardiometabolic health (Bromfield *et al.* 2014). This study also found that the absence of seminal fluid at conception caused an increased placental weight and size, and estimated that placental efficiency was reduced compared to placentas sired from intact males (Bromfield *et al.* 2014). These studies indicate a role for the presence of seminal plasma around the time of conception influencing subsequent placental development, thus the potential for the father to alter maternal response to pregnancy. However, as successful pregnancy can occur in many species in the absence of seminal plasma, its role in the establishment of a healthy pregnancy is still to be defined in detail.

Epigenetic mechanisms of paternal effects

As many studies and models have established a link between paternal health and offspring well-being, the focus of many paternal programming studies is now on defining the underlying mechanism(s). Here, the father may influence maternal health and offspring development through two main pathways, the first being the genomic and epigenomic contributions of the sperm and their influences on foetal growth (Fig. 1).

Multiple studies have identified links between paternal health and sperm quality. In humans and rodents, elevated male BMI is associated with reduced sperm motility (Hammoud *et al.* 2009), increased incidences of sperm abnormality (Kort *et al.* 2006) and sperm DNA fragmentation (Chavarro *et al.* 2011). Reduced sperm DNA integrity, prevalent in obesity and diabetes, correlates with reduced embryonic development and decreased pregnancy rates (Bakos *et al.* 2011). In addition to sperm genomic integrity, the epigenetic complexity of the mature mammalian sperm has been a centre of focus

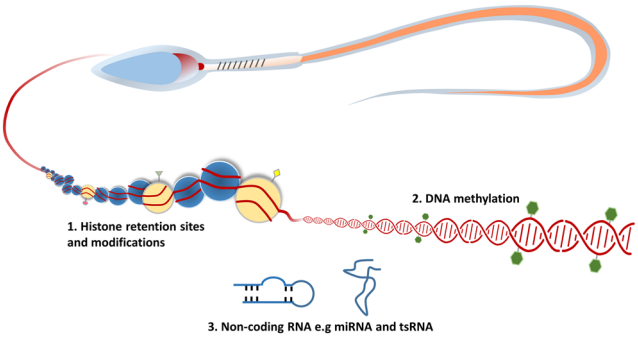

Figure 1 An overview of the principal epigenetic alterations in sperm modifiable by environmental factors. The sperm genome contains a small (<10% dependent on species) histone fraction (pale spheres) who's location and modifications can be altered in relation to insults such as poor diet, age and fertility. The sperm genome contains high amounts of DNA methylation, found in histone rich regions and may reflect the nature of the testicular environment in which they matured as well as male fertility. Sperm also contains a range of RNA species including microRNA (miRNA) and tRNA-derived small RNAs (tsRNAs) as well as mRNA and piRNA which can be affected in their levels by paternal lifestyle or environmental stress.

over recent years. In both men and mice, sperm contain a small, but significant amount of histones, which are located at key developmental and pluripotency genes such as Oct4 (Hammoud *et al.* 2011) suggesting they may influence early zygotic gene expression and trophoblast lineage determination. Separately, perturbed levels of sperm DNA methylation have been linked to reduced rates of embryo development (Aston *et al.* 2015) and increased rates of pregnancy loss (Benchaib *et al.* 2005). Recent studies have also shown sperm to contain a range of RNA species including mRNA, microRNA, short and long ncRNA and small interfering RNAs (Colaco & Sakkas 2018). In mice, injection of tRNA-derived small RNAs from sperm of high fat diet fed male mice into control zygotes resulted in impaired glucose metabolism and insulin secretion in the resultant offspring (Chen *et al.* 2016). Our own studies have shown that male mice fed a sub-optimal low protein diet have sperm with significantly reduced levels of global DNA methylation and sire offspring with significantly increased foetal growth and weight at birth, yet with reduced placental growth (Watkins & Sinclair 2014, Watkins *et al.* 2017, 2018, Morgan *et al.* 2020). The significance of these changes in male fertility, pregnancy loss and/or patterns of foetal growth on maternal health during pregnancy have not been fully investigated. However, it would be anticipated that an increase in pregnancy loss, or the impact of gestating significantly larger offspring would place maternal physiology and wellbeing under additional strain.

Maternal responses to paternal seminal plasma

In addition to the sperm, the seminal plasma may influence maternal health and post-fertilisation development via its effect on the maternal uterine tract during early pregnancy (Fig. 2). The seminal plasma delivers more than just sperm to the maternal reproductive tract, it also contains bioactive signalling factors that have the ability to induce a maternal immune response and encourage uterine remodelling (Schjenken & Robertson 2020). One of the first studies to identify a seminal mediated paternal influence on maternal health during pregnancy observed an increase in the incidence of PE in women that had previously used contraceptive methods that prevented sperm and seminal fluid exposure within the female reproductive tract (Klonoff-Cohen *et al.* 1989). Subsequent studies have revealed that exposure to a partner's semen for less than 6 months placed a woman at increased risk from developing PE (Einarsson *et al.* 2003, Kho *et al.* 2009, Sadat *et al.* 2012). These studies indicate that an increased duration of exposure to a partner's semen may be beneficial for a woman's gestational wellbeing, and is attributed to a dampening of the maternal immune response to 'familiar' paternal antigens present on the placenta (Kyrou *et al.* 2010). In addition to the duration of exposure, a change in partner has also been linked as a risk factor for PE (Skjaerven *et al.* 2002, Zhang & Patel 2007).

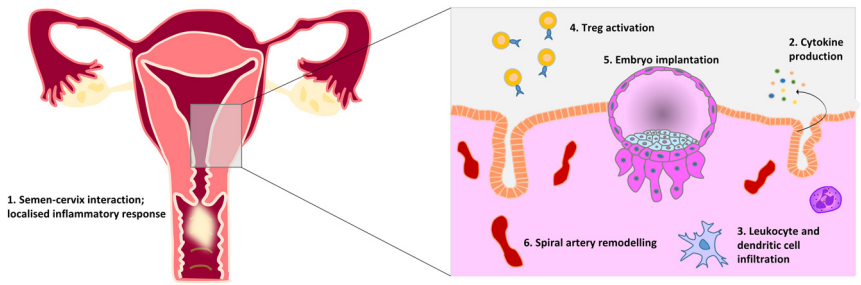

Figure 2 Seminal plasma elicits a range of inflammatory and immunological responses within the female reproductive tract that may impact post-fertilisation development and maternal gestational health. Female reproductive tract engages in an integrated and overlapping series of responses including the clearance of excess sperm and microorganisms from the vagina and cervix, endometrial cytokine production, immune cell infiltration and activation, embryo implantation and uterine spiral artery remodelling. Impairments in any of these mechanisms may impact negatively on the development of the embryo or the ongoing health of the mother.

A Californian cohort study utilising linked birth certificates and historical records of PE and eclampsia found a 30% increase in the occurrence of PE in women who changed partners, independent of factors such as parity and the interval between pregnancies (Li & Wi 2000). However, this study also found that in their cohort the women who changed partners tended to be younger in age and there was a racial disparity with more Black or Hispanic mothers changing partner after the first birth (Li & Wi 2000). Furthermore, these findings have been contradicted by a more recent Norwegian cohort study that found in couples undergoing assisted reproductive technologies the change in partner does not increases the risk of PE (Tandberg *et al.* 2015). Interestingly, this group and others have shown that the longer the duration between pregnancies the more likely subsequent PE will occur (Basso *et al.* 2001, Skjaerven *et al.* 2002).

The observations outlined above indicate the presence of a 'memory of exposure' within the female reproductive tract to paternal antigens present within the seminal plasma. As the highest risk for PE is typically associated with a first pregnancy, it is believed that repeated exposure of the maternal immune system to the paternal seminal antigens helps reduce risk in subsequent pregnancies. Upon deposition of seminal plasma into the female reproductive tract a range of uterine cellular and immune cell changes are initiated which influence female reproductive physiology to increase the likelihood of conception (Morgan & Watkins 2020). Transcriptomic analysis of uterine tissue from female mice after mating shows dramatic changes in expression of genes for cytokines and factors which stimulate the immune system (Schjenken *et al.* 2015). The impact of these changes is to induce a pro-inflammatory response resulting in the recruitment of leukocytes into the reproductive tract (Robertson *et al.* 2003). Following the initial responses, increased numbers of macrophages and dendritic cells are recruited into the uterine tissue prior to a dampening of the immune responses under the influence of progesterone and an increase in the number of uNK cells (Schjenken & Robertson 2020). In women, while similar inflammatory immune responses are observed within the tissue of the cervix, the precise underlying mechanisms are less well defined. A critical aspect of these responses is the induction of the Treg cells which are necessary for the immune tolerance of the embryo following implantation (Johansson *et al.* 2004). Indeed, in women who suffer repeated miscarriages, reduced numbers of Tregs have been observed within the decidual tissue as well as the peripheral circulation (Robertson *et al.* 2013) indicating inappropriate immune priming as one cause of pregnancy loss.

Interestingly, the response of the uterine Treg cells can be modulated in response to seminal plasma signals (Johansson *et al.* 2004) suggesting changes in seminal plasma composition may underlie essential uterine adaptations in early pregnancy. We have shown that male mice fed a low protein diet elicit a dampened uterine cytokine response coupled with a decreased expression of genes associated with central immune cell regulators and altered vascular morphology (Watkins *et al.* 2018). Offspring derived from these males displayed increased postnatal growth and adiposity and impaired metabolic and cardiovascular health. These observations suggest inappropriate post-conception uterine immunological responses may underlie compromised embryonic and foetal development, impacting potentially on maternal wellbeing during gestation. Obesity has also been shown to influence seminal plasma composition and embryonic development in a paternal high fat diet mouse model (Binder *et al.* 2015*b*), while in men, obesity has been associated with higher seminal plasma levels of fructose (Eisenberg *et al.* 2015) and the pro-inflammatory cytokine IL-8 (Lotti *et al.* 2011). These observations indicate that seminal plasma composition at the time of conception not only reflects the physiological wellbeing of the male, but may also reflect the quality of his sperm and the uterine inflammatory responses and implantation potential of the embryo.

Conclusions

The research examining the father's contribution to pathological complications of pregnancy is sparse, and has often been confused by confounding maternal factors in humans. However, the involvement of poor paternal health in the development of long-term health complications in his offspring, and crucially its role in directing implantation and placental development is becoming more apparent. This highlights that the paternal contribution to pregnancy health can last well after conception. While this connection is now gaining appreciation, there needs to be a move to defining the underlying mechanisms involved. Animal models provide an ideal opportunity to manipulate the reproductive environment, both of the father and the mother. Use of rodents afford unappalled insight into the genomic and epigenetic mechanisms involved, while farm and domestic animals provide data from models who's pregnancies are more akin to that of humans. We also believe that a significant insight can be gained from the large body of human ART data that now exists. Here, assisted reproduction practices are routinely conducted in a seminal plasma free environment, while the embryos are often transferred to a uterine environment that has not been exposed recently to the paternal semen. However, while a detailed history regarding the woman is often taken, information about the father is not routinely collected. Therefore, a more comprehensive focus on the role a father plays in gestational dynamics is needed. We believe that providing detailed lifestyle information to both the intending father will dramatically improve both their reproductive health, the health of their offspring and the health of the mother during pregnancy.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Funding

A J W and his research are supported by funding from the BBSRC (BB/R003556/1).

Author contribution statement

A K H, E E, H L M and A J W all contributed to the conception, design, writing and editing of this narrative review.

References

Alio AP, Salihu HM, Mcintosh C, August EM, Weldeselasse H, Sanchez E & Mbah AK 2012 The effect of paternal age on fetal birth outcomes. *American Journal of Men's Health* **6** 427–435. (https://doi.org/10.1177/1557988312440718)

Allen CP, Marconi N, Mclernon DJ, Bhattacharya S & Maheshwari A 2020 Outcomes of pregnancies using donor sperm compared with those using partner sperm: systematic review and meta-analysis. *Human Reproduction Update* **27** 190–211. (https://doi.org/10.1093/humupd/dmaa030)

Aston KI, Uren PJ, Jenkins TG, Horsager A, Cairns BR, Smith AD & Carrell DT 2015 Aberrant sperm DNA methylation predicts male fertility status and embryo quality. *Fertility and Sterility* **104** 1388.e1–1397.e5. (https://doi.org/10.1016/j.fertnstert.2015.08.019)

Auroux M, Nawar NN, Naguib M, Baud M & Lapaquellerie N 1998 Post-pubescent to mature fathers: increase in progeny quality? *Human Reproduction* **13** 55–59. (https://doi.org/10.1093/humrep/13.1.55)

Bakos HW, Henshaw RC, Mitchell M & Lane M 2011 Paternal body mass index is associated with decreased blastocyst development and reduced live birth rates following assisted reproductive technology. *Fertility and Sterility* **95** 1700–1704. (https://doi.org/10.1016/j.fertnstert.2010.11.044)

Basso O, Christensen K & Olsen J 2001 Higher risk of pre-eclampsia after change of partner. An effect of longer interpregnancy intervals? *Epidemiology* **12** 624–629. (https://doi.org/10.1097/00001648-200111000-00008)

Benchaib M, Braun V, Ressnikof D, Lornage J, Durand P, Niveleau A & Guerin JF 2005 Influence of global sperm DNA methylation on IVF results. *Human Reproduction* **20** 768–773. (https://doi.org/10.1093/humrep/deh684)

Binder NK, Beard SA, Kaitu'u-Lino TJ, Tong S, Hannan NJ & Gardner DK 2015*a* Paternal obesity in a rodent model affects placental gene expression in a sex-specific manner. *Reproduction* **149** 435–444. (https://doi.org/10.1530/REP-14-0676)

Binder NK, Sheedy JR, Hannan NJ & Gardner DK 2015*b* Male obesity is associated with changed spermatozoa Cox4i1 mRNA level and altered seminal vesicle fluid composition in a mouse model. *Molecular Human Reproduction* **21** 424–434. (https://doi.org/10.1093/molehr/gav010)

Bowen JM, Chamley L, Keelan JA & Mitchell MD 2002 Cytokines of the placenta and extra-placental membranes: roles and regulation during human pregnancy and parturition. *Placenta* **23** 257–273. (https://doi.org/10.1053/plac.2001.0782)

Brennan LJ, Morton JS & Davidge ST 2014 Vascular dysfunction in preeclampsia. *Microcirculation* **21** 4–14. (https://doi.org/10.1111/micc.12079)

Brett KE, Ferraro ZM, Yockell-Lelievre J, Gruslin A & Adamo KB 2014 Maternal-fetal nutrient transport in pregnancy pathologies: the role of the placenta. *International Journal of Molecular Sciences* **15** 16153–16185. (https://doi.org/10.3390/ijms150916153)

Bromfield JJ, Schjenken JE, Chin PY, Care AS, Jasper MJ & Robertson SA 2014 Maternal tract factors contribute to paternal seminal fluid impact on metabolic phenotype in offspring. *PNAS* **111** 2200–2205. (https://doi.org/10.1073/pnas.1305609111)

Brosens IA, Robertson WB & Dixon HG 1972 The role of the spiral arteries in the pathogenesis of preeclampsia. *Obstetrics and Gynecology Annual* **1** 177–191.

Cartwright JE, Fraser R, Leslie K, Wallace AE & James JL 2010 Remodelling at the maternal-fetal interface: relevance to human pregnancy disorders. *Reproduction* **140** 803–813. (https://doi.org/10.1530/REP-10-0294)

Casagrande SS, Linder B & Cowie CC 2018 Prevalence of gestational diabetes and subsequent Type 2 diabetes among U.S. women. *Diabetes Research and Clinical Practice* **141** 200–208. (https://doi.org/10.1016/j.diabres.2018.05.010)

Catalano PM, Hoegh M, Minium J, Huston-Presley L, Bernard S, Kalhan S & Hauguel-De Mouzon S 2006 Adiponectin in human pregnancy: implications for regulation of glucose and lipid metabolism. *Diabetologia* **49** 1677–1685. (https://doi.org/10.1007/s00125-006-0264-x)

Chapman AB, Abraham WT, Zamudio S, Coffin C, Merouani A, Young D, Johnson A, Osorio F, Goldberg C, Moore LG *et al*. 1998 Temporal relationships between hormonal and hemodynamic changes in early human pregnancy. *Kidney International* **54** 2056–2063. (https://doi.org/10.1046/j.1523-1755.1998.00217.x)

Chavarro JE, Furtado J, Toth TL, Ford J, Keller M, Campos H & Hauser R 2011 Trans-fatty acid levels in sperm are associated with sperm concentration among men from an infertility clinic. *Fertility and Sterility* **95** 1794–1797. (https://doi.org/10.1016/j.fertnstert.2010.10.039)

Chen Q, Yan M, Cao Z, Li X, Zhang Y, Shi J, Feng GH, Peng H, Zhang X, Zhang Y *et al*. 2016 Sperm tsRNAs contribute to intergenerational inheritance of an acquired metabolic disorder. *Science* **351** 397–400. (https://doi.org/10.1126/science.aad7977)

Christoforou ER & Sferruzzi-Perri AN 2020 Molecular mechanisms governing offspring metabolic programming in rodent models of in utero stress. *Cellular and Molecular Life Sciences* **77** 4861–4898. (https://doi.org/10.1007/s00018-020-03566-z)

Claycombe-Larson KG, Bundy AN & Roemmich JN 2020 Paternal high-fat diet and exercise regulate sperm miRNA and histone methylation to modify placental inflammation, nutrient transporter mRNA expression and fetal weight in a sex-dependent manner. *Journal of Nutritional Biochemistry* **81** 108373. (https://doi.org/10.1016/j.jnutbio.2020.108373)

Colaco S & Sakkas D 2018 Paternal factors contributing to embryo quality. *Journal of Assisted Reproduction and Genetics* **35** 1953–1968. (https://doi.org/10.1007/s10815-018-1304-4)

Constância M, Hemberger M, Hughes J, Dean W, Ferguson-Smith A, Fundele R, Stewart F, Kelsey G, Fowden A, Sibley C *et al*. 2002 Placental-specific IGF-II is a major modulator of placental and fetal growth. *Nature* **417** 945–948. (https://doi.org/10.1038/nature00819)

Crawford G, Ray A, Gudi A, Shah A & Homburg R 2015 The role of seminal plasma for improved outcomes during in vitro fertilization treatment: review of the literature and meta-analysis. *Human Reproduction Update* **21** 275–284. (https://doi.org/10.1093/humupd/dmu052)

Crews JK, Herrington JN, Granger JP & Khalil RA 2000 Decreased endothelium-dependent vascular relaxation during reduction of uterine perfusion pressure in pregnant rat. *Hypertension* **35** 367–372. (https://doi.org/10.1161/01.hyp.35.1.367)

Cunningham MW & LaMarca B 2018 Risk of cardiovascular disease, end-stage renal disease, and stroke in postpartum women and their fetuses after a hypertensive pregnancy. *American Journal of Physiology: Regulatory, Integrative and Comparative Physiology* **315** R521–R528. (https://doi.org/10.1152/ajpregu.00218.2017)

Denomme MM, Parks JC, Mccallie BR, Mccubbin NI, Schoolcraft WB & Katz-Jaffe MG 2020 Advanced paternal age directly impacts mouse embryonic placental imprinting. *PLoS ONE* **15** e0229904. (https://doi.org/10.1371/journal.pone.0229904)

Dimasuay KG, Boeuf P, Powell TL & Jansson T 2016 Placental responses to changes in the maternal environment determine fetal growth. *Frontiers in Physiology* **7** 12. (https://doi.org/10.3389/fphys.2016.00012)

Duley L 2009 The global impact of pre-eclampsia and eclampsia. *Seminars in Perinatology* **33** 130–137. (https://doi.org/10.1053/j.semperi.2009.02.010)

Einarsson JI, Sangi-Haghpeykar H & Gardner MO 2003 Sperm exposure and development of preeclampsia. *American Journal of Obstetrics and Gynecology* **188** 1241–1243. (https://doi.org/10.1067/mob.2003.401)

Eisenberg ML, Kim S, Chen Z, Sundaram R, Schisterman EF & Louis GM 2015 The relationship between male BMI and waist circumference

on semen quality: data from the LIFE study. *Human Reproduction* **30** 493–494. (https://doi.org/10.1093/humrep/deu322)

Ernst S, Demirci C, Valle S, Velazquez-Garcia S & Garcia-Ocana A 2011 Mechanisms in the adaptation of maternal beta-cells during pregnancy. *Diabetes Management* **1** 239–248. (https://doi.org/10.2217/dmt.10.24)

Eskild A, Romundstad PR & Vatten LJ 2009 Placental weight and birthweight: does the association differ between pregnancies with and without preeclampsia? *American Journal of Obstetrics and Gynecology* **201** 595.e1–595.e5. (https://doi.org/10.1016/j.ajog.2009.06.003)

Frattarelli JL, Miller KA, Miller BT, Elkind-Hirsch K & Scott Jr RT 2008 Male age negatively impacts embryo development and reproductive outcome in donor oocyte assisted reproductive technology cycles. *Fertility and Sterility* **90** 97–103. (https://doi.org/10.1016/j.fertnstert.2007.06.009)

Fullston T, Ohlsson Teague EM, Palmer NO, Deblasio MJ, Mitchell M, Corbett M, print CG, owens JA & lane M 2013 Paternal obesity initiates metabolic disturbances in two generations of mice with incomplete penetrance to the F2 generation and alters the transcriptional profile of testis and sperm microRNA content. *FASEB Journal* **27** 4226–4243. (https://doi.org/10.1096/fj.12-224048)

Galaviz-Hernandez C, Sosa-Macias M, Teran E, Garcia-Ortiz JE & Lazalde-Ramos BP 2018 Paternal determinants in preeclampsia. *Frontiers in Physiology* **9** 1870. (https://doi.org/10.3389/fphys.2018.01870)

Gallo LA, Tran M, Moritz KM, Mazzuca MQ, Parry LJ, Westcott KT, Jefferies AJ, Cullen-McEwen LA & Wlodek ME 2012 Cardio-renal and metabolic adaptations during pregnancy in female rats born small: implications for maternal health and second generation fetal growth. *Journal of Physiology* **590** 617–630. (https://doi.org/10.1113/jphysiol.2011.219147)

Goffin SM, Derraik JGB, Groom KM & Cutfield WS 2018 Maternal pre-eclampsia and long-term offspring health: is there a shadow cast? *Pregnancy Hypertension* **12** 11–15. (https://doi.org/10.1016/j.preghy.2018.02.003)

Gonzalez-Comadran M, Urresta Avila J, Saavedra Tascon A, Jimenez R, Sola I, Brassesco M, Carreras R & Checa MÁ 2014 The impact of donor insemination on the risk of preeclampsia: a systematic review and meta-analysis. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* **182** 160–166. (https://doi.org/10.1016/j.ejogrb.2014.09.022)

Hammoud SS, Nix DA, Zhang H, Purwar J, Carrell DT & Cairns BR 2009 Distinctive chromatin in human sperm packages genes for embryo development. *Nature* **460** 473–478. (https://doi.org/10.1038/nature08162)

Hammoud SS, Nix DA, Hammoud AO, Gibson M, Cairns BR & Carrell DT 2011 Genome-wide analysis identifies changes in histone retention and epigenetic modifications at developmental and imprinted gene loci in the sperm of infertile men. *Human Reproduction* **26** 2558–2569. (https://doi.org/10.1093/humrep/der192)

Hanson MA & Gluckman PD 2008 Developmental origins of health and disease: new insights. *Basic and Clinical Pharmacology and Toxicology* **102** 90–93. (https://doi.org/10.1111/j.1742-7843.2007.00186.x)

Harlap S, Paltiel O, Deutsch L, Knaanie A, Masalha S, Tiram E, Caplan LS, Malaspina D & Friedlander Y 2002 Paternal age and preeclampsia. *Epidemiology* **13** 660–667. (https://doi.org/10.1097/00001648-200211000-00010)

Hemberger M 2007 Epigenetic landscape required for placental development. *Cellular and Molecular Life Sciences* **64** 2422–2436. (https://doi.org/10.1007/s00018-007-7113-z)

Hunter S & Robson SC 1992 Adaptation of the maternal heart in pregnancy. *British Heart Journal* **68** 540–543. (https://doi.org/10.1136/hrt.68.12.540)

Hurley EG & DeFranco EA 2017 Influence of paternal age on perinatal outcomes. *American Journal of Obstetrics and Gynecology* **217** 566.e1–566.e6. (https://doi.org/10.1016/j.ajog.2017.07.034)

Jansson T, Myatt L & Powell TL 2009 The role of trophoblast nutrient and ion transporters in the development of pregnancy complications and adult disease. *Current Vascular Pharmacology* **7** 521–533. (https://doi.org/10.2174/157016109789043982)

Johansson M, Bromfield JJ, Jasper MJ & Robertson SA 2004 Semen activates the female immune response during early pregnancy in mice. *Immunology* **112** 290–300. (https://doi.org/10.1111/j.1365-2567.2004.01876.x)

Kasman AM, Zhang CA, Li S, Stevenson DK, Shaw GM & Eisenberg ML 2020 Association of preconception paternal health on perinatal outcomes: analysis of U.S. claims data. *Fertility and Sterility* **113** 947–954. (https://doi.org/10.1016/j.fertnstert.2019.12.026)

Khandwala YS, Baker VL, Shaw GM, Stevenson DK, Lu Y & Eisenberg ML 2018 Association of paternal age with perinatal outcomes between 2007 and 2016 in the United States: population based cohort study. *BMJ* **363** k4372. (https://doi.org/10.1136/bmj.k4372)

Kho EM, Mccowan LM, North RA, Roberts CT, Chan E, Black MA, Taylor RS, Dekker GA & SCOPE Consortium 2009 Duration of sexual relationship and its effect on preeclampsia and small for gestational age perinatal outcome. *Journal of Reproductive Immunology* **82** 66–73. (https://doi.org/10.1016/j.jri.2009.04.011)

Kim SM & Kim JS 2017 A review of mechanisms of implantation. *Development and Reproduction* **21** 351–359. (https://doi.org/10.12717/DR.2017.21.4.351)

Kingdom JC, Audette MC, Hobson SR, Windrim RC & Morgen E 2018 A placenta clinic approach to the diagnosis and management of fetal growth restriction. *American Journal of Obstetrics and Gynecology* **218** S803–S817. (https://doi.org/10.1016/j.ajog.2017.11.575)

Klonoff-Cohen HS, Savitz DA, Cefalo RC & Mccann MF 1989 An epidemiologic study of contraception and preeclampsia. *JAMA* **262** 3143–3147.

Kort HI, Massey JB, Elsner CW, Mitchell-Leef D, Shapiro DB, Witt MA & Roudebush WE 2006 Impact of body mass index values on sperm quantity and quality. *Journal of Andrology* **27** 450–452. (https://doi.org/10.2164/jandrol.05124)

Kublickiene K-R, Grunewald C, Lindblom B & Nisell H 1998 Myogenic and endothelial properties of myometrial resistance arteries from women with preeclampsia. *Hypertension in Pregnancy* **17** 271–281. (https://doi.org/10.3109/10641959809009600)

Kublickiene KR, Lindblom B, Krüger K & Nisell H 2000 Preeclampsia: evidence for impaired shear stress-mediated nitric oxide release in uterine circulation. *American Journal of Obstetrics and Gynecology* **183** 160–166. (https://doi.org/10.1067/mob.2000.105820)

Kyrou D, Kolibianakis EM, Devroey P & Fatemi HM 2010 Is the use of donor sperm associated with a higher incidence of preeclampsia in women who achieve pregnancy after intrauterine insemination? *Fertility and Sterility* **93** 1124–1127. (https://doi.org/10.1016/j.fertnstert.2008.12.021)

Lambrot R, Xu C, Saint-Phar S, Chountalos G, Cohen T, Paquet M, Suderman M, Hallett M & Kimmins S 2013 Low paternal dietary folate alters the mouse sperm epigenome and is associated with negative pregnancy outcomes. *Nature Communications* **4** 2889. (https://doi.org/10.1038/ncomms3889)

Lash GE, Robson SC & Bulmer JN 2010 Review: functional role of uterine natural killer (uNK) cells in human early pregnancy decidua. *Placenta* **31** (Supplement) S87–S92. (https://doi.org/10.1016/j.placenta.2009.12.022)

Li DK & Wi S 2000 Changing paternity and the risk of preeclampsia/eclampsia in the subsequent pregnancy. *American Journal of Epidemiology* **151** 57–62. (https://doi.org/10.1093/oxfordjournals.aje.a010122)

Li W, Mata KM, Mazzuca MQ & Khalil RA 2014 Altered matrix metalloproteinase-2 and -9 expression/activity links placental ischemia and anti-angiogenic sFlt-1 to uteroplacental and vascular remodeling and collagen deposition in hypertensive pregnancy. *Biochemical Pharmacology* **89** 370–385. (https://doi.org/10.1016/j.bcp.2014.03.017)

Liu S, Diao L, Huang C, Li Y, Zeng Y & Kwak-Kim JYH 2017 The role of decidual immune cells on human pregnancy. *Journal of Reproductive Immunology* **124** 44–53. (https://doi.org/10.1016/j.jri.2017.10.045)

Lotti F, Corona G, Colpi GM, Filimberti E, Degli Innocenti S, Mancini M, Baldi E, Noci I, Forti G, adorini L *et al*. 2011 Elevated body mass index correlates with higher seminal plasma interleukin 8 levels and ultrasonographic abnormalities of the prostate in men attending an andrology clinic for infertility. *Journal of Endocrinological Investigation* **34** e336–e342. (https://doi.org/10.3275/7855)

Lyall F, Robson SC & Bulmer JN 2013 Spiral artery remodeling and trophoblast invasion in preeclampsia and fetal growth restriction: relationship to clinical outcome. *Hypertension* **62** 1046–1054. (https://doi.org/10.1161/HYPERTENSIONAHA.113.01892)

Marconi G, Auge L, Oses R, Quintana R, Raffo F & Young E 1989 Does sexual intercourse improve pregnancy rates in gamete intrafallopian

transfer? *Fertility and Sterility* **51** 357–359. (https://doi.org/10.1016/s0015-0282(16)60507-1)

Matoba S, Nakamuta S, Miura K, Hirose M, Shiura H, Kohda T, Nakamuta N & Ogura A 2019 Paternal knockout of Slc38a4/SNAT4 causes placental hypoplasia associated with intrauterine growth restriction in mice. *PNAS* **116** 21047–21053. (https://doi.org/10.1073/pnas.1907884116)

Mitchell M, Bakos HW & Lane M 2011 Paternal diet-induced obesity impairs embryo development and implantation in the mouse. *Fertility and Sterility* **95** 1349–1353. (https://doi.org/10.1016/j.fertnstert.2010.09.038)

Morgan HL & Watkins AJ 2020 The influence of seminal plasma on offspring development and health. *Seminars in Cell and Developmental Biology* **97** 131–137. (https://doi.org/10.1016/j.semcdb.2019.06.008)

Morgan HL, Aljumah A, Rouillon C & Watkins AJ 2020 Paternal low protein diet and the supplementation of methyl-donors impact fetal growth and placental development in mice. *Placenta* **103** 124–133. (https://doi.org/10.1016/j.placenta.2020.10.020)

Nijs H & Benhalima K 2020 Gestational diabetes mellitus and the long-term risk for glucose intolerance and overweight in the offspring: a narrative review. *Journal of Clinical Medicine* **9** 599. (https://doi.org/10.3390/jcm9020599)

Oh-McGinnis R, Bogutz AB, Lee KY, Higgins MJ & Lefebvre L 2010 Rescue of placental phenotype in a mechanistic model of Beckwith-Wiedemann syndrome. *BMC Developmental Biology* **10** 50. (https://doi.org/10.1186/1471-213X-10-50)

Pijnenborg R, Anthony J, Davey DA, Rees A, Tiltman A, Vercruysse L & Van Assche A 1991 Placental bed spiral arteries in the hypertensive disorders of pregnancy. *British Journal of Obstetrics and Gynaecology* **98** 648–655. (https://doi.org/10.1111/j.1471-0528.1991.tb13450.x)

Pijnenborg R, Vercruysse L & Hanssens M 2006 The uterine spiral arteries in human pregnancy: facts and controversies. *Placenta* **27** 939–958. (https://doi.org/10.1016/j.placenta.2005.12.006)

Reichenberg A, Gross R, Weiser M, Bresnahan M, Silverman J, Harlap S, Rabinowitz J, Shulman C, Malaspina D, Lubin G *et al*. 2006 Advancing paternal age and autism. *Archives of General Psychiatry* **63** 1026–1032. (https://doi.org/10.1001/archpsyc.63.9.1026)

Robertson SA, Bromfield JJ & Tremellen KP 2003 Seminal 'priming' for protection from pre-eclampsia-a unifying hypothesis. *Journal of Reproductive Immunology* **59** 253–265. (https://doi.org/10.1016/s0165-0378(03)00052-4)

Robertson SA, Prins JR, Sharkey DJ & Moldenhauer LM 2013 Seminal fluid and the generation of regulatory T cells for embryo implantation. *American Journal of Reproductive Immunology* **69** 315–330. (https://doi.org/10.1111/aji.12107)

Robson A, Harris LK, Innes BA, Lash GE, Aljunaidy MM, Aplin JD, Baker PN, Robson SC & Bulmer JN 2012 Uterine natural killer cells initiate spiral artery remodeling in human pregnancy. *FASEB Journal* **26** 4876–4885. (https://doi.org/10.1096/fj.12-210310)

Sadat Z, Abedzadeh Kalahroudi M & Saberi F 2012 The effect of short duration sperm exposure on development of preeclampsia in primigravid women. *Iranian Red Crescent Medical Journal* **14** 20–24.

Sanghavi M & Rutherford JD 2014 Cardiovascular physiology of pregnancy. *Circulation* **130** 1003–1008. (https://doi.org/10.1161/CIRCULATIONAHA.114.009029)

Sattar N & Greer IA 2002 Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening? *BMJ* **325** 157–160. (https://doi.org/10.1136/bmj.325.7356.157)

Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels J, Gülmezoglu AM, Temmerman M & Alkema L 2014 Global causes of maternal death: a WHO systematic analysis. *Lancet: Global Health* **2** e323–e333. (https://doi.org/10.1016/S2214-109X(14)70227-X)

Schjenken JE & Robertson SA 2020 The female response to seminal fluid. *Physiological Reviews* **100** 1077–1117. (https://doi.org/10.1152/physrev.00013.2018)

Schjenken JE, Glynn DJ, Sharkey DJ & Robertson SA 2015 TLR4 signaling is a major mediator of the female tract response to seminal fluid in mice. *Biology of Reproduction* **93** 68. (https://doi.org/10.1095/biolreprod.114.125740)

Sferruzzi-Perri AN & Camm EJ 2016 The programming power of the placenta. *Frontiers in Physiology* **7** 33. (https://doi.org/10.3389/fphys.2016.00033)

Sferruzzi-Perri AN, Macpherson AM, Roberts CT & Robertson SA 2009 Csf2 null mutation alters placental gene expression and trophoblast glycogen cell and giant cell abundance in mice. *Biology of Reproduction* **81** 207–221. (https://doi.org/10.1095/biolreprod.108.073312)

Skjaerven R, Wilcox AJ & Lie RT 2002 The interval between pregnancies and the risk of preeclampsia. *New England Journal of Medicine* **346** 33–38. (https://doi.org/10.1056/NEJMoa011379)

Soma-Pillay P, Nelson-Piercy C, Tolppanen H & Mebazaa A 2016 Physiological changes in pregnancy. *Cardiovascular Journal of Africa* **27** 89–94. (https://doi.org/10.5830/CVJA-2016-021)

Steegers EA, Von Dadelszen P, Duvekot JJ & Pijnenborg R 2010 Pre-eclampsia. *Lancet* **376** 631–644. (https://doi.org/10.1016/S0140-6736(10)60279-6)

Strom-Roum EM, Haavaldsen C, Tanbo TG & Eskild A 2013 Paternal age, placental weight and placental to birthweight ratio: a population-based study of 590,835 pregnancies. *Human Reproduction* **28** 3126–3133. (https://doi.org/10.1093/humrep/det299)

Tandberg A, Klungsøyr K, Romundstad LB & Skjærven R 2015 Pre-eclampsia and assisted reproductive technologies: consequences of advanced maternal age, interbirth intervals, new partner and smoking habits. *BJOG* **122** 915–922. (https://doi.org/10.1111/1471-0528.13051)

Tremellen KP, Valbuena D, Landeras J, Ballesteros A, Martinez J, Mendoza S, Norman RJ, Robertson SA & Simon C 2000 The effect of intercourse on pregnancy rates during assisted human reproduction. *Human Reproduction* **15** 2653–2658. (https://doi.org/10.1093/humrep/15.12.2653)

Wang JX, Knottnerus AM, Schuit G, Norman RJ, Chan A & Dekker GA 2002 Surgically obtained sperm, and risk of gestational hypertension and pre-eclampsia. *Lancet* **359** 673–674. (https://doi.org/10.1016/S0140-6736(02)07804-2)

Watkins AJ & Sinclair KD 2014 Paternal low protein diet affects adult offspring cardiovascular and metabolic function in mice. *American Journal of Physiology: Heart and Circulatory Physiology* **306** H1444–H1452. (https://doi.org/10.1152/ajpheart.00981.2013)

Watkins AJ, Sirovica S, Stokes B, Isaacs M, Addison O & Martin RA 2017 Paternal low protein diet programs preimplantation embryo gene expression, fetal growth and skeletal development in mice. *Biochimica et Biophysica Acta: Molecular Basis of Disease* **1863** 1371–1381. (https://doi.org/10.1016/j.bbadis.2017.02.009)

Watkins AJ, Dias I, Tsuro H, Allen D, Emes RD, Moreton J, Wilson R, Ingram RJM & Sinclair KD 2018 Paternal diet programs offspring health through sperm- and seminal plasma-specific pathways in mice. *PNAS* **115** 10064–10069. (https://doi.org/10.1073/pnas.1806333115)

Watkins AJ, Rubini E, Hosier ED & Morgan HL 2020 Paternal programming of offspring health. *Early Human Development* **150** 105185. (https://doi.org/10.1016/j.earlhumdev.2020.105185)

Zeng Z, Liu F & Li S 2017 Metabolic adaptations in pregnancy: a review. *Annals of Nutrition and Metabolism* **70** 59–65. (https://doi.org/10.1159/000459633)

Zhang J & Patel G 2007 Partner change and perinatal outcomes: a systematic review. *Paediatric and Perinatal Epidemiology* **21** (Supplement 1) 46–57. (https://doi.org/10.1111/j.1365-3016.2007.00837.x)

Received 12 November 2020
First decision 24 December 2020
Revised Manuscript received 8 January 2021
Accepted 5 February 2021