Health outcomes in children conceived using assisted reproductive technologies

Strategic delivery:	☒ Setting standards	☐ Increasing and informing choice	☐ Demonstrating efficiency economy and value
Details:			
Meeting	Scientific and Clinical Advances Advisory Committee (SCAAC)		
Agenda item	5		
Paper number	SCAAC(10/15)02		
Meeting date	21 October 2015		
Author	Anna Quinn, Scientific and Clinical Policy Officer		
Output:			
For information or decision?	For decision		
Recommendation	Members are asked to put forward their views on whether the HFEA should: • consider any areas of work in further detail or monitor any areas for particular attention; • consider reviewing information clinics are required to make available to patients and the information the HFEA makes available to patients		
Resource implications	None		
Implementation date	None		
Communication(s)	None		
Organisational risk	☐ Low	☒ Medium	☐ High
Annexes	Annex A: Additional references provided by Daniel Brison		

1. Introduction

1.1. Assisted reproductive technology (ART) includes techniques such as egg freezing, in vitro fertilisation (IVF) and intra cytoplasmic sperm injection (ICSI). It has been suggested that ART techniques may be associated with an increased risk of birth defects and long term health impacts on 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 children conceived as a result of ART are more rigorously monitored.

1.2. SCAAC last discussed birth defects following ART in October 2013. The committee agreed that it would be useful to communicate recent findings related to cancer risk via the HFEA website, following the publication of relevant studies.

1.3. SCAAC also discussed the evidence relating to outcomes of low birth weight and pre-term birth in children conceived using ART. At that time, it concluded that further randomised trials are needed for conclusive findings and highlighted that further information is required on longer term risks of ART.

1.4. Since 2013, 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 and this will be reviewed in a separate paper.

Information currently provided by the HFEA to centres and the public

1.5. 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 clinic 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

1.6. Information for patients on the HFEA's website, 'Risks associated with fertility treatment' also provides some information about the risks of birth defects and longer-term health issues associated with ART. However, it also states that research in this area is ongoing and a direct causal link is yet to be conclusively agreed. This section of the website also references the study by Williams et al. 2013 which found no increased risk of cancer in ART children.

1.7. The HFEA website information also details that certain genetic and developmental defects have been identified in a very small number of children born after ICSI treatment. However, it also points out that problems that have been linked with ICSI may have been caused by the underlying infertility, rather than the technique itself.

1.8. This paper summarises key research findings between October 2013 and October 2015.

2. Research

Effect of ART on health outcomes

2.1. Conti et al. (2013) examined whether children born after assisted reproductive technologies are at increased risk of autism spectrum disorders. This systematic review identified seven relevant observational studies and concluded that there is currently no evidence that ART is significantly associated with autism spectrum disorders.

2.2. A retrospective Nordic population-based cohort study by Sundh et al. (2014) compared cancer rates in children born after ART (n= 91,796) with rates in children born after spontaneous conception (n= 358,419), mean follow-up time was 9.5 years. The study found no significant increase in overall cancer rates between the two groups, however there was a small but statistically significant increase in risk for two of the 12 cancers evaluated (central nervous system tumours and malignant epithelial neoplasms).

2.3. Kettner et al. (2015) carried out a systematic review to assess the effects of ART on physical health and hospital use in childhood. 38 studies were deemed to be eligible for inclusion in the review, 30 of these were cohort studies and eight were case-control. The results indicated that ART conceived children were at increased risk of unspecified and parasitic diseases, asthma, genitourinary diseases and epilepsy or convulsions when compared with spontaneously conceived children. ART conceived children appeared to experience the same risk and number of hospital

admissions compared to spontaneously conceived children but remain in hospital for a longer period of time per admission. However, several results in individual studies were not statistically significant and there was some inconsistency between study results. No differences between groups were found regarding use of medication and outpatient visits. Results regarding mortality, unspecified cancer, pneumonia, allergy, respiratory and gastrointestinal diseases were contradictory. On average, studies included in the review were well performed with an average quality score, measured by the Newcastle-Ottawa scale[1], of 6.7.

Effect of ART on health outcomes – congenital anomalies

Studies indicating no increased risk of congenital anomalies

2.4. Moses et al. (2014) carried out a retrospective cohort study on congenital anomalies identified at birth among infants born following ART in Colorado. Incidence of congenital anomalies identified at birth was assessed for children born following ART (n=2071) and children born following natural conception (n=342, 496). The adjusted odds ratio of a congenital anomaly following conception with ART was 1.01 (0.67-1.52), suggesting that conception by ART is not associated with an increased risk of congenital anomalies compared with natural conception.

2.5. 277,043 newborns were recruited into an Italian study by Parazzini et al. (2015) which included 7057 births following non-spontaneous conception. Initially the frequency of birth defects was calculated to be higher in the non-spontaneous conception group (OR 1.67; 1.5-1.9). However after adjusting for maternal age and other factors associated with non-spontaneous conception, no significantly increased risk was found. The authors concluded that any increased risk of birth defects after ART was mostly due to confounding factors.

Studies indicating an increased risk of congenital anomalies

2.6. Seggers et al. (2015) carried out a registry-based analysis to assess whether congenital anomalies occur more often with a history of subfertility and/or the use of IVF/ICSI. Live births, still births and terminated pregnancies between 1997 and 2010, with congenital anomalies without a known cause were included. 4185 cases were born to fertile parents and 340 to subfertile couples, of whom 139 had conceived after IVF/ICSI and 201 had conceived naturally after more than 12 months. Subfertility was associated with an increased in abdominal wall defects, penoscrotal hypospadias, right ventricular

[1] The Newcastle-Ottowa scale is a tool for assessing the quality of non-randomised studies included in a systematic review. Studies are evaluated on the basis of eight items categorised into three groups: the selection of the study groups, the comparability of the groups and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively.

outflow tract obstruction and methylation defects causing imprinting disorders. IVF/ICSI was associated with an increased risk of polydactyly (being born with extra fingers or toes), more specifically of the hands. Limitations of this study included using fertility records that excluded those with unconfirmed subfertility, lack of a control group made up of individuals without any congenital anomalies and collection of information by questionnaire up to 10 years post pregnancy.

2.7. A cohort study comparing 326 ART infants and 652 naturally conceived infants found a greater risk of major congenital malformations in ART conceived infants , with musculoskeletal and urogenital malformations the most commonly reported major congenital malformations in this group (Farhangniya et al. 2013).

2.8. Qin et al. (2015) carried out a systematic review and meta-analysis that included 57 studies comprising a total of 119,874 infants conceived by ART and 1, 212, 320 infants conceived naturally. Analysis showed that ART conceived infants were at increased risk of congenital malformations when compared with those conceived naturally (RR 1.33; 1.24-1.43). The increased risk remained statistically significant when data were restricted to singleton births only, major congenital malformations and high quality studies. Results were, however, to be reviewed with caution due to heterogeneity between studies.

2.9. A recent review summarised the literature on neonatal outcomes of offspring conceived through IVF. This included literature on low birth weight and intrauterine growth restriction in IVF conceived singletons, congenital malformations and genetic disorders and imprinting disorders. The authors noted that while it is clear that IVF pregnancies are at increased risk of adverse perinatal outcomes, the majority of the children born following IVF will have a good outcome. The authors went on to conclude that for those with poorer outcomes this inevitably reflects aspects of the treatment but also the interplay with the underlying features that the couple bring to the pregnancy. Further research is needed to untangle this complex relationship to allow effective targeted interventions (Babooa & Chen 2015).

2.10. In 2014 a panel set up by European Society of Human Reproduction and Embryology (ESHRE) discussed the literature regarding birth defects and congenital health risks in children conceived through ART. The group concluded that babies born after assisted reproduction differ from neonates born form pregnancies originating from natural conception. They are born earlier, smaller and as a group tend of exhibit a small increase in birth defects. It was also concluded that the long-term developmental effects of ART on child and subsequent adult health

remains a subject worthy of further monitoring and investigation (ESHRE Capri Workshop Group 2014).

Effect of ART on genetic and epigenetic status

2.11. Epigenetics refers to the information in the genome over and above that contained in the DNA sequence. Epigenetic activity is closely linked with critical developmental steps which occur around the time of conception. A key phenomenon in early development is imprinting, where genes are epigenetically regulated and expressed according to parental origin. Imprinting syndromes can result in significant pathology and, although uncommon in the general population these conditions are thought to occur more frequently in the offspring of subfertile patients.

Studies indicating no relationship between ART and genetic/epigenetic status

2.12. A Canadian study evaluated X-chromosome inactivation in female newborns conceived by ART. X-chromosome inactivation is the process by which one of the two copies of the X-chromosome is silenced in the cells of females. Skewing occurs when one X-chromosome is silenced more often than the other and has been associated with spontaneous abortion, cancer and chromosome abnormalities. Umbilical cord blood was taken from 185 newborn females and a DNA methylation-sensitive assay was used to determine the degree of X-chromosome inactivation skewing. The results showed no significant difference in frequency of mild or extreme skewing, the distribution of skewing or the mean level of skewing between the IVF, ICSI and natural conception groups (Wu et al. 2015).

2.13. Lazaraviciute et al. (2014) conducted a systematic review and meta-analysis of DNA methylation levels and imprinting disorders in children conceived by IVF/ICSI compared with children conceived spontaneously. 18 papers were included in the review that found a higher risk of imprinting disorders in children conceived by IVF or ICSI compared to spontaneously conceived children. The review identified studies that looked at the following specific regions: KvDMR/KCNQIOTI, PEGI/MEST, IGF2, GRBI0, PEG3, HI9 or SNRPN. Within these regions, no association was found between ART status and DNA methylation.

Studies indicating a relationship between ART and genetic/epigenetic status

2.14. A retrospective cohort study by Whitelaw et al. (2014) examined DNA methylation in buccal cell DNA to compare the epigenetic status of children born following spontaneous or assisted conception. DNA methylation was assessed in PEG3, IGF2, SNRPN, LINE1 and INS. These regions were chosen on the basis of their known functions and

relevance to reproduction. Method of conception was significantly associated only with SNRPN. Methylation within SNRPN was higher in the ICSI group compared with spontaneous conception, but was not higher in the standard IVF group. SNRPN methylation was also related to duration of infertility, this effect was observed in the combined IVF/ICSI group and in the IVF group alone.

2.15. A review by Kurinczuk & Bhattacharya (2015) summarised the literature relating to rare chromosomal, genetic and epigenetic-related risks associated with infertility treatment. The review focused on structural chromosomal anomalies, chromosomal microdeletions, cystic fibrosis and congenital bilateral absence of the vas deferens and imprinting related disorders. The authors concluded that apart from the single gene defects associated with cystic fibrosis, it is unclear whether excess risks result from ART techniques or from the underlying infertility being treated.

Effect of embryo transfer stage on health outcomes

2.16. Chambers et al. (2015) used contemporary registry data from Australia and New Zealand to determine the risk of preterm birth after blastocyst embryo transfer. 43, 952 singleton and 3, 418 twin deliveries after transfer of blastocyst or cleavage stage embryos were included in the study. Among singleton deliveries, 34.9% were after transfer of cleavage stage embryos and 65.1% were after transfer of blastocysts. The results showed that blastocyst transfer was not associated with excess risk of preterm, low birth weight or being small for gestational age for singletons compared with cleavage stage embryo transfer. This result was in contrast to previous studies carried out in Canada, Sweden and the United States.

Effect of frozen embryo transfer on health outcomes

2.17. Pelkonen et al. (2014) carried out a register based cohort study to find out if there is a different risk of major congenital anomalies in children born after frozen-thawed embryo transfer (FET), (n= 1830), and children born after fresh embryo transfer (ET), (n= 2942). A group of 31 243 children born after spontaneous pregnancies was included as a reference group. The results showed no difference in risk between the two ART groups, however when comparing the combined ART with the reference group, risk of congenital anomaly was increased (aOR 1.24; 1.05-1.47).

2.18. In another study, Pelkonen et al. (2015) evaluated whether there is any difference in the physical health of singleton children born after FET (n=1825) compared to children born following fresh ET (n=2933) during a three year follow up. No difference in hospital admissions was found

between the FET and fresh ET groups. However when the combined ART group was compared to a reference group of children born following spontaneous pregnancies (n=31 137) the risk of hospital admission in the ART group was slightly increased (aOR 1.10; 1.02-1.19).

Effects of PGD on health outcomes

2.19. A study by Winter et al. (2014) compared the cognitive and psychomotor development and 5 to 6 year old singletons born after preimplantation diagnosis (PGD), (n=47), with matched controls born after ICSI (n=49) and spontaneous conception (n=48). Cognitive development did not differ between the three conception groups. Analysis of motor development showed that motor capacity of PGD singletons did not differ significantly from the two control groups. However, ICSI children demonstrated poorer motor development than spontaneously conceived children, especially on balance tasks. The authors speculate that this difference may be related to low fertility in ICSI patients.

2.20. A prospective cohort study was carried out to determine whether embryo biopsy for PGD influences neonatal outcomes. Children born following PGD (n=242) were recruited along with children born after ICSI (n=242) and children born following spontaneous conception (n=733), matched for maternal age, parity and body mass index. The results showed that there was no increased risk of intrauterine growth restriction or low birth weight in the PGD group compared to the spontaneous conception group. However, the ICSI group was at increased risk of both these complications even after controlling for a number of factors. The fact that increased risk was found in the ICSI group, but not in the PGD group who will have also undergone an ICSI procedure, suggests that the increased risk could be due to the underlying infertility in the ICSI group (Eldar-Geva et al. 2015)

Effect of in vitro maturation on health outcomes

2.21. Foix-L'Hélias et al. (2014) carried out a prospective cohort study including infants conceived by ICSI with (n=38) or without (n=38) in vitro maturation (IVM). Mothers of infants born after ICSI with IVM all had polycystic ovarian syndrome, whilst infants born after ICSI alone mostly had fathers with severe infertility. The results of the study showed no difference in height and weight development of boys born following ICSI and IVM compared with boys born following ICSI alone. However, ICSI with IVM girls had greater weight, height and head circumference than controls at birth and the difference was maintained over time. At aged one and two years, the ICSI with IVM girls had greater BMI than girls born following ICSI alone. Limitations of this study include small sample size and an inability to separate out a possible effect of the underlying polycystic ovarian syndrome in the mothers of IVM girls.

Effect of egg activation on health outcomes

2.22. One study in Belgium evaluated neonatal and neurodevelopmental outcomes of children aged 3-10 years born following assisted oocyte activation (AOA). Vanden Meerschaut et al. (2015) collected data on 21 children aged three to 11 years, born following ICSI with AOA in their centre. The process involved injecting the sperm into the egg along with injection of calcium chloride, followed by a 2-fold calcium ionophore exposure of the injected egg. A control group was not included in this study as validated norm values were available for the tests and questionnaires used. No serious adverse effects of AOA on neonatal and neurodevelopmental outcomes were identified in the study; however sample size was too small to reach a definitive conclusion.

Effect of assisted hatching on health outcomes

2.23. Jwa et al. (2015) carried out a retrospective cohort study to assess the risk of major congenital anomalies in children born after embryo transfer with assisted hatching. Among the 72, 125 cycles that were included in the analysis, assisted hatching was performed in 35, 488 cycles. Overall risk for major congenital anomalies were not significantly different between the assisted hatching and non-assisted hatching groups after adjusting for maternal age, calendar year, fetal sex, embryo stage at transfer and status of cryopreservation.

Effect of ovarian hyperstimulation on health outcomes

2.24. Seggers et al. (2014) investigated whether ovarian hyperstimulation is associated with higher blood pressure in 4-year-old IVF offspring. The study compared blood pressure measurements between children born after IVF with controlled ovarian hyperstimulation (COH-IVF), (n=68), children born after IVF in a modified natural cycle (MNC-IVF), (n=57), and children conceived naturally to subfertile couples (Sub-NC), (n=90). Splitting IVF groups into COH-IVF and MNC-IVF allowed the effects of controlled ovarian hyperstimulation to be assessed. Systolic blood pressure (SBP) percentiles were found to be significantly lower in the MNC-IVF group, compared to the COH-IVF and Sub-NC groups. The difference between COH-IVF and MNC-IVF remained significant after adjusting for current, early life and parental characteristics. This supports the hypothesis that controlled ovarian hyperstimulation is associated with higher SBP percentiles in 4-year-old offspring. Skinfold thickness at the bottom point of the shoulder blade (a measure for truncal fat) was also found to be higher in the COH-IVF group compared to the Sub-NC group.

Hospital costs associated with ART

2.25. An Australian study carried out by Chambers et al. (2014) calculated the

hospital utilisation and associated costs of ART and non-ART singletons during the first five years of life. The results showed that ART children (n=2 199) had a significantly longer length of hospital stay during their birth admission and a 20% increased risk of being readmitted during the first five years of life compared with non-ART children (n=224 425). Being an ART child also predicted higher costs of hospital care both during the birth admission and up to five years of life.

3. Conclusion

3.1. This paper outlines research looking at health outcomes in children conceived using ART, published between October 2013 and October 2015. Of the 24 studies identified, 16 indicated that ART technologies are associated with an increased risk of adverse health outcomes, six studies found no relationship between ART and health outcomes and two studies compared different ART techniques with no control group of spontaneously conceived children.

3.2. Since October 2013, a number of large-scale studies have been carried out in this area. The largest study investigated congenital anomalies and included nearly 350,000 children. However, the results of several of the studies presented should be interpreted with caution due to low participant numbers. For example, one study included only 21 participants some had less than 50 participants per group. SCAAC members are asked to consider the research outlined and inform the executive of any future or current research to note.

3.3. Members are asked to put forward their views on whether the HFEA should:

- consider any areas of work in further detail or monitor any areas for particular attention.
- consider reviewing information clinics are required to make available to patients and the information the HFEA makes available to patients.

4. References

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Annex A – Additional references provided by Daniel Brison

Embryo Quality

- The phenotype of an IVF child is associated with peri-conception measures of follicular characteristics and embryo quality. (Green et al 2014)
- Birth weight in IVF singleton births is not associated with blastocyst quality (Stewart 2015) SUPPLEMENT
- Birth weight is associated with inner cell mass grade of blastocysts (Licciardi at al 2015)

Extended Embryo Culture

- Male gender explains increased birthweight in children born after transfer of blastocysts (Kaartinen 2015)

Number of Oocytes Retrieved

- Increased risk of preterm birth and low birthweight with very high number of oocytes following IVF: an analysis of 65 868 singleton live birth outcomes (Sunkara et al 2015)

IVF vs Natural

- Influence of in vitro fertilization and embryo transfer on the physical and intellectual development of the children at pre-school age. (Zuo et al 2014) ABSTRACT: http://europepmc.org/abstract/med/25512286
- Singleton birth weight by gestational age following in vitro fertilization in the United States (Dickey et al 2015)
- Association of in vitro fertilization with global and IGF2/H19 methylation variation in newborn twins (Loke 2015)
- Asthma and asthma medication use among 4-year-old offspring of subfertile couples – association with IVF? (Kuiper et al 2015)
- Right ventricular dysfunction in children and adolescents conceived by assisted reproductive technologies (von Arx 2015)
- Long term prognosis of children born through assisted reproductive technologies in Japan (Kojima et al 2015) (SUPPLEMENT)]
- Perinatal outcomes associated with assisted reproductive technology: the Massachusetts Outcomes Study of Assisted Reproductive Technologies (MOSART) (Declerq et al 2015)

Fresh vs FET

- Changes in singleton live birth weights in a large IVF practice over an 18 year period. (Maas et al 2015) (SUPPLEMENT)
- Difference in birth weight of consecutive sibling singletons is not found in oocyte donation when comparing fresh versus frozen embryo replacements (Galliano 2015)
- Surveillance of congenital malformations in infants conceived through assisted reproductive technology or other fertility treatments (Heisy et al 2015)
- Effect of embryo freezing on perinatal outcome after assisted reproduction techniques: lessons from the Latin American Registry of Assisted Reproduction (Schwarze 2015)

- Siblings conceived with assisted reproductive technology: birthweight and gestation differences in fresh vs frozen cycles (Luke, Wantman et al 2015) (SUPPLEMENT)

Birth Defects

- Comparison of live-birth defects after luteal-phase ovarian stimulation vs. conventional ovarian stimulation for in vitro fertilization and vitrified embryo transfer cycles (Chen et al 2015)
- Neonatal complications and birth defects in infants conceived by in vitro fertilization (Xy et al 2015) ABSTRACT: http://europepmc.org/abstract/med/25919554
- Birth defects after assisted reproductive technology according to the method of treatment in Japan: nationwide data between 2004 and 2012 (Ooki et al 2015)

ADHD

- I was born following ART: how will I get on at school? (Abdel-Mannan & Sutcliffe 2014)