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5

Intergenerational trends in reproduction: Infertility and pregnancy loss

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A B S T R A C T

This review article summarises the evidence for intergenerational trends observed to date within infertility and pregnancy loss. There appears to be evidence of intergenerational trends between mothers and daughters for the age at menopause, endometriosis, polycystic ovarian syndrome (PCOS), male factor infertility and miscarriage. At present, there is no evidence for a predisposition to stillbirth between mothers and daughters. One study found an association with familial predisposition for ectopic pregnancy. Very few studies have considered the potential for paternal transmission of risk of infertility or pregnancy loss. The majority of studies to date have significant limitations because of their observational design, risk of recall bias and risk of confounding. Therefore, high-quality well-designed research, with multi-centre collaboration and utilisation of registry-based data sources and individual patient data, is needed to understand whether infertility and pregnancy loss may have heritable factors. Epidemiological findings need to be followed up and investigated with translational research to determine the possible causalities as well as any implications for clinical practice.

Introduction

The recognition of intergenerational patterns of diseases has led to great strides in the understanding of genetic predisposition of diseases and fuelled a number of hypotheses on the heritability of

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reproductive outcomes. Conditions such as pre-eclampsia and preterm birth appear to show a clear association with family history [1–4]. Anecdotally, women often wonder whether their own risk of adverse pregnancy outcomes may be exacerbated by a similar history in their mothers or sisters. The inheritance of adverse outcomes in pregnancy may also be possible through the male line [5]. Whether such familial patterns are due to genetic or epigenetic mutations or caused by environmental (including in utero exposures), socioeconomic and lifestyle risks remain uncertain. It is plausible that infertility may be influenced by genetics as well as environmental and lifestyle factors, all of which could be transmitted through generations of the same family. Given the potential for shared pathophysiology between conditions of placental dysfunction such as pre-eclampsia and pregnancy loss, it is also possible that familial predisposition may similarly exist for pregnancy loss. Infertility and pregnancy loss, including late losses (stillbirth), are often unexplained; thus further research on the aetiology is needed to understand these adverse reproductive outcomes. This article will summarise the current evidence and hypotheses for intergenerational trends observed in infertility and pregnancy loss. Pregnancy loss will be considered across the gestational spectrum, with miscarriage defined in this review as spontaneous pregnancy loss until 23 + 6 weeks of gestation, and stillbirth can be defined as pregnancy loss from 24 weeks of gestation, unless otherwise specified in the text. Intergenerational trends will be considered throughout this review by considering the following potential mechanisms of familial transmission:

(1) Genetic or epigenetic inheritance.
(2) Familial tendencies for particular behaviours, lifestyles or environmental exposures.
(3) In utero exposures.

Sanchez-Garrido et al. [6] summarise in Fig. 1 the potential environmental influences and intergenerational early programming which may affect reproductive function in the offspring.

Infertility

Infertility, defined as the inability to conceive after 12 months of regular, unprotected intercourse, affects 1 in 7 couples [7,8]. Infertility is broadly categorised into male factor, female factor (ovulatory dysfunction, tubal or uterine disease) and unexplained infertility, though infertility for many couples is multifactorial. Unexplained infertility, where standard tests of ovulation, semen parameters and tubal patency are normal, affects around 25% of couples [7]. Intergenerational effects predisposing couples to infertility could conceivably manifest through direct genetic transmission, familial tendencies to particular lifestyle, diet or environmental exposures or in utero exposures affecting the later reproductive health of the foetus.

Ovulatory dysfunction

As oocyte numbers are decided in utero, it is conceivable that maternal exposures during pregnancy could impact the daughter's and potentially even the grandchildren's reproductive outcomes. Ye et al. [9] suggest that the exposure to smoking in utero exerted a small potential effect on the female offspring fertility in a study of over 40,000 women. However, two subsequent cohort studies failed to find any association with fertility in women having in utero exposure to maternal smoking [10,11]. Other reviews have also suggested that the environmental exposures to chemicals, endocrine disruptors, as well as radiation may detrimentally affect offspring reproductive outcomes including time of conception; however, evidence is limited [12,13].

Anti-mullerian hormone (AMH) is a recognised marker of ovarian reserve which reduces with advancing age [14]. Eubanks et al. [15] suggest that vitamin exposure in utero was associated with high AMH levels in women trying to conceive, and conversely, caffeine exposure in utero was associated with low AMH levels. Their study was, however, at high risk of recall bias because of self-reported and historical exposures [15]. Rosen et al. [16] and Bentzen et al. [17] reported that daughter's declining ovarian reserve (AMH level [17] and antral follicle count [16]) was inversely associated with mother's

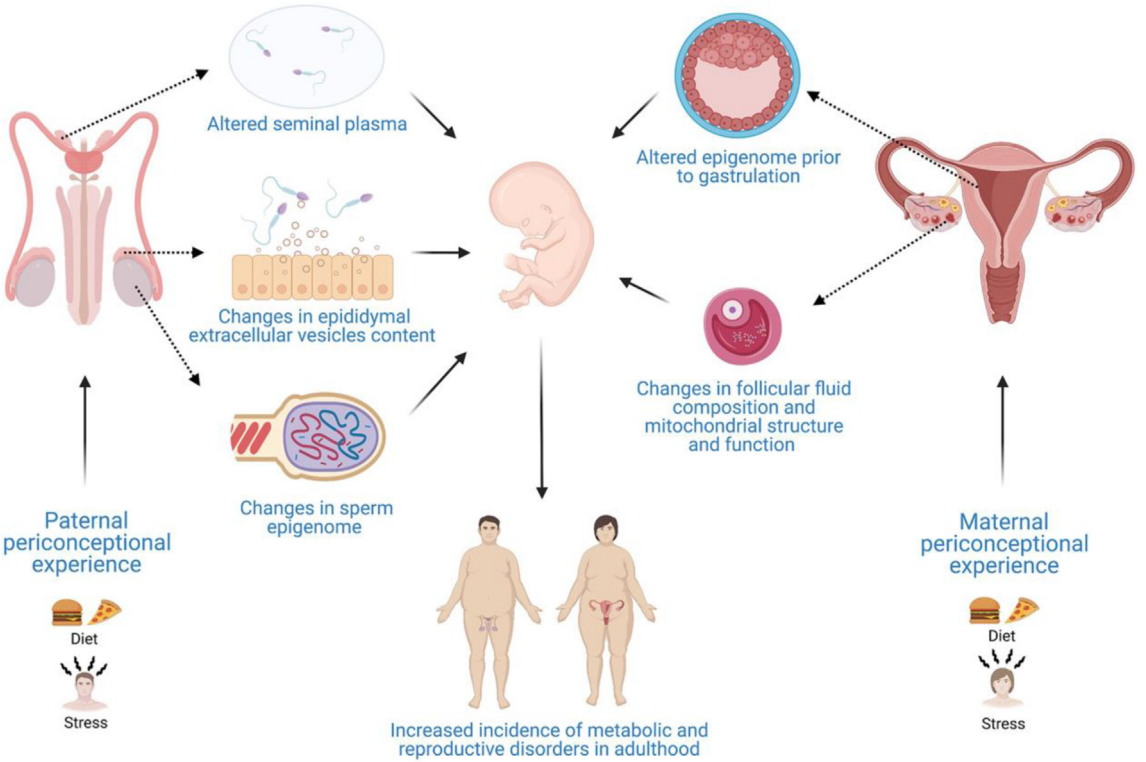

Fig. 1. Periconceptional programming of reproductive function. A schematic is presented of the potential mechanisms that may underlie the impact of environmental fluctuations during the periconceptional period on adult reproductive function in the offspring. The paternal environment around conception has been reported to alter seminal plasma composition and induce changes in the sperm epigenome and epididymal extracellular vesicle content; perturbations that may lead to the development of reproductive disorders in adult offspring. Similarly, the maternal environment around conception has also been shown to alter the epigenome of the developing offspring and the composition of follicular fluid; changes that may also compromise the correct development of the embryo and increase the occurrence of reproductive abnormalities in adulthood. Figure created with BioRender (San Francisco, CA, USA). *Reproduced with permission: Hum Reprod Update*, Volume 28, Issue 3, May–June 2022, Pages 346–375, [1] https://doi.org/10.1093/humupd/dmac005.

earlier age at menopause. This suggests that mothers who went through menopause earlier were more likely to have daughters with lower ovarian reserve at the time of fertility investigation. An epidemiological study suggested that there is a strong association between mothers and daughters experiencing premature or early menopause (<40 years old and <45 years old, respectively; odds ratio (OR) 6.02 (95% confidence interval (CI) 3.39 to 10.66)) [18]. Another study has suggested that there may be a genetic basis for predetermination of menopausal age [19]. Premature ovarian insufficiency (POI), whereby ovarian failure occurs below the age of 40, may have heritable factors [20]. It is reported that 4–31% of women with POI have an identifiable familial association where at least two women from the same family share the diagnosis; however, currently available studies have small sample sizes [20]. Fragile-X premutation carriers are at greater risk of POI, and the European Society for Human Reproduction and Embryology (ESHRE) recommends testing for fragile-X premutation in women with POI, as this can be the familial cause of POI [20]. However, other genetic predispositions to POI are largely unknown [20]. While the evidence base is uncertain, it may be that some women are predisposed to a reduction in ovarian reserve at younger ages [20].

The ovarian reserve declines with age; therefore, another possible explanation for any intergenerational trend in infertility may relate to age at first conception and the increasing trend for delaying childbearing in many societies. Basso et al. [21] found that women who were born to older mothers were more likely to be childless (dose–response seen from the age 25 years old advancing to mothers aged ≥35 years old where relative risk (RR) was 1.40 (95% CIs 1.31–1.50)). Reassuringly, a large cohort study in the US and Canada investigated the association between a mother's age at birth and her daughter's fertility and found that being born to a mother aged ≥35 years did not impact the daughter's fertility [22]. However the researchers did note that younger maternal age at birth (under 20 years old) appeared to be associated with reduced fertility in daughters [22]. The explanation for why such an association might exist with younger maternal age is unclear. The results from Reynolds et al. agreed with the findings that a mother's age at birth did not affect her daughter's fertility [23].

Gonadotropic dysfunction

Gonadotrophin and gonadotrophin receptor gene polymorphisms have been suggested as a potential pathophysiological mechanism for infertility [24]. The impact of such polymorphisms and whether these are heritable causes of infertility is not clear. There are recognised genetic conditions which lead to gonadotrophin deficiency; for example, there have been over sixty genes associated such as congenital hypogonadotropic hypogonadism (CHH) [25]. However, authors of a recent review suggest that further large-scale cohort studies are needed to delineate the inheritance pattern of many of the variants found for CHH [25]. Additionally, a systematic review published in 2022 summarises the effects of possible environmental exposures such as bisphenol A, nutritional factors and hormonal influences preconception, in utero and neonatal exposures. It also highlights growing evidence of the impact on puberty, gonadotrophin function and fertility [6]. All of these could result in intergenerational patterns of reduced fertility secondary to gonadotrophin dysfunction.

Male factor infertility

The effect of maternal smoking exposure in utero on male fertility is conflicting, though an association with reduced sperm concentration has been noted [26]. Another recent cohort study suggested that sons exposed to maternal smoking in utero had lower sperm counts, with an inverse dose–response relationship seen [27]. Interestingly, the sons of women who stopped smoking in early pregnancy experienced similar reductions in sperm counts, suggesting that the detrimental effect of maternal smoking may occur very early in foetal development or may have a preconceptual influence with no mitigation achieved by smoking cessation during early pregnancy [27]. A Swedish cohort study revealed that the sperm counts were lower in men with either a mother or father who smoked prenatally [28]. A review article summarised the transgenerational effects of paternal smoking and suggested that paternal smoking exposure is associated with foetal aneuploidies, DNA damage and de novo mutations which can be transmitted to the offspring through the sperm [29]. They estimate at a global scale that smoking may lead to millions of de novo mutations within the sperm through

transgenerational inheritance [29]. However, the evidence is limited; hence, further research is needed on the exposures in utero or preconception which may or may not affect the fertility of the sons [27].

Meschede et al. [30] suggest that male infertility may run in families. Researchers found that in couples undergoing intracytoplasmic sperm injection (ICSI), there was a greater association with family history of infertility in those with male factor infertility than the female factor [30]. They also noted that 1 in 15 of their included couples had fertility with a genetic basis and suggested that the infertile couples were likely to have fewer siblings than the fertile controls [30]. However, their study was small and at a risk of recall bias [30]. Another study suggests positive identification of three single-nucleotide polymorphisms (SNPs) which may be related to reduced spermatogenesis [31]. Another study of couples with recurrent miscarriage also found that male family history of infertility was greater in men with recurrent miscarriage, though results should be interpreted with caution as this was a small case–control study and risk of recall bias of familial exposure is high [32]. Overall, very little is known about the heritability of male factor infertility and thus family history is not yet a clinically useful tool to determine risk of infertility in men.

Polycystic ovarian syndrome

Polycystic ovarian syndrome (PCOS) is widely recognised to be associated with infertility and miscarriage. It is also linked to a heightened risk of cardiovascular diseases and metabolic disorders across the lifespan of affected women. Given its multi-system effects and impact on chronic health, it is plausible that PCOS could have heritable factors. An increased aggregation of PCOS between mothers and sisters (first-degree relatives) has been reported, where 40% of the women with PCOS had a positive family history of PCOS [33]. Furthermore, a systematic review identified familial trends in first-degree relatives for related conditions such as metabolic syndrome and dyslipidaemia [34]. A large genome-wide association study found 2 possible genetic variants associated with PCOS which could explain the familial patterns [35]. A recent study [36] has highlighted increased childhood morbidity in children born to women with PCOS. Whilst disadvantaged by generic limitations of observational studies, long-term follow-up studies should endeavour to determine whether children born to women with PCOS are at greater risk of PCOS or fertility effects in their own pregnancies to enable earlier screening and lifestyle education for this the most common endocrine disorders affecting women.

Endometriosis

Endometriosis is a benign condition whereby the endometrial tissue explants outside the uterus and is associated with infertility and can be associated with multiple sequalae such as dysmenorrhoea and chronic pelvic pain. It has been hypothesised that there may be a familial predisposition to endometriosis which may in turn account for intergenerational trends in infertility or miscarriage. A large Danish cohort study found that daughters born to mothers with endometriosis were twice as likely to develop endometriosis than daughters whose mothers had no history of endometriosis [37]. A study published in 1993 suggests that mothers and sisters of women with endometriosis had a sevenfold increased risk of having endometriosis [38]. Epidemiological evidence suggests heritability, but no clear causal pathway or definite genetic mutation has been isolated. Endometriosis is notoriously difficult to diagnose, and its aetiology is unknown; therefore, future research investigating any potential for genetic inheritance or intergenerational exposures is vital to improve our understanding of this condition.

Pregnancy loss

Miscarriage

Miscarriage affects 15% of pregnancies [39], and is defined as spontaneous loss of pregnancy prior to viability, though the definition of viability varies globally [39–42]. The criteria for recurrent miscarriage vary from 2 or more miscarriages [40] to 3 or more miscarriages [42]. It is thought that 1–2% of couples trying to conceive will have 3 or more consecutive miscarriages [39,42,43]. Most miscarriages

are thought to be because of foetal chromosomal abnormalities [44] but the cause of miscarriage can be multifactorial and is often unexplained. It has been widely hypothesised that there may be particular phenotypes and genotypes associated with recurrent miscarriage and that the risk of a miscarriage may be transmitted through generations of the same family [45].

Epidemiological studies suggest a possible familial predisposition to miscarriage transmitted through the female line [45–52]. The sisters of women with recurrent miscarriage were found to have a higher incidence of miscarriage than the normal population, but sisters-in-law did not [53]. Studies have found an association with particular human leukocyte antigen (HLA) Class II genotypes and the risk of recurrent miscarriage within first-degree female relatives [54,55]. Kolte et al. [46] published a study of couples with unexplained recurrent miscarriage and the association with siblings' reproductive history. The authors compared the cases to the nationally published population estimates of miscarriage risk in Denmark and suggested that sisters and sisters-in-law of women with recurrent unexplained miscarriage were twice as likely to suffer a miscarriage (OR 2.04 (95%CI 1.40–3.0)). A systematic review of observational studies summarising the literature on familial predisposition to miscarriage concluded that women with a history of miscarriage are more likely to report a family history of miscarriage [45]. However, most studies included self-reported data [45]. This raises a risk of recall bias as it is plausible that women with a history of miscarriage may be more likely to speak to family members to enquire regarding their relative's history of miscarriage. However, a register-based study investigating intergenerational risk of miscarriage in over 31,000 mother–daughter pairs found that women with mothers who had a history of miscarriage were more likely to have daughters with a miscarriage, though the association was small [51]. This eliminated the risk of recall bias as the study used routinely collected hospital data only in a population with low outmigration rate [56]. Furthermore, a *trans*-ethnic genome-wide association meta-analysis published in 2020 found 4 distinct susceptibility loci for sporadic and multiple consecutive miscarriage using a definition of recurrent miscarriage as 3 or more miscarriages [57]. Conversely, Kolte et al. [58] suggest that family history of miscarriage among first-degree relatives did not influence the chance of livebirth in women attending recurrent miscarriage clinics (with an existing personal history of 3 or more miscarriages). Of note, women with a family history of recurrent miscarriage were noted to be referred to the recurrent miscarriage clinic at a younger age in this population, suggesting that awareness of family history of miscarriage may influence presentation to reproductive healthcare [58]. Therefore, there is some evidence that there may be a familial predisposition to miscarriage through the female relatives, but further research is needed to confirm or refute this association.

It is plausible that a risk of miscarriage or recurrent miscarriages could be inherited through any of the possible causal pathways for miscarriage. For example, some women may inherit a thrombophilic tendency which puts them at greater risk of miscarriage such as a propensity to having antiphospholipid antibodies or Factor V Leiden, both associated with miscarriage risk [59–62]. Antiphospholipid syndrome (ALPS) is thought to be found in 15% of couples with recurrent miscarriages [42,59], and a recent paper suggests that there may be particular genotypes associated with obstetric APLS [63]. In addition, it is possible that shared lifestyle factors could be present between mothers and daughters such as smoking as it is recognised that parental smoking influences the chance of offspring smoking [64]. However, the findings by Woolner et al. [51] were adjusted for smoking, socioeconomic status and age of the daughters, suggesting that there remained an association between mothers and daughters after these key confounding factors were addressed.

It is possible that some families may be particularly susceptible to recurrent aneuploidies; however, studies to date largely refute this. Sullivan et al. [65] suggested that while aneuploidy was high in sporadic miscarriage, couples with recurrent miscarriage were less likely to have recurrent aneuploidy. This is echoed in another study which showed that the rate of euploid pregnancies miscarried was increased in couples with higher numbers of recurrent miscarriages, suggesting that the majority of couples with recurrent miscarriage were miscarrying foetuses with demonstrably normal karyotypes (Fig. 2) [66]. Whilst these studies do not rule out a small proportion of couples who may miscarry repeatedly because of a predisposition to aneuploidy, further research is needed to determine the foetal genome from the first miscarriage onwards and map to any other parental risks. This would enable detection of couples who might be at risk of repeated miscarriages because of aneuploidy as well as understanding how the loss of a euploid foetus may affect a couple's future risk of subsequent miscarriage.

It is estimated that 2–5% of couples with recurrent miscarriage will have a balanced translocation [42]. This could be a de novo translocation or an inherited structural translocation. A balanced translocation found in either parent can be passed onto the offspring which may consequently lead to an intergenerational increased risk of miscarriage.

A propensity to smoking appears to be transmitted from parents to children [64], though whether this propensity is purely because of environmental exposure or genetics is not clear. Epidemiological evidence suggests that smoking exposure in utero could affect reproductive outcomes such as miscarriage in a female offspring [10]. Many other environmental, chemical and occupational exposures are thought to contribute to the risk of miscarriage [39], but there is no clear evidence of familial patterns in such exposures in relation to miscarriage other than with cigarette smoking. It is therefore likely that in utero exposure could have a detrimental impact on a developing foetus' own reproductive function, but research is urgently needed to understand more about the effects of in utero exposures on future reproduction. Paternal obesity has been hypothesised as a potential route for epigenetic mutations in the offspring which could lead to changes in pregnancy outcome as well as offspring health, but more research is needed [67].

With advances in the understanding of possible endometrial factors, immunity, as well as the role of progesterone in miscarriage and recurrent miscarriage [39], it is possible that genes related to implantation, endometrial function and progesterone metabolism could be associated with a predisposition to miscarriage. Granne et al. [68] recently found that women with recurrent miscarriage had altered Treg gene transcriptomes – involved in T-cell regulation – though the clinical implications of such findings are not yet clear; they suggest women with recurrent miscarriage may have an altered genotype.

Pregnancy loss at any gestation increasingly appears to be related to lifelong health. The fact that recurrent first trimester miscarriage is associated with adverse cardiovascular health in later life could also suggest a heritable phenotype [69] – again this could be linked with a transmitted genotype, epigenetic mutations or specific lifestyle factors or heritability of metabolic conditions such as PCOS. Women who had 3 or more miscarriages before their first liveborn child had a significantly higher chance of having a parent with ischaemic heart disease (IHD) (HR 1.56 (95% CI 1.14 to 2.15)), shown in one observational study [69]. Additionally, a personal history of miscarriage, recurrent miscarriage or stillbirth conferred an increased risk of IHD in later life [70–72]. Having a stillbirth, and particularly a recurrent stillbirth, increases a woman's risk of adverse cardiovascular and renal health [73]. Given the

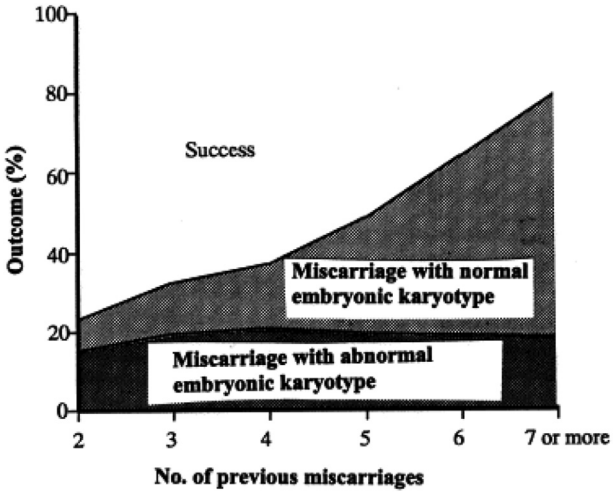

Fig. 2. Number of miscarriages according to embryonic karyotype analysis. Estimated miscarriage rates with normal and abnormal embryonic karyotypes if analyzed rate is 100%. The normal karyotype rate significantly increased with the number of previous miscarriages. The abnormal karyotype rate did not change with the number of previous miscarriages. *Reproduced with permission: Embryonic karyotype of abortuses in relation to the number of previous miscarriages. Fertility and Sterility* Volume 73 Issue 2 Pages 300–304 (February 2000) DOI: 10.1016/S0015-0282 (99)00495–1 [1].

proposed theory of endothelial dysfunction in miscarriage [74] and the possibility of intergenerational transmission of cardiovascular disease risk related to endothelial function, it is entirely plausible that there could be a familial predisposition to pregnancy disorders and losses associated to endothelial dysfunction. This compounds the theory that pregnancy loss or repeated pregnancy losses may be associated with a particular phenotype or genotype in women, who face risks not only in their pregnancies but also with regards to their long-term health.

Late miscarriages, which are defined as a pregnancy loss in the second trimester from >12 weeks until 23 + 6 weeks of gestation prior to the threshold of viability (though definitions again vary globally), account for 1–2% of all miscarriages [75]. There are clear similarities and potentially shared pathophysiology with late miscarriage and preterm birth as well as stillbirth. Preterm birth has repeatedly been shown to exhibit patterns of familial predisposition [4,76]. However at present we found no studies investigating a familial predisposition to late miscarriage in the published literature.

Predisposition to pregnancy loss (miscarriage and stillbirth) through the male line should be investigated in future epidemiological as well as translational research. Pre-eclampsia and growth restriction in the offspring have been associated with a father's history [2,5,77]. Another study tried to identify generational pathway of any genetic inheritance for pre-eclampsia risk using Swedish data and family pedigrees [1]. The researchers concluded, however, that the genetic predisposition to pre-eclampsia was primarily because of transmission of risk from mothers' and secondly from the foetus' own genotype [1]. In contrast, the increasing recognition of the impact that paternal age has on risk of miscarriage and recurrent miscarriage [78] suggests that it is possible that inherited factors could be passed through the male line which increase the risk of miscarriage. The authors of a small case–control study suggest a male familial association with miscarriage, though the study was of poor quality [32]. While we are increasingly beginning to recognise that sperm DNA fragmentation may have a potential role in recurrent miscarriage [79], our understanding of the potential intergenerational transmission of risk of miscarriage through the sperm is limited. More research is needed to determine whether there are familial patterns of miscarriage transmitted through the male line.

Stillbirth

Given the pathophysiological links with placental dysfunction and late pregnancy loss, it is possible that there may be inherited factors which predispose women to a greater risk of stillbirth. There is a recognised familial predisposition to pre-eclampsia, whereby a family history of pre-eclampsia appears to confer increased risk to offspring [2,5,77]. Studies have also consistently shown a positive intergenerational association for growth restriction passed from the mothers to the offspring [80–82]. One study also found a familial association with placental abruption in mother to offspring pairs (adjusted OR (aOR) 1.60 (95% CI 1.23–2.09)) [77]. All of these placental disorders are associated with a risk of stillbirth; therefore, it is plausible to hypothesise that stillbirth could have a heritable component [83,84]. However, a register-based study found that there was no familial predisposition to stillbirth in a sample of over 26,000 mother–daughter pairs [85]. The study, however, may be underpowered; therefore, larger intergenerational studies are needed to confirm or refute these results in larger populations. Similarly, an Australian study to design a prediction model for stillbirth found that the addition of family history (including grandmothers' obstetric history and parental birth outcomes) did not significantly improve the predictability of stillbirth beyond what was achieved by including only factors related to the index generation and their current pregnancy factors [86]. The findings also agree with a similar intergenerational study which found that mothers who were born small for gestational age (SGA) had a higher risk of pre-eclampsia and placental abruption but after adjusting for confounding factors no familial association was found for the risk of stillbirth in daughters who were born SGA (adjusted OR 1.24 (95% CI 0.84 to 1.82)) [77]. While the findings are reassuring, it is important that further research is undertaken to understand whether there may be any heritable factors related to stillbirth.

Wikstrom et al. [77] investigated mothers who were born SGA and the outcomes in their own pregnancies to determine whether there was an intergenerational risk of placental dysfunction. Mothers who been born SGA were at a significantly higher risk of placental abruption, pre-eclampsia and preterm birth [77]. Further research to determine whether there is a familial predisposition to placental abruption is needed as this may also reflect a risk for stillbirth between family members

which may be specific to the underlying pathophysiological cause of stillbirth rather than the outcome of stillbirth itself.

Similarly, an intergenerational study found that stillbirths were significantly higher in diabetic daughters born to diabetic mothers (aOR 13.6 (95% CI 2.7–67.6)) after adjustment for daughter's age, pre-eclampsia, placenta praevia, placental abruption and pre-pregnancy hypertension [87]. However, it is possible that it is the daughter's diabetes itself (not any familial predisposition) which exerts the higher risk of stillbirth. One study, however, found that diabetic (non-gestational or gestational) daughters with non-diabetic mothers were at less risk of stillbirth (pre-gestational diabetic daughters aOR 3.3 (95% CI 1.9–5.9); gestational aOR 0.5 (95% CI 0.1–2.0)) than the diabetic daughters born to diabetic mothers [87]. It is well documented that diabetes confers a greater risk of stillbirth [83,88]; however, it would suggest that having a mother with diabetes may compound this risk.

Ectopic pregnancy

A Danish cohort study found that daughters were at 50% higher risk of developing an ectopic pregnancy if they were born to mothers with a history of ectopic pregnancy (rate ratio 1.50, 95% CI 1.19–1.88) [89]. Interestingly, they found no difference in miscarriage rates in the daughters born to mothers with and without a history of ectopic pregnancy [89] which may reflect the different pathophysiology involved with ectopic pregnancies. When considering ectopic pregnancy, it is plausible that there could be a genetic predisposition to abnormal tubal function, endometriosis [37] or risk factors such as smoking. It may be that some women inherit a genetic predisposition to susceptibility to pelvic inflammatory disease. However very little evidence exists on familial predisposition to ectopic pregnancy, and information on potential confounding factors such as prior pelvic infection is needed [89]. Further research is needed to delineate whether the epidemiological evidence presented [89] has a biological basis, and any new research needs to account for potential confounding factors such as infection.

Summary

There is some epidemiological evidence for intergenerational trends through the female line for miscarriage, endometriosis, PCOS and early menopause. Evidence is limited, and few studies exist on the familial associations for male factor infertility, tubal disease, ectopic pregnancy and stillbirth. Although biological plausibility exists, a clear causal pathway for heritable factors in infertility and pregnancy loss (miscarriage or stillbirth) is lacking. The published evidence is fraught with potential bias and often studies are small. Emerging genetic evidence is beginning to highlight possible causal loci for such recognised intergenerational trends. How to use this information to identify couples at risk to prevent adverse reproductive health remains unclear.

Intergenerational evidence is important to understand whether the underlying aetiology of adverse pregnancy outcomes could be inherited. We need to determine whether such familial patterns relate to epigenetic or genetic mutations: shared exposures such as environmental, occupational or lifestyle factors. By understanding potential heritable risk factors, it may be possible to develop earlier screening, public health campaigns and therapeutic targets for infertility and pregnancy loss. Given the impact of infertility, recurrent miscarriage and stillbirth on the maternal life course, it is possible any aetiological or genetic patterns may influence long-term health. Transgenerational inheritance of epigenetic factors is an emerging field, and more research is needed to understand intergenerational trends in reproduction. Equally, researchers and clinicians need to be mindful of the potential implications of endeavours to determine the biological explanation of pregnancy loss at any gestation while ensuring that women are not unnecessarily worried by any reported associations.

Implications for future research

Large-scale and global collaborations are needed to understand whether there are heritable factors associated with infertility and pregnancy loss at any gestation. If genetic inheritance could be proven, screening could enable women and their partners to make earlier informed choices about their

reproductive risks and may warrant further investigation of treatments to reduce risk of miscarriage in "high-risk" genetic variant couples.

Future research should investigate potential genetic and epigenetic genotypes predisposing to a high risk of miscarriage which may run in families. Genome-wide association studies should be undertaken on a larger scale in women with high risk of miscarriage to identify any genetic markers which may predispose to miscarriage. By understanding any potential mode of inheritance, whether genetic or through shared risk factors, this might help to identify couples at greater risk of infertility and pregnancy loss as well as enable new therapeutic targets or strategies to be developed.

More research is needed to understand how transgenerational epigenetic epimutations may be transmitted or avoided in humans such as the evidence suggests occurs in other mammals [90]. If we understood how environmental exposures led to intergenerational epimutations, it is possible that new therapies could counteract such mutations.

An individual patient data (IPD) meta-analysis using the intergenerational data sets from different populations could be carried out to further investigate the potential familial risks of infertility and pregnancy loss. This could increase the sample size available, particularly for rare outcomes such as stillbirth, and allow sufficient power to detect a difference if it exists. Appropriate adjustment and consideration of confounding factors are needed for intergenerational research. Further research is required to understand how couples perceive their family history and any risks associated with their reproductive health.

Implications for clinical practice

While intergenerational trends in aspects of infertility and pregnancy loss are recognised, further research is needed to understand the possible causality and implications of any such familial associations. While there are hypotheses that exist, women and their partners should be reassured that there is no conclusive proof or implications for their management at present. However, women and their partners should be encouraged to highlight any relevant family history during clinical consultations so that further study and investigation can be considered at an individual level, particularly where known genetically inherited conditions are identified. It is important to recognise the potential for familial predisposition in POI where genetic counselling and testing is already recommended by ESHRE [20]. Clinicians should be aware that given the epidemiological and emerging genetic evidence, it is possible that couples will report family history of infertility and/or pregnancy loss, and clinicians must also recognise the anxiety this may cause.

In future, if high-risk genotypes were identified within families, these may alter genetic testing available to women with miscarriage(s). High-quality intergenerational studies using large or multiple populations could contribute to the development of a risk stratification model for women with infertility, related disorders and pregnancy loss in the future. Furthermore, greater understanding of preconception and in utero exposures and detrimental effects on the developing foetus are needed to guide public health campaigns as well as preconception counselling.

Practice points

- Clinicians should consider family history of pregnancy loss and infertility and the impact that this may have on the individuals and also the concerns for their chances of future pregnancy.
- There is insufficient evidence on the impact of family history of infertility and pregnancy loss to change practice currently in terms of earlier screening or investigations with the exception of POI.
- A proportion of POI can be familial and genetic counselling should be offered.
- Importance of lifestyle advice to reduce the risk of infertility and pregnancy loss, given the potential for shared familial lifestyle choices should be continued, including the importance of smoking cessation.

Research agenda

- High-quality, large prospective cohort studies as well as genome studies are needed to determine any intergenerational trends in infertility and pregnancy loss.
- Large-scale international collaborations should consider observational data sharing to enable individual data meta-analysis.
- Research strategies should align epidemiological findings with next stage study design to determine causal pathway for the identified associations.

Declaration of competing interest

None.

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