Scientific and Clinical Advances Advisory Committee Paper

Paper Title	**Health outcomes in children conceived using assisted reproductive technologies**
Paper Number	SCAAC(10/13)01
Meeting Date	30 October 2013
Agenda Item	4
Author	Anna Rajakumar
For information or decision?	Decision
Resource Implications	None
Implementation	None
Communication	Recommendations regarding patient information will be actioned by the Communications Team. Information on the HFEA website will be updated where relevant.
Organisational Risk	Medium
Recommendation to the Committee	SCAAC is asked to consider the research outlined and identify any further relevant studies. Members are also asked to put forward their views on whether the HFEA should review the information clinics are required to make available to patients and the information the HFEA makes available to patients, and what information they believe would be useful to patients.
Evaluation	The patient information on the HFEA website is reviewed on a regular basis.
Annexes	None

1. Lay summary

1.1. Assisted reproductive technology (ART) includes techniques such as egg freezing, in vitro fertilisation (IVF), and intra-cytoplasmic sperm injection (ICSI). Some research suggests that these techniques are associated with birth defects in babies and longer-term health issues in the children born. Whether there is a direct causal link is yet to be conclusively agreed, as it is possible that the association is due to other factors. These could relate to underlying subfertility in the patients.

1.2. To reflect the progress of research, the HFEA may need to update the information that clinics are required to give to patients and the information the HFEA publishes via its website.

2. Background

2.1. It has been suggested that ART techniques may be associated with an increased risk of birth defects and long term health impacts in the children born. However, a direct causal link is yet to be shown conclusively. The association may be due to other reasons and compounding factors, such as underlying subfertility in patients, or a bias because infants conceived as a result of ART are more rigorously monitored.

2.2. SCAAC last discussed birth defects following ART, in depth, in 2009. At this time it concluded that there was no substantial evidence to suggest that ART affects the risk of resulting babies developing cancer, suffering from impairments in neurological development, or having impaired psychosocial wellbeing.

2.3. However, SCAAC did suggest there was some evidence to show that infants born as a result of ART have an increased risk of the imprinting conditions Angelman Syndrome and Beckwith-Wiedemann Syndrome.

2.4. Since 2009, SCAAC has continued to monitor follow-up studies through its horizon scanning processes. Further to this, SCAAC continues to consider the impacts of culture media on long term health in a separate strand of work involving annual reporting of research in this area. It should be noted that this paper will not include discussion on long term health outcomes and culture media as this will be reviewed in a separate paper in 2014.

Information currently provided by the HFEA to centres and the public

2.5. The HFEA's Code of Practice (section 4.2) currently requires clinics to provide certain information on health outcomes to patients. It specifically states that before treatment is offered, the centre should give the woman seeking treatment and her partner, if applicable, information about:

> *(e) the likely outcomes of the proposed treatment (data provided should include the centre's most recent live birth rate and clinical*

pregnancy rate per treatment cycle, verified by the HFEA, and the national live birth rate and clinical pregnancy rate per treatment cycle)

(f) the nature and potential risks of the treatment, including the risk of children conceived having developmental and birth defects

(l) the nature and potential risks (immediate and longer term) of IVF/ICSI with in vitro matured eggs, including reference to the clinic's experience.

2.6. The HFEA also publishes some information for patients via its website. The HFEA patient information references the following risks that have been associated with ICSI:

Certain genetic and developmental defects in a very small number of children born using this treatment. However, problems that have been linked with ICSI may have been caused by the underlying infertility, rather than the technique itself.

2.7. Information on the HFEA's website, 'Risks associated with fertility treatment' does not however provide information on whether there is an increased risk of birth defects as a result of using ART in general.

2.8. Section 3 outlines research in this area published during 2012-13.

3. Summary of recent developments

Studies indicating no increased health risk

3.1. A study examined children born from IVF for imprinted and genome-wide DNA methylation abnormalities at four imprinted gene loci (H19, SNRPN, KCNQ1OT1 and IGF2). The study used methylation-sensitive quantitative polymerase chain reaction, concluding that low-level imprinting errors are not common in the IVF population (Oliver et al 2012).

3.2. A study by Dommering et al (2012) evaluated the suggested association between IVF, retinoblastoma, and tumour methylation characteristics. DNA from frozen retinoblastoma tumours was tested for mutations in the RB1 gene and for methylation status. Two RB1 mutations were found to cause tumours. None of the tumours showed hypermethylation of the RB1 promoter. Examination of retinoblastoma tumours of seven children conceived by IVF or ICSI did not show hypermethylation. This demonstrates that an association between IVF or ICSI and retinoblastoma through this epigenetic mechanism is unlikely.

3.3. Fedder et al (2012) explored whether neonatal outcomes including congenital malformations in children born after ICSI with epididymal and testicular sperm [testicular sperm extraction (TESE)/percutaneous epididymal sperm aspiration (PESA)/testicular sperm aspiration (TESA) (TPT)] differ from neonatal outcomes in children born after ICSI with

ejaculated sperm, IVF and natural conception. Children born after TPT have similar neonatal outcomes, including total malformation rates, as have children born after ICSI and IVF with ejaculated sperm. The study concluded that testing for variance over the four groups may indicate smaller differences in specific malformation rates, with TPT as the highest risk group. Accumulating data showed that TPT treatment is as safe as conventional ICSI and IVF treatment, and as natural conception with regard to neonatal outcome, including congenital malformation.

Studies indicating an increased health risk

3.4. Wen et al (2012) conducted a meta-analysis of studies assessing the effect of IVF and ICSI on birth defects. They identified all studies published by September 2011 with data related to birth defects in children conceived by IVF and/or ICSI compared with spontaneously conceived children, or birth defects in the children conceived by IVF compared with those by ICSI. The analysis concluded that children conceived by IVF and by ICSI are at significantly increased risk of birth defects, and there is no risk difference between children conceived by IVF and those conceived by ICSI.

3.5. A recent study by Sandin et al (2013) examined neurodevelopment after IVF, exploring the association between IVF procedures and the risk of autistic disorders and mental retardation. The study concluded that there was a small statistically significant increase of mental retardation associated with IVF procedures. The study highlighted that ICSI (using surgically extracted sperm and fresh embryo transfer) for paternal infertility (as opposed to IVF without ICSI) also demonstrated an increase in the relative risk for autistic disorders and mental retardation. The authors highlighted the study's limitations in terms of its statistical analysis, and suggest that further studies are needed in different populations.

3.6. In July 2013 the HFEA's Horizon Scanning Panel met and discussed the above cited research, conducted by Sandin et al (2013), concluding that the results were not conclusive as it relied on a small cohort and analysis needed further refining.

3.7. The risk of congenital heart defects (CHDs) associated with ARTs has been evaluated; however, there is limited information on the risks for specific CHDs. A study by Tarabit et al (2012) used data from the Paris Registry of Congenital Malformations (n=5493) suggested that children born as a result of ART had a higher incidence of CHD than controls. ARTs were specifically associated with significant increases in the chance of specific malformations, including the outflow tracts, ventriculoarterial connections, cardiac neural crest defects and of the double outlet right ventricle. This study suggests that there may be specific associations between methods of ART and subcategories of CHD. However the study could not rule out compounding factors such as underlying infertility. During the 2013 Horizon scanning Panel meeting the group reiterated the

importance of focussing on particular conditions such as this.

3.8. At the 2013 meeting of the European Society of Human Reproduction and Embryology (ESHRE), research linking the HFEA dataset and the Congenital Abnormalities System and the Childhood Cancer Registry was presented. Williams et al (2013) presented their investigation exploring whether children born after ART, such as IVF, have a higher risk of developing cancer than other children. The researchers also aimed to assess whether different types of infertility or different fertility treatments may be associated with different types of childhood cancer.

3.9. The findings presented showed that there was no overall increased risk of cancer in ART children born (n=106,381). The data highlighted that 108 cancers were identified in the ART children, comparable to the 109.7 cases which could have been expected from general population. The study did suggest a slight increased risk relating to rare cancers; however, due to their rareness any firm conclusions on the significance of this result could not be made. Further to this the study suggested that, of the children born after assisted conception who did develop cancer, no co-morbidity indicative of an imprinting disorder was found, consistent with the hypothesis that ART does not result in an increase in epigenetic imprinting.

3.10. A similar study was also presented at ESHRE 2013, looking at the risk of cancer in children and young adults born after IVF, in a smaller (comprised 92,809 born after IVF) Nordic Cohort (Jerhamr Sundh et al 2013). The group also found that children born after IVF had no overall increased risk of cancer when compared with children in the general population.

3.11. A review by Pinborg et al, carried out in 2012 summarised the literature on the association between ART and congenital anomalies with respect to subfertility, fertility treatment other than ART, and different ART methods including ICSI, blastocyst culture and cryotechniques. Trends over time in ART and congenital anomalies were also discussed by Pinborg et al (2012).

3.12. More recently, Hargreaves et al (2013) published the largest systematic meta-analysis to date, on research relating to fertility treatment and childhood cancer risk. The review concluded that there is an association between fertility treatment and cancer in offspring, purporting an increased risk for specific cancer types - leukaemias, neuroblastomas and retinoblastomas. However, the results do not rule out compounding factors related to underlying subfertility.

3.13. Further to this, in 2013, Hart et al conducted a two part review exploring longer-term health outcomes for children born as a result of IVF treatment. In part 1 the group examined general outcomes providing evidence that cardiovascular and metabolic risk factors that are responsible for long term cardiometabolic diseases may be more prevalent in children born as

a result of ART.

3.14. Part 2 of the review identified the lack of long-term follow-up data, although they noted an increase in the incidence of cerebral palsy and neurodevelopmental delay. The prevalence of such disorders were reported as being attributed to prematurity and low birthweight. Previous reports of associations with autism and attention-deficit disorder were cited as being potentially attributable to maternal and obstetric factors. The study also highlighted a potential increase in the incidence of early adulthood clinical depression and binge drinking. The data showed no changes with respect to cognitive development, school performance, social functioning. However, as in Part 1, compounding factors were not ruled out.

ICSI and long term outcomes

3.15. In 2012 SCAAC considered a study by Davies et al (2012) exploring the extent to which birth defects in children born from fertility treatment may be explained by underlying parental factors. The study showed that an increased risk of birth defects associated with IVF was no longer significant after adjustment for parental factors. The risk of birth defects associated with ICSI remained increased after multivariate adjustment, although the possibility of residual confounding factors could not be excluded. SCAAC also raised concerns about the extrapolation of the study's findings, suggesting that the study was confined to two regionally specific sites and a small sample size.

3.16. It is of note that at the 2013 Horizon Scanning Panel annual meeting the group further discussed the potential risk to offspring, of the increasing use of ICSI. They suggested that an investigation of comparative outcomes for ICSI at clinics which just use this technique to treat male factor infertility, and clinics which use this technique less discriminately or for all patients should be conducted.[1]

4. Conclusion

4.1. SCAAC members are asked to consider the research outlined and inform the Executive of any future or current research to note.

4.2. Members are asked to put forward their views on whether the HFEA

[1] During the meeting a Committee member brought the following further recent papers to the attention of the Committee, which highlight the importance of studies exploring data on birth weight or pre-term birth:

- A broad overview piece that summarizes systematic reviews that explores the effectiveness of ART technologies (Farquhar et al 2013).
- A study that suggests that elective cryopreservation of all embryos in patients with elevated peak serum E2 for subsequent cryothaw embryo transfer (ET) in cycles with a better physiologic hormonal milieu may reduce the odds of small for gestational age infants and preeclampsia in IVF singleton deliveries (Imudia et al 2013).
- An observation study showing that ET at the blastocyst stage is associated with a higher risk of very preterm delivery. The article highlights that RCT'S are required for further conclusive analysis (Maheshwari et al 2013).

should:

- consider any areas of work in further detail or monitor any areas for particular attention (e.g. the use of ICSI as highlighted by the Horizon Scanning Panel).

- consider reviewing the information clinics are required to make available to patients and the information the HFEA makes available to patients.

5. References

- Davies et al (2012) Reproductive technologies and the risk of birth defects. *N Engl J Med* 366(19):1803-1813.

- Dommering CJ et al (2012) IVF and retinoblastoma revisited. *Fertility and Sterility* 97(1):79-81.

- Farquhar et al (2013) Assisted reproductive technology: an overview of Cochrane Reviews (Review)

- Fedder et al (2012) Neonatal outcome and congenital malformations in children born after ICSI with testicular or epididymal sperm: A controlled national cohort study. *Hum Reproduction* 28(1):230-240.

- Hargreave M et al (2013) Fertility treatment and childhood cancer risk: a systematic meta-analysis. *Fertility and Sterility* 100(1):150-161.

- Hart and Norman (2013) The longer-term health outcomes for children born as a result of IVF treatment. Part 1 – General health outcomes. *Human Reproduction Update* 19(3):232-243.

- Hart and Norman (2013) The longer-term health outcomes for children born as a result of IVF treatment. Part II – Mental health and development outcomes. *Human Reproduction Update 19(3):244-250.*

- Imudia et al (2013) Elective cryopreservation of all embryos with subsequent cryothaw embryo transfer in patients at risk for ovarian hyperstimulation syndrome reduces the risk of adverse obstetric outcomes: a preliminary study. *Fertility and Sterility 99(1)* 168-173

- Jerhamre Sundh K. (2013) Risk of cancer in children and young adults born after IVF ñ a Nordic cohort study from the CoNARTaS group. *Abstracts of the 29th Annual Meeting of the European Society of Human Reproduction and Embryology Human Reproduction 28(1):O-167.*

- Maheshwari et al (2013) Obstetric and perinatal outcomes in singleton pregnancies resulting from the transfer of blastocyst-stage versus cleavage-stage embryos generated through in vitro fertilization treatment: a systematic review and meta-analysis. Fertility and Sterility 98 (2) 368-377.e9

- Oliver VF et al (2012) Defects in imprinting and genome-wide DNA methylation are not common in the in vitro fertilization population. *Fertility and Sterility* 97(1):147-153 e7.

- Pinborg et al (2012) Congenital anomalies after assisted reproductive technology. *Fertility and Sterility* 99(2):327-332.

- Sandin S et al (2013) Autism and mental retardation among offspring born after in vitro fertilization. *JAMA* 310(1):75-83.

- Tarabit K et al (2012) The risk for four specific congenital heart defects associated with assisted reproductive techniques: A population-based evaluation. *Eur Heart J* 32(4):500-508.

- Wen J et al (2012) Birth defects in children conceived by in vitro fertilization and intracytoplasmic sperm injection: a meta-analysis. *Fertility and Sterility* 97(6):1331-1337 e4.

- Williams et al (2013) Cancer risk in children born after assisted conception. *Abstracts of the 29th Annual Meeting of the European Society of Human Reproduction and Embryology Human Reproduction* 28(1):O-168.