Seminars in Fetal & Neonatal Medicine 19 (2014) 250–253

Contents lists available at ScienceDirect

Seminars in Fetal & Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Review

Rare chromosomal, genetic, and epigenetic-related risks associated with infertility treatment

Jennifer J. Kurinczuk [a,*], Siladitya Bhattacharya [b]

[a] National Perinatal Epidemiology Unit, University of Oxford, Oxford, UK
[b] Division of Applied Health Sciences, School of Medicine and Dentistry, University of Aberdeen, Aberdeen Maternity Hospital, Aberdeen, UK

Keywords:
IVF
ART
Chromosome anomalies
Cystic fibrosis
Genomic imprinting
Health outcomes
Imprinting disorders
Microdeletions

SUMMARY

This article reviews the rarer chromosomal, genetic, and epigenetic-related risks of adverse child outcomes associated with infertility and its treatment. Excess structural chromosomal anomalies have been found in both male and female partners undergoing infertility treatment, and these risk direct transmission to offspring. Microdeletions of the Y-chromosome associated with male infertility have been transmitted to sons following treatment with intracytoplasmic sperm injection. It is thus possible that male offspring of men with infertility could experience fertility problems in adulthood. Infertility treatment for men with cystic fibrosis, or with congenital bilateral absence of the vas deferens in the absence of cystic fibrosis, who have azoospermia is now possible using surgically retrieved sperm. Transmission of known cystic fibrosis mutations can be avoided by testing the female partner prior to treatment and offering pre-implantation genetic diagnosis if she is a carrier. The effect of infertility and its treatment on genomic imprinting is of increasing concern as our understanding of the mechanisms of imprinting in germ cell development and embryogenesis expands. At present, it is far from clear whether there are longstanding effects of infertility *per se* or of its treatment on the health of adults who were conceived following assisted reproductive technologies, but available data suggest that this should be of concern and long-term follow-up studies are required.

1. Introduction

In-vitro fertilisation (IVF) has led to great joy for millions of infertile couples worldwide. At the same time, the ability of fertility treatment to overcome natural selection processes has led to concerns about the vertical transmission of genetic and epigenetic disorders, and about chromosomal anomalies to the children born through assisted reproductive technologies (ART). The development in the early 1990s of intracytoplasmic sperm injection (ICSI), a variant of IVF in which a single sperm is selected and injected into a single egg, raised particular concerns – not just about the potential transmission of genetic conditions associated with infertility, but also about mechanical or biochemical damage to the embryo as a consequence of the technique itself.

ICSI was developed for the treatment of couples with profound male infertility where the sperm count is extremely low (oligozoospermia) or there are no sperm present at all in the ejaculate (azoospermia) and natural conception is highly unlikely, yet the desire is to have a genetically related child rather than to use donor sperm. Further refinements have meant that it is possible to carry out ICSI even in the absence of ejaculated sperm. In men with azoospermia, some centres offer testicular biopsy to retrieve immature spermatids which can be used in the absence of mature spermatozoa. In addition to men with oligozoospermia or azoospermia of unknown origin, others who benefit from ICSI treatment include men with a vasectomy, a failed vasectomy reversal, and those who have infertility as a consequence of chemotherapy. Whereas infertility may have a genetic origin in some men, the risk of transmission of genetic conditions for the latter three groups is likely to be low, although they will experience any technique-related risks if indeed such risks exist.

In contrast to the other articles in this issue dealing with the more common outcomes of ART, in this paper we review the rarer chromosomal, genetic, and epigenetic-related risks of adverse child outcomes associated with infertility and its treatment. We cover

* Corresponding author. Address: National Perinatal Epidemiology Unit, University of Oxford, Old Road Campus, Headington, Oxford OX3 7LF, UK. Tel.: +44 (0) 1865 289719; fax: +44 (0) 1865 289701.
E-mail address: jenny.kurinczuk@npeu.ox.ac.uk (J.J. Kurinczuk).

http://dx.doi.org/10.1016/j.siny.2014.04.005
1744-165X/

the topics of structural chromosomal anomalies, chromosomal microdeletions, single gene defects, and we conclude with consideration of the epigenetic phenomenon of imprinting. The use of ICSI is of particular concern with regard to these topics because of its highly invasive nature and because of the capacity to use ICSI in circumstances that may be associated with a heritable cause of male infertility.

2. Structural chromosomal anomalies

The risk of congenital anomalies of both structural and chromosomal origin in children born following conception by ART is considered by Hansen and Bower (Chapter 2 in this issue). We deal here with parental chromosomal anomalies in which an excess frequency of somatic structural chromosomal abnormalities has been found in infertile men and women. Oligozoospermic men presenting for treatment have been found to have a prevalence of autosomal translocations and inversions of 4.6% with a higher prevalence of 13.7% in azoospermic men [1], whereas infertile women reportedly have a lower prevalence of chromosomal anomalies, with one series reporting 1.14% for autosomal reciprocal balanced translocations [2]; however, this latter value needs to be interpreted against the background population prevalence estimate of 0.16%. For the children born following ART the potential transmission of such defects is clearly of concern.

Karyotyping of both members of the couple prior to ICSI indicated for oligozoospermia or azoospermia of unknown origin enables the offer of pre-implantation genetic diagnosis (PGD) to allow the selection of chromosomally normal embryos for transfer during an IVF treatment cycle. Due to such strategies, parental karyotypic abnormalities are unlikely to explain all or indeed any of the excess risk of congenital anomalies of chromosomal origin seen in children born following ART (Hansen and Bower, Chapter 2 in this issue).

3. Chromosomal microdeletions

Genetic causes of infertility include microdeletions on the long arm of the Y chromosome (Yq) associated with spermatogenic disorders resulting in oligozoospermia or azoospermia. Three azoospermic factor regions (AZFa, AZFb and AZFc) are recurrently deleted in some men with infertility. An estimated 10–15% of men with azoospermia and 5–10% with oligozoospermia have these Y microdeletions [3]. Sons born to fathers with an AZFc deletion following ICSI have been shown to have the same microdeletion as their father [4–6] and so will experience infertility. By overcoming the effects of a zero or low sperm count, ICSI can perpetuate the transmission of these genetic causes of infertility, and further expansion of the deletions or *de-novo* deletions may occur, resulting in a more severe phenotype being expressed in the sons [7].

4. Cystic fibrosis and congenital bilateral absence of the vas deferens

Cystic fibrosis is one of the commonest autosomal recessive conditions in European populations. It is caused by mutations in the transmembrane regulator CFTR gene. More than 800 CFTR mutations have been identified; in the UK the most widespread mutation is in the three base pair deletion ΔF508 which affects 75% of carriers. The majority of adult males with cystic fibrosis have congenital bilateral absence of the vas deferens (CBAVD) which renders them infertile. For men affected by cystic fibrosis, ICSI using surgically retrieved testicular sperm offers the opportunity of genetic parenthood with the possibility of avoiding vertical transmission of the common mutations by using PGD if the partner is a carrier.

CBAVD can also occur in the absence of cystic fibrosis from a combination of the 5T allele in one copy of the CFTR gene with a cystic fibrosis mutation in the other copy of the gene [8]. As in the situation where CBAVD is caused by cystic fibrosis, testicular sperm retrieval followed by ICSI can offer the chance of genetic parenthood. Not all mutations have been identified; however, multiple mutation assay will detect about 90% of carriers of the CFTR mutation and should be offered to men with CBAVD in the absence of cystic fibrosis and indeed to all men with oligozoospermia and azoospermia contemplating ICSI. Inevitably, because not all CFTR mutations have been identified, a small number of children born following ICSI for CBAVD are at risk of cystic fibrosis, though the rate of cystic fibrosis will be lower than in the general population due to the targeted testing. Parents should have been fully counselled in preparation for this outcome alongside the offer of carrier testing of the female partner.

5. Imprinting-related disorders

Epigenetics refers to the highly orchestrated mechanisms that facilitate the complex patterning and stable regulation of gene expression required to ensure normal human development [9]. Genomic imprinting is an epigenetic phenomenon in which the expression of a particular gene is determined by its parental origin, and, for a particular gene, only one specific maternal or paternal allele will be expressed in certain cell types at specific times in development. The genes that will not be expressed are 'labelled' or 'marked' for suppression by the process of DNA methylation, histone modification, or DNA-binding proteins; epigenetics thus encompasses potential heritable changes in gene expression [10]. In germ cells and in the developing embryo, epigenetic programming of the entire genome underpins the process of erasing and re-establishing the correct epigenetic patterns required for continued normal development. As with genetic mutations, epigenetic alterations, known as epimutations, can arise leading to a number of different human disorders referred to as 'imprinting disorders' as well as subfertility [9].

Many of the estimated 100 human genes that are imprinted in this way are involved in embryonic, fetal and placental growth as well as neurodevelopment, and these imprinted genes tend to cluster together in imprinted domains [9]. So far, these domains have been found on chromosomes 6, 7, 11, 14, 15 and 20. Imprinted genes are subject to more complex epigenetic regulation than non-imprinted genes, leading to more opportunities for epigenetic errors to arise. The complex process of imprinting appears particularly vulnerable to physical and chemical stresses [11] and the concern is that some aspects of ART, including the superovulation used to produce multiple oocytes [12] prior to fertilisation, may act as a stressor leading to perturbations in the imprinting process and thus disrupting the function of the imprinted genes. Loss or disrupted function of these genes can have devastating, although rare, consequence as illustrated by the imprinting-related syndromes of Beckwith–Wiedermann (BWS), Russell–Silver, Prader–Willi, and Angelman, which, in some (but not all) cases, result from disruption of imprinted genes on chromosomes 11, 11, 15 and 15 respectively [9].

Two case reports of imprinting-related Angelman syndrome in children born following ICSI raised the possibility of ICSI causing a disruption in the imprinting process [13]. A subsequent report of children with BWS born following ICSI further added to the concerns [14], as did the finding from a case–control study of a nine-fold increased risk of BWS following ICSI compared with natural conception [15]. Interestingly both Angelman syndrome and BWS