Impacts of paternal environment and lifestyle on maternal health during pregnancy

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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.

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 complicates 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 2003).
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. 2015a). 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 (PIGF), 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 (Sierruzzi-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 (Galzo 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 vasodilatation (Brooks 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 adipoikines 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 (Sierruzzi-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. 2015a, 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.
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 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.

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).
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. 2015b), 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.

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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.

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