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Mini-review **Open Access**

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Non-Genetic Inheritance, Fertility and Assisted Reproductive Technologies

Abstract: The concept of non-genetic inheritance is gaining considerable attention in the assisted reproductive technology (ART) community due to the reported differences between children born from ART and those that are conceived naturally. It has been demonstrated that children conceived via ART have differences in fetal growth, birth weight, congenital abnormalities, cardiometabolic parameters, glucose homeostasis as well as changes to body composition compared to children conceived naturally. Although these changes may have a parental contribution and may be influenced by the pathology of infertility there is concern that the technologies themselves may play a role. In support of this, is emerging evidence that aspects of ART technology such as culture media formulation and insemination method can alter offspring phenotype. In addition it is also documented that exposure to environmental factors, such as toxins can impact on offspring gametogenesis such that these perturbations persist through generations. With the increasing use of ART and the development of new technologies it is vital that we understand whether ART can effect non-genetic inheritance so that we can optimise technology and prevent abnormal programming and its impact on all aspects of offspring health including fertility and a possible transmission to subsequent generations.

Keywords: non-genetic inheritance, ART, IVF, epigenetics, ICSI, culture media, programming

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1 Non-Genetic Inheritance

It is well understood that heritable traits which influence phenotype are transmitted from parents to offspring via DNA (Mendelian genetics/genetic inheritance) and that, aside from exposure to environmental factors such as mutagens which can target DNA in a non-random manner (i.e. histone bound DNA in sperm is more prone to DNA damage than the tightly package DNA bound by protamines [1]), sequence changes are primarily random [2]. Studies have linked DNA mutations in single/small groups of genes to specific phenotypic changes in the offspring; however it is becoming increasingly evident that environmental factors can also influence offspring phenotype and although genome wide association studies have identified weak associations between single nucleotide polymorphisms (SNP's) and altered phenotype including risk of disease onset later in life, epigenetic programming is likely the primary determinant of environment based phenotypic programming [3]. Non-genetic inheritance or 'epigenetics' describes the transmittable change in the function of the genetic material without altering the DNA sequence. These changes can occur at the DNA level (i.e. methylation of CpG dinucleotides), chromatin level (i.e. acetylation/deacetylation of histones) and at the translation regulation level (i.e. microRNAs and other small non-coding RNAs) with these epigenetic processes able to be regulated by environmental factors [4].

2 Parental environmental exposures influence offspring health

There is accumulating evidence that the environment the developing fetus (and thus the developing germ line) is exposed to can significantly influence phenotype and

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susceptibility to disease later in life and that these changes can persist across multiple generations. One early example of this is demonstrated through the use of diethylstilbestrol (DES), a non-steroidal estrogen which was prescribed to women during pregnancy in the 1970's to decrease the risk of miscarriage [5]. The use of DES during the first trimester increased the risk of cancer in female offspring and this increased risk was also seen in the subsequent generation [6] as well as inducing reproductive tract dysfunction and poor pregnancy outcomes [7, 8]. It is believed that these abnormalities are due to altered DNA methylation of a homeobox gene (HOXA10) which was passed directly through the germline providing evidence of non-genetic inheritance of disease [9].

Further evidence from the Dutch winter famine demonstrated that babies, born to women suffering poor nutrition due to food embargos during World War II, were significantly smaller at birth and that this was repeated in the subsequent generation despite no further dietary restrictions [10]. This decreased birth weight was linked to obesity, increased risk for coronary heart disease and impaired glucose tolerance later in life [11]. In addition it has also been shown that paternal grandparent's food supply is also linked to the mortality rate in the grandchildren in a sex specific manner [12]. Interesting, while parental under-nutrition significantly altered their children's risk for chronic disease, it did not appear to impact their fertility, with subsequent females having increased numbers of children born compared with females born from mothers who were normally fed [13, 14]. In direct contrast, parental over nutrition does appear to play a role in programming offspring fertility, with maternal overweight/obesity during pregnancy increasing premature onset of puberty in daughters [15] and reducing sperm concentration, semen volume, sperm motility and testosterone levels in sons [16, 17]. This is also supported by studies in animal models that show that paternal obesity at conception perturbs sperm function of male offspring (decreased sperm motility and increased sperm reactive oxygen species and DNA damage) and alters oocyte quality in female offspring (reduced meiotic progression and altered mitochondrial membrane potential) [18].

In addition to nutrition, other parental environmental perturbations prior to or during pregnancy have been linked to infertility in offspring. Maternal smoking during gestation decreases testes weights and the number of developing germ cells in male fetuses [19] leading to an overall reduction in adult sperm counts and fertility [20]. Intrauterine growth restriction (IUGR) is also linked to fertility issues in both male and female offspring by reducing ovarian and testes size, inducing cryptorchidism, reducing numbers of primordial follicles, increasing FSH levels, decreasing uterine volume and reducing sperm counts and testosterone levels after puberty [21-25]. However whether all of these changes are due to direct effects (including genetic effects) as a consequence of in utero exposure cannot be ruled out at this stage. While human studies have not demonstrated a mechanism for these changes to offspring fertility, studies on in utero exposures of male offspring to different environmental toxins which results in perturbed fertility of the males also results in alteration to the epigenetic signature of the sperm with changes to methylation marks in spermatogonia detected in the F3 generation giving support to the fact that this may be non-genetic in origin [26, 27].

3 Environment Impairing Epigenetic Signatures Of Gametes

The developing gamete is highly sensitive to the surrounding environment with both maternal and paternal health/diet and exposure to toxins having a significant effect on, not only gamete viability, but also on the epigenetic fingerprint of the gametes. While little is known about the specific effects of smoking on the epigenetic composition of the oocyte, there are several studies that have linked smoking to inducing aberrant changes to epigenetic marks in sperm [12, 28-30]. One study determined that the microRNA content of sperm was altered in smokers and interestingly these microRNAs were associated with pathways important for the development of the embryo [28] and it has been demonstrated that smoking increases the oxidative stress in sperm, which increases DNA damage and oxidative adducts that may contribute to altered transcriptome and the observed poorer embryo development [31]. Epigenetic programming also plays a critical role in male fertility with aberrant epigenetic regulation/modifications being linked to a wide variety of sperm morphological defects [32, 33]. There are now several studies that have related oligiospermia and azospermia to perturbed DNA methylation including both hypomethylation and hypermethylation [34]. In addition, male infertility is linked to alterations in the abundance and composition of non-coding RNA content of sperm with infertility as well as retention of histones [35] however the environmental cause of this is currently unknown.

Further, small non-coding RNAs represent a group of RNAs that are 18-24 bases long and include repetitive elements, transcription start sites, (piRNAs, miRNAs, snRNAs, snoRNAs, mse-tsRNA and YRNAs) which are

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important for controlling epigenetic reprogramming of the male and female pronucleus [36-39]. Both oocyte and sperm specific small non coding RNAs have been proposed to aid in the degradation of maternal mRNA [36], provide signals for early embryonic histone replacement in the male pronucleus [40], transcriptionally poise the genome for early embryonic expression [41], and are vital for first cleavage division [42] and regulation of epigenetic state [43]. Both maternal and paternal environmental factors (i.e. smoking and diet/weight) have been shown to influence small non coding RNAs [44, 45], implicating them as potential mediators in the developmental origins of adult disease.

4 Non-Genetic Inheritance and IVF Technology- is there a Link?

Although it has been demonstrated that some children born from assisted reproductive technology (ART) have a different phenotype compared to children born from natural conception, the definitive link between ART and non-genetic inheritance has yet to be made although the early emerging evidence is cause for concern.

The demonstration that epigenetic marks of gametes and early preimplantation embryos are susceptible to environmental insults is of interest for assisted reproductive technologies where the gametes and early embryos are manipulated in vitro. A number of recent studies have now shown that children born as a result of ART have an increased risk of being born preterm, are at increased risk of neonatal death, display higher rates of birth defects and increased rates of genetic disorders [46, 47]. Whether such changes are genetic or non-genetic in origin is currently unclear as sub-fertile couples who conceive naturally display similar risks of pregnancy complications and neonatal risks as those conceived by ART [46, 47], with the contribution of the technology itself in programming offspring phenotype also the subject of some contention. Considerable advances have been made in IVF technology since the birth of the first IVF child, Louise Brown, in 1978. Changes to the culture environment and media, drugs used for ovarian stimulation, insemination technique and cryopreservation have led to the significant improvement in IVF outcomes as measured by pregnancy rates with an increase in singleton births. However, despite these considerable advances, the technology has been suggested to increase risk of altering non-genetic inheritance and programming [48-50].

4.1 Ovarian Hyperstimulation

One of the most common components of an IVF cycle is the use of hormones to stimulate the development of multiple follicles designed to improve the success rates of IVF by providing more oocytes to begin the process. It is well understood that this time of follicle and oocyte growth involves significant epigenetic remodelling in the developing and maturing oocyte which are sensitive to environmental exposures [51-53]. Data from animal models supports the notion that 'over-riding' of the natural hormonal cycle is in itself associated with molecular changes to the oocyte which may impact on development of the embryo and pregnancy. A mouse study established that the superovulation process altered the epigenetic marks in oocytes with disrupted H19 expression and loss of methylation in several maternally imprinted genes in a dose-dependent manner [54]. Further, studies on both mice and cows have demonstrated changes to the epigenetic marks in the oocytes as well as fundamental changes in the epigenetic machinery of the oocyte obtained from superovulation [55]. While studies in humans are more difficult to interpret due to confounding factors, there are now several reports showing an increase in imprinting disorders in children from follicle stimulation and ovulation induction without IVF [56, 57]. Further, a recent human study examining 4 year outcomes of patients that had IVF treatment either with or without hormonal stimulation determined that an increase in blood pressure in the children was coincident with administration of ovarian stimulation [58]. In addition human oocytes retrieved after controlled ovarian hyperstimulation present a different methylation pattern to those ovulated naturally and have hypomethylation in the imprinted region KCNQ1OT1 gene indicating ovarian hyperstimulation can alter oocyte epigenetic marks [59, 60].

4.2 Embryo Culture Media

Embryo culture media design has moved from a simple balanced salt solution to the complex commercial media systems used today (both single phase and sequential) which contain an array of nutrients including carbohydrates and amino acids with the composition based on the contents of the reproductive tract milieu [61]. During the development of these culture media, studies found that embryo development and blastocyst quality and viability were heavily influenced by their composition. The presence of metal ions, serum, ammonium as well as media lacking key ingredients such as amino acids were

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shown to delay embryo development as well as alter perinatal outcomes including birth weight [62-65]. Further, rodent models have demonstrated that both imprinting and epigenetic marks such as changes to methylation marks in embryos can be influenced by the composition of the culture media, with sub-optimal media or conditions (such as supplementation with BSA, use of high oxygen) resulting in altered expression of imprinted genes [66, 67].

The first evidence that culture media may influence development of the offspring in the human was reported in 2010 in a study that compared two well known sequential culture media systems [68]. This study demonstrated a shift in the birth weight curve, with babies born from embryos cultured in media from one manufacturer being in average 200g heavier than those born from embryos cultured in a different manufacturer's media [68]. These results were subsequently confirmed in a larger cohort with similar trends seen in children born after frozen embryo transfer [69]. In addition culture media also influenced the number of children born with low birth weight (<2500g) and low birth weight for gestational age [69]. There are studies that have failed to replicate these findings however it should be noted that all of these studies have small numbers of patients involved and there are often differences in other aspects of the culture systems (such as culture media type and gas phase used) and patient drug regimes that may also be contributing to these outcomes [70, 71].

In addition to altering birth weight, embryo culture media has also been shown to significantly alter placental weight [72] and that the changes to offspring development are evident as early as the second trimester measured by changes to head circumference, trans-cerebellar diameter as well as free β-hCG [73]. Even at this early time point and after adjusting for confounding factors it was determined that fetal size was consistent with a gestational age of approximately 3 days longer. Although the impacts of this altered growth is currently unknown it has previously been demonstrated that low free β-hCG levels (which is produced by the syncytiotrophblast cells) is associated with fetal growth restriction and small for gestational age (SGA) [74, 75]. It was postulated that these changes in birth weights of the infants may be due to epigenetic alterations in the embryo which may in turn alter developmental programming of fetal and placental tissues. To this end a recent study demonstrating that gene expression levels and methylation levels are altered in both fetuses and placenta of children born from assisted reproductive techniques [76]. However, large cohort studies are required to further examine this phenomenon.

4.3 Intracytoplasmic Sperm Injection (ICSI)

ICSI was first reported in the 1990's primarily to treat male factor infertility with the first live birth in 1992 [77]. Although now a routine part of IVF treatment, studies have demonstrated that children born from ICSI have an increased risk for congenital birth defects compared to those conceived from natural conception [78, 79]. Studies have primarily focused on perinatal outcomes and the incidence of congenital abnormalities and neurodevelopmental factors have found that along with decreased birth weight, ICSI is associated with a significant increased risk of major birth defects (8.6%, primarily musculoskeletal and chromosomal abnormalities) in children compared to those conceived via natural conception (4.2%) [80]. In this study however standard insemination IVF was also associated with a similar increase in congenital malformations (9.0%) therefore demonstrating that ICSI alone may not be responsible for the increased risk of birth defects. A subsequent study in older children (aged 5 years) showed that children conceived from ICSI had an increased odds ratio of having a major congenital malformation (2.77 CI 1.41-5.46) which was higher than children created by standard insemination IVF (1.80 CI 0.85-3.81). The difference between the two insemination methods was primarily due to an increase in malformations in the male offspring urogenital system [80] which has also been demonstrated in other studies [79, 81]. Children born from ICSI were also more likely to have significant childhood illness, surgical operations and admissions to hospital [82]. More recently in a large study of over 300,000 births it was concluded that children born from ICSI have a significantly higher odds ratio for birth defects (1.77 (CI: 1.47-2.12: 9.9%) compared to IVF of 1.26 (CI 1.07-1.48: 7.2%) [47]. It therefore has been concluded from these studies that there was a pressing need to do further monitoring of children born from IVF technology to assess changes in susceptibility to other associated issues such as increased risk of cancer and decreased fertility (especially in light of the urogenital abnormalities in the male ICSI children) [80, 83]. In addition to congenital abnormalities it has also been documented that the mental developmental capacity of boys born from ICSI was significantly lower at 1 year than compared to children born from IVF, and ICSI children also showed delayed development in memory, problem solving and language skills [84]. It is possible that these differences may be due to variation in the patient cohort (ICSI is primarily used for male factor infertility where as standard insemination is used primarily for maternal infertility) or the technology itself (ICSI requires the

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invasive injection of a sperm into the oocyte which occurs along with culture media and PVP (polyvinylpyrrolidone) which is used for sperm immobilisation and isolation) and this requires further investigation. Again whether these effects of ICSI are a result of genetic or epigenetic factors are unclear. Although a recent study did demonstrate that the dsyregulation in methylation in placentas from ICSI conceived children were more altered compared to IVF children [76], another study determined no increased risk of DNA methylation changes at 6 differentially methylated regions (DMRs) in children conceived by either IVF or ICSI [85]. However, a key limitation to date is the small size of studies which may be underpowered to detect minor differences.

4.4 Frozen Embryo Transfer

The outcomes of offspring born after fresh or frozen (FET) embryo transfer has been the focus of a number of studies and there is now a significant body of evidence that demonstrates that elective frozen embryo transfer (eFET) may lead to improved ART outcomes. The first study to report on this was in 2010, demonstrating that children born from fresh transfer had an increased risk of blastogenesis associated birth defects compared to FET pregnancies [86]. It was proposed that this difference may likely due to either the transfer of a fresh embryo into an abnormal endometrial hormonal milieu induced by ovarian stimulation or from the cryopreservation process acting as a 'selection gate' thus ensuring that only the most viable embryos survived for transfer. To follow on a meta-analysis also concluded that children born from FET had a significantly decreased risk of perinatal mortality, pre-term birth, low birth weight and SGA than those born from fresh embryo transfer [87]. Although there is some concern that FET may actually be associated with large for gestational age and fetal macrosomia [88], the evidence of increases in fetal weight with FET compared to fresh transfer means that the possibility of eFET is gaining traction. However, large randomised controlled trials (RCT's) are required before the field changes practice and further studies on offspring health from either technology are required also to determine why the children born from different ART technology have different phenotypes and how epigenetic programming may be involved [89].

4.5 ART, epigenetics and imprinting disorders

Recent studies have suggested a link between ART and epigenetic modifications providing a possible mechanism for this non-genetic inheritance of altered phenotype [90]. Pre-implantation embryo culture has been demonstrated to alter methylation and imprinted gene expression in animal models when compared to in vivo derived embryos [91-93]. In addition, large offspring syndrome (LOS) in ruminants, which is seen after in vitro maturation and in the presence of serum in the culture media, and has been linked to altered methylation patterns and reduced expression of imprinted genes [91]. In the human, several case studies have suggested an association between ART and imprinting disorders, with an increase in Beckwith-Wiederman and Angelman syndrome as well as changes to imprinted loci in these children although more recent studies have failed to show any association [49, 94-99]. Due to the fact that the relative risk for imprinting disorders appears to be the same between sub-fertile couples with or without ART the increase in these imprinting disorders may in fact be attributed the subfertility rather than the ART however this remains to be confirmed [50].

5 Non-genetic inheritance and alternative art technologies

The increasing push to improve patient care and clinical pregnancy rates via advancements and new treatment options in the ART industry means that clinicians are now able to access a number of new technologies that may have not undergone a standard pathway of preclinical through clinical trials. Previous examples of this include the introduction of ICSI in the early 1990s for the treatment of male infertility and more recently embryo biopsy for providing pre-implantation genetic testing, both which were adopted quickly into main stream clinical practice. In addition new technologies are now being investigated that are focused on not only maintaining the inherent viability of the embryo but trying to improve its quality and thus increasing the chance of pregnancy. Therefore it is of vital importance that these technologies are vetted for safety before they are implemented as the impact on offspring phenotype and long term disease susceptibility is currently unknown.

5.1 Ooplasmic transfer

The first live birth as a result of ooplasmic transfer occurred back in 1997 and was first adapted for women who had recurrent implantation failure [100]. Ooplasmic transfer is the process whereby the cytoplasm of a healthy donor oocyte is injected and replaces the cytoplasm of the recipient oocyte, and has been offered to infertile patients in the past who are proposed to have perturbed

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cytoplasmic factors such as mtDNA, mRNA, abnormal mitochondria function or an inheritable mitochondrial disorder [101] with live births being reported [102-104]. One of the main concerns with ooplasmic transfer is the generation of heteroplasmic oocytes where both donor and recipient mitochondrial haplotypes are present. Although no apparent abnormalities have been detected in live heteroplasmic children [105] it is now known in animal models that phenotypic and epigenetic modifications are apparent [106-109]. In mammals the oocyte cytoplasm supplies the necessary mRNA and protein requirements for the initial epigenetic reprogramming events that occur in the male and female pronucleus before activation of the maternal and paternal genomes [110, 111]. Therefore it's plausible that undesired epigenetic modifications could arise from the donor ooplasm of one genotype on the maternal and paternal pronucleus of different genotypes therefore altering early epigenetic reprogramming at fertilisation and impacting on offspring health [109]. The long term safety of cytoplasmic transfer has not been validated and more research should be performed before it is routinely offered to patients.

5.2 Growth factors in embryo culture media

A number of different growth factors (GF) all proposed to improve blastocyst development rates and clinical pregnancy outcomes have been supplemented in human embryo culture media with the intent to improve embryo development and increase the chance of achieving a viable pregnancy. These include epidermal growth factor [112], insulin-like growth factor [113], heparin-binding epidermal growth factor [114], leukemia inhibitory factor [115], platelet-derived growth factor [116], brain-derived neurotrophic factor [117], platelet activation factor [118] and more recently granulocyte-macrophage colony-stimulating factor (GM-CSF) [119]. The addition of GF to media is proposed to be beneficial to embryo growth promoting faster growth, and also act on embryo receptors to reduce apoptosis [120-122]. However, the use of GF in human embryo culture media is not well regulated and in animal models a number of these GFs have been associated with large offspring syndrome in sheep [91] a number of these GF's (present due to either serum or co-culture with granulosa cells) have been associated. With improvements to offspring phenotypes only seen when embryos were grown in suboptimal culture conditions [123, 124], which was somewhat mirrored by a recent RCT on GM-CSF which showed a benefit only when the albumin concentration was reduced to a level that reduced pregnancy rates in the control group [119]. In other cell types GFs have been shown to alter activity of methyltransferases (DNMTs) causing hypermethylation of CpG islands in cancer cells [125]. These same pathways are important in early embryogenesis which therefore raises the possibility that similar epigenetic pathways could be regulated by growth factors added to embryo culture media. Until further research determines long term impacts of GFs in embryo culture media on children's health, GFs in clinical practice should be viewed with caution.

5.3 Methyl donors

A more recent phenomenon is the addition of either methyl donors to human embryo culture media (i.e. methionine, vitamin B_{12}, folic acid, choline, and vitamin B_6) [126], or through patient ingestion through natural/alternative medicines at conception (i.e. high levels of folate) [127]. Many of these methyl donors can alter DNA methylation by interfering with 5-adenosylmethionine mediated methylation an essential precursor for establishing de novo methylation patterns as well as duplicating methylation patterns following DNA replication during early embryo development, while its by-product 5-adenosyl homocysteine can directly inhibit DNA methyltransferase activity [128]. As mammalian one-carbon metabolism is dependent on dietary methyl donors and cofactors [129], the nutritional components within embryo culture media could plausibly alter embryo epigenetics by influencing the establishment of DNA and histone methylation. The methyl donor levels in commercially available human embryo culture media display a remarkably wide range for example the concentration of methionine ranges from 0 to 100 μM [126]. While the addition of methyl donors is required for cell culture, numerous studies have now shown that methyl donor levels (in culture or via diet) can directly influence DNA methylation levels. For example diet supplementation of female agouti mice before and during pregnancy with extra folic acid, vitamin B12, betaine, and choline increased DNA methylation at Axin(Fu), thereby reducing by half the incidence of tail kinking in offspring [130]. While folic acid dietary supplementation after 12 weeks of gestation altered offspring repeat element and imprinted gene methylation in human cord blood [131]. Additionally when added to cell culture media methyl donors altered the methylation patterns of regulatory sequences of key imprinting genes in rodent oocytes [132]. A number of studies have linked human ART within increased imprinting disorders in humans [133-135], whether these changes are due to the sub fertility of the patients or ART technologies, including methyl donors in culture media, remain to elucidated.

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6 Conclusion

There is now significant evidence, at least in animal models, that the environment in which the developing gamete matures can alter the phenotype of resultant offspring. With the primary mechanism hypothesised to occur via alterations to critical non-genetic programming such as epigenetic modifications. In the human, in vivo environmental exposures of maternal and paternal gametes to changes in nutrition as well as toxins and smoking can significantly alter offspring phenotype. In addition concern has been raised about the children born from ART as they also can display altered phenotypes compared to children conceived naturally. Although there is speculation that this is due to the parents being infertile, there is also early emerging evidence that changes to in vitro environmental conditions during ART (i.e. media compositions, use of ICSI and oxygen concentrations) can alter epigenetic marks of gametes and embryos thus raising the possibility of non-genetic inheritance determining fetal phenotypes after ART. This therefore warrants the need for adequately powered studies to examine whether these observations are due to parental subfertility or whether ART technology can change offspring phenotypes through epigenetic mechanisms and, if so, how can the technology be improved to prevent this from occuring.

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