

Health outcomes in children born from assisted reproduction

Strategic delivery: Safe, ethical effective treatment Consistent outcomes and support Improving standards through intelligence

Details:

Meeting Scientific and Clinical Advances Advisory Committee (SCAAC)

Agenda item 4

Paper number SCAAC(19/06/2017)02

Meeting date 19 June 2017

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Output:

For information or decision? For information

Recommendation Members are asked to:

- consider any areas of work in further detail or monitor any areas for particular attention; and
- 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

1. Introduction

- 1.1. Assisted reproductive technology (ART) includes techniques such as egg freezing, in vitro fertilisation (IVF) and intra cytoplasmic sperm injection (ICSI). There is a possibility that children born from ART may be at risk of birth defects or developing longer term health issues, though this could be due to underlying infertility rather than the ART procedure.
- 1.2. SCAAC last discussed health outcomes following ART in October 2015. SCAAC raised concern that research in this area involved small sample sizes meaning that results must be interpreted with caution. The Committee agreed that patient information about birth weights should be drafted to be put on the HFEA website.
- 1.3. Since 2015, 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.
- 1.4. 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*
- 1.5. 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.
- 1.6. This paper summarises key research findings between October 2015 and May 2017

2. Research

Studies comparing fresh and frozen embryo transfer

- 2.1.** Shapiro et al. (2016) investigated birth weight differences between fresh and thawed embryo transfer. It was found that the adjusted mean birth weight was 166g lower after fresh blastocyst transfer than after thawed embryo transfer.
- 2.2.** A study by Maheshwari et al. (2016) using HFEA data compared neonatal outcomes of 95,911 fresh cycles and 16,521 frozen cycles. The adjusted risk ratios of low birth weight (RR 0.73 ,0.66-0.80) and very low birth weight (RR 0.78 ,0.63-0.96) were lower after frozen embryo transfer, though risk of high birth weight was higher (RR 1.64, 1.53-1.76). No difference was found in the risk of preterm birth, very preterm birth and congenital abnormalities.
- 2.3.** Prevalence of congenital abnormalities following four different ART procedures were analysed in a study by Beltran Anzola et al. (2017). There was a total of 2750 babies and fetuses included in the study born from either standard IVF, ICSI, FET-IVF, FET-ICSI. Congenital anomalies were found in 134 babies and fetuses (4.9%). Risk of congenital anomalies was not increased in fresh embryo transfer.

Comparing different IVF procedures

- 2.4.** Comparisons were made in a retrospective cohort study by Mak et al. (2016) between unstimulated/natural cycle IVF(NCIVF) and stimulated IVF. The overall mean birthweight was 163g higher in the NCIVF group, and there was a reduced risk of low birthweight. After adjustment for maternal age, infertility diagnosis, ICSI fertilisation, blastocyst transfer and number of embryos transferred, reduced risk of low birthweight in NCIVF was still significant.
- 2.5.** A population-based registry study by Ginström Ernstad et al. (2016) compared neonatal outcomes of 4819 singletons after blastocyst transfers with outcomes after 25,747 cleavage stage transfer and 1,1986,394 after spontaneous conception. Rate of low birthweight and being small for gestational age were both lower in singletons born after blastocyst transfer compared to cleavage stage transfer. Singletons born after blastocyst transfer were not at increased risk of birth defects compared with cleavage stage transfer and spontaneous conception.
- 2.6.** A Japanese study by Tatsumi et al. (2017) compared 3136 natural fresh single embryo transfer (SET) cycles with 792 cycles that were induced with a drug called letrozole. There was no significant difference in congenital abnormalities between the two groups.

Comparing ART children with spontaneously conceived children

Studies indicating elevated risk of adverse outcomes

- 2.7.** A study by Dhalwani et al. (2016) comparing risks of adverse perinatal outcomes between ART and naturally conceived singleton births found that

ART conceived singletons were 33g lighter than singletons conceived naturally. The odds of being small for gestational age and low Apgar score¹ were not significantly different between the two groups.

- 2.8.** A systematic review by Qin et al. (2016) found 15 studies involving 6,420 dichorionic twins conceived with ART and 13,650 dichorionic twins conceived naturally published between 2003 and 2014. Preterm birth in four studies (out of 12) and very preterm birth in three studies (out of 10) were significantly higher in ART pregnancies. Very preterm birth was significantly associated with ART in three studies of the ten studies. Overall, there was higher risk of preterm birth and very preterm birth in ART pregnancies, with substantial evidence of heterogeneity². Low birthweight also occurred more in ART twins in 7 out of 9 studies, also with high heterogeneity. In 8 studies reporting neonatal intensive care unit admission, there was similar risk in the ART group as the control with high heterogeneity. In 14 studies reporting congenital malformations, there was a higher risk in ART with low heterogeneity.
- 2.9.** A study by Luke et al. (2017a) compared birth and infant outcomes of IVF pregnancies (n= 10,149) with naturally conceived pregnancies that were either fertile women (n= 441,420) or subfertile (n= 8054). Risks of low birthweight and preterm birth were greater in the IVF group. When compared with subfertile pregnancies, IVF had increased risks for low and very low birthweight and preterm and very preterm birth.
- 2.10.** A study by Luke et al. (2017b) compared infant outcomes in twin pregnancies, 6090 of which were fertile women, 724 subfertile and 3538 were IVF. The subfertile group had increased risk of very preterm birth and neonatal and infant death. The IVF group also had increased risk of preterm birth as well as birth defects. The authors concluded that their findings support use of single embryo transfer.

Studies indicating no risk of adverse outcomes

- 2.11.** A cohort study by Deltombe-Bodart et al. (2017) did not find any differences in obstetric, childbirth complications and neonatal outcomes between 575 ART twin pregnancies and 1005 spontaneous twin pregnancies.
- 2.12.** Neonatal outcomes of triplet births were studied by Morency et al (2016). The mean birth weight of infants born after 24 weeks was 1655 ± 550 g and rate for small for gestational age was 28%. There were no differences in gestational age at birth, obstetrical, or neonatal outcomes between spontaneous and ART triplet conception.

¹ An Apgar score is an assessment of the physical condition of a newborn infant. Measures include heart rate, respiratory effort, muscle tone, response to stimulation and skin colouration which are scored from 0-2. The final score is the total number of points, with a score of 10 being the best.

² Heterogeneity is used in meta-analysis to describe the amount variation in study outcomes between studies included in a systematic review

2.13. An Iranian study by Pourali et al. (2016) looked at perinatal outcomes in ART twins compared with spontaneously conceived twins. Between 96 spontaneously conceived twins and 21 ART twins, neonatal outcomes such as weight, Apgar score <7, neonatal intensive care unit (NICU) hospitalisation, mortality, respiratory distress, and jaundice did not differ significantly.

Studies comparing ART children with spontaneously conceived siblings

2.14. A study by Seggers et al. (2016) looked at the Netherlands Perinatal Registry to assess neonatal outcomes of first and second-born children. There were two approaches: one involved four groups of siblings, who were either both spontaneously conceived (SC1-SC2), both IVF (IVF1-IVF2), or one IVF and one spontaneously conceived (IVF1-SC2 or SC1-IVF2). IVF was not seen to influence adverse outcomes. They also analysed all IVF children (n= 1,813) who had a naturally conceived sibling (n = 1,813). Neither approach found adverse effects of IVF, though maternal characteristics were thought to have influence over birthweight in the first approach.

2.15. Luke et al. (2016) carried out a longitudinal cohort study of women having two consecutive singleton births. Three fertility statuses were used: ART (A), fertile (F) and subfertile (S). They were divided into six groups depending on their fertility status at each birth: A-A, A-S, S-A, S-S, F-A, F-S and F-F. Birthweights were higher at second births (74-155g higher average) except for F-A women (average -16 lower). First births had an increase in risk for low birth weight in both subfertile and ART women. Second births also had increased risks for low birth weight as well as preterm birth for subfertile and ART women.

Neonatal outcomes in PGD

2.16. Birthweight after PGD/PGS was investigated by Jing et al. (2016). Two groups were included, 166 patients who underwent blastocyst-stage biopsy and frozen embryo transfer (BB-FET) and 129 patients who underwent cleavage-stage biopsy and fresh embryo transfer (CB-FET). In twins, birthweight was higher in the BB-FET than in CB-FET (2.70kg vs 2.50kg). No differences in incidences of perinatal deaths, birth defects, gender of newborns, and large for gestational age were detected.

2.17. A retrospective cohort study by Chang et al. (2016) assessed outcomes in IVF cycles in which PGD was used and compared with non-PGD cycles. The results consisted of 97,069 non-PGD cycles and 9,833 PGD cycles. The purpose of PGD included PGD for aneuploidy (55.6%), PGD for other reasons (PGD Other) 29.1% and PGD for genetic testing 15.3%. PGD for genetic testing cycles had reduced odds of lower birth weights than non-PGD cycles. In contrast, PGD aneuploidy cycles had higher odds of low birth weight compared with cycles without PGD.

2.18. In a study by Bay et al. (2016) PGD birth outcomes were compared with outcomes in children conceived spontaneously or after IVF with or without ICSI. They found that PGD pregnancies were significantly more at risk of preterm birth (adjusted OR 1.6; 95% confidence interval CI 1.0, 2.7), shorter gestation

(mean difference -3.4 days; 95% CI -5.7, -1.1 days), and longer neonatal admission (mean difference 21 days; 95% CI 15, 28 days). Risks were comparable to IVF/ICSI pregnancies. In subanalyses adverse outcomes in PGD for monogenetic disorders were comparable to those of children born from parents with monogenetic disorder without PGD. Risk of adverse outcomes were concluded to be more related to the underlying parental condition rather than the PGD procedure.

Weight in early childhood

- 2.19.** Weight in early childhood in different modes of conception was investigated by Yeung et al. (2016b). Smaller size was significantly associated with fertility treatment from birth to 3 years, though this was a result of higher rate of multiples in fertility treatment. They found that 969 singletons conceived with fertility treatment did not differ in growth with children conceived without treatment (n=2471). Twins conceived with ovulation induction with or without intrauterine insemination (OI/IUI) (n=368) weighed 122g less after follow up when compared with twins conceived without treatment (n=1076). No differences in growth measures were observed between twins conceived with ART and twins conceived without fertility treatment. Odds of rapid weight gain at 4, 9 and 12 months was found to be 2-3 times greater in infants conceived without infertility treatment in earlier months.
- 2.20.** Longitudinal growth of French singleton children born after IVF with or without ICSI was compared with spontaneously conceived children in a study by Meddeb et al. (2017) from birth to 5 years of age. The study compared 118 children born after IVF-ICSI with 320 spontaneously conceived children. BMI means were not significantly different between groups. Children in the IVF-ICSI group had a significant decrease in BMI ($p < 0.05$) between birth and one year of age.

Congenital abnormalities

- 2.21.** A study by Levi Setti et al. (2016) compared perinatal outcomes and incidence of congenital abnormalities in infertile couples. This consisted of 2414 ART pregnancies with 582 spontaneous conceptions. There was no difference found in birth weight. Congenital anomalies were diagnosed in 90 babies (3.8%) in the ART group, compared to 15 (3.3%) in the control group. The rate of overall rate of major congenital anomalies across both groups (105/2800) was significantly higher (2.0% vs 3.75%, $p = 0.0002$) than those recorded by the European Surveillance of Congenital Anomalies (EUROCAT).
- 2.22.** A study by Iwashima et al. (2017) measured rates of congenital heart defects (CHD) in newborns born from ART and spontaneous conception. There were 2746 births, 410 of which were from ART. A total of 111 cases of CHD were found: 17 cases in the ART group (4.1%) and 94 cases (4.0%) in the spontaneous conception group. There were 19 severe cases of CHD in the ART group and five severe cases in the spontaneously conceived group,

though this was not significant ($P=0.892$). Overall, there was not an increased risk identified with ART.

- 2.23.** A case control study by Schofield et al. (2017) collected data from a paediatric cardiac service at the Royal Brompton Hospital, to determine rates of ART in cases of children who were diagnosed with congenital heart disease (CHD). They found that 5.4% of cases were ART children. Their findings did not suggest an overall association between CHD and ART.

Risk of cancer

- 2.24.** A population-based cohort study carried out by Reigstad et al. (2016) involved an analysis of 1,628,658 children born between 1984 and 2011, 25,782 of whom were conceived via ART. Cancer occurred in 4554 children, 51 of whom were ART children. Risk of overall cancer was not significantly elevated; however increased risk of leukaemia and Hodgkin lymphoma was observed in ART conceived children compared to non-ART children.
- 2.25.** An Israeli study (Lerner-Geva et al. 2016) considered risk of cancer in 9042 ART children compared to 211,763 spontaneously conceived children from 1997 to 2004. Overall risk of cancer was elevated in the ART group, but this was not statistically significant. Based on small numbers, there was higher risk of retinoblastoma and renal tumours in the ART group.
- 2.26.** A review by Reigstad et al. (2017) found 23 studies assessing the risk of childhood cancer in ART. In 11 of 12 studies that assessed overall risk of cancer, there was not an elevated risk of cancer. The remaining study did find a significantly increased risk of cancer. Six out of 10 studies looking at risk of childhood leukaemia found there was an increased risk of leukaemia in ART children. There were conflicting findings for studies looking at cancer of the central nervous system.

Mental, social and cognitive development

Studies indicating hindered development

- 2.27.** Academic performance in ART conceived adolescents was compared with spontaneously conceived adolescents in a registry based cohort study by Spangmose et al. (2017). A total of 4766 ART conceived adolescents (2836 singletons and 1930 twins) were compared with 5660 singletons and 1930 twin controls. Academic performance was assessed by comparing test scores. The crude mean test score was higher in both ART conceived singletons and ART conceived twins compared with spontaneously conceived adolescents. Adjusted mean scores were found to be significantly lower in ART conceived singletons compared with spontaneously conceived singletons.
- 2.28.** A study by Punamäki et al. (2016) compared ART children with naturally conceived children to see if there was a difference in mental health or social and cognitive developmental problems. They found that ART children ($n=255$) and spontaneously conceived children ($n=278$) did not have differences in symptoms, however there was a gender specific difference where ART boys

showed lower levels of cognitive problems than spontaneously conceived boys and ART girls showed higher levels than spontaneously conceived girls.

Studies indicating normal development

- 2.29.** Yeung et al. (2016a) carried out a questionnaire based study to examine development up to 36 months of children born from fertility treatment including OI/IUI (n=742) and ART (n=679), compared with children born without fertility treatment (n=3402), measuring five developmental domains: (fine motor, gross motor, communication, personal-social functioning, and problem-solving ability). ART (n=679) was associated with an increased risk for failing any developmental domain, and specifically the personal-social and problem solving domain, which was attributed to a higher proportion of twins in the ART group. 73 children had a developmental disability, frequency of diagnosis was not significantly different between children born without treatment and children born from any fertility treatment.
- 2.30.** A study by Anderson et al. (2016) of IVF twins and IVF singletons between the ages of 11-17 found that there was no difference between IVF twins (n=122) and IVF singletons' (n=158) parent depressive symptoms, parent-adolescent interactions or adolescent adjustment outcomes.
- 2.31.** Meijerink et al. (2016) carried out a study measuring behavioural performance, cognitive performance and motor performance in 5 year olds (n=103) born after TESE-ICSI. Of 89 children who completed follow up, behavioural, cognitive and motor performance were in the normal range compared with the theoretic distribution in the general population. Developmental problems/delays occurred in 4 children (3.8%), and autism was diagnosed in two children.
- 2.32.** Health outcomes in ART-conceived adolescents were analysed in a cohort study by Fruchter et al. (2017). A total of 253 ART-conceived children born between 1982 and 1993 were matched with controls. There were no differences found in general and mental health between the two groups. There were fewer cases of discharge from the military due to health reasons in the ART group (4% vs 8.3%). Male ART conceived adolescents had significantly more doctor's appointments than the reference group.
- 2.33.** A prospective cohort study by Kuiper et al. (2017) evaluated whether there was a difference in cognitive development and neurological conditions between 4-year-old IVF twins (n=48) and four-year-old IVF singletons (n=103). Unadjusted IQ scores were found to be lower in twins than in singletons with a mean difference of -5.4 points. In addition, weight and height of twins were lower than singletons. Neurological outcomes, systolic and diastolic blood pressure were similar between the two groups. Adverse effects in twins disappeared after adjustment for mediators and confounders suggesting that increased risk for impaired health and development in twins is not a result of IVF.
- 2.34.** A recent systematic review by Rumbold et al. (2017) identified 35 studies that assessed cognitive development from age four years or more in children conceived naturally and children born from fertility treatment. Among seven of

the studies that were rated high quality, no difference in cognitive outcomes was found between children conceived with conventional IVF and those conceived naturally. Findings for children born from ICSI were inconsistent, with one study comparing with spontaneously conceived children reporting lower IQ (5-7 points, on average) in ICSI children whereas two other studies reported no difference between the groups. There were also inconsistencies among the three studies when comparing ICSI children with conventional IVF, as one study found a significant increase in risk of mental retardation, one reported a small difference in IQ (three points lower, on average) and one found no difference at all. This suggests that further research is required to determine whether ICSI has an impact on the long term cognitive development of children.

- 2.35.** A study by Ramoğlu et al. (2016) assessed neonatal outcomes and neurodevelopment in infants born after IVF and spontaneous conception at 24-36-month follow-up. They looked at a total of 125 preterm infants, 65 from spontaneous conception and 60 from IVF. One infant in the IVF group had cerebral palsy. Neurodevelopmental outcomes were similar between the two groups; the most common neurodevelopmental abnormalities were delays in language and personal-social development.
- 2.36.** Neurodevelopmental assessment was carried out at two years of age in a study by Balayla et al. (2017). Children born after ART (n=175) show no difference in cognitive, motor or language scores when compared with naturally conceived children (n=1345).

Risk of neoplasms

- 2.37.** Risks of neoplasms among children based on mode of conception was studied by Wainstock et al. (2017) up to the age of 18 years. A total of 242,187 infants were included: 2603 (1%) conceived after IVF; 1721 (0.2%) conceived after ovulation induction treatments and 237,863 (98.3%) were conceived spontaneously. A total of 1498 neoplasms (0.6%) were diagnosed. Incidence density rate for neoplasms was higher for both children conceived after IVF (1.5/1000 person years) and ovulation induction treatments (1.0/1000 person years), as compared with naturally conceived children (0.5/1000 person years; Kaplan-Meier log rank, $P < 0.001$).

3. Conclusion

- 3.1.** This paper outlines research looking at health outcomes in children conceived using ART, published between October 2015 and May 2017. Since SCAAC last considered health outcomes in children conceived by ART, there has been an increase in the number of studies investigating the possible long term social, mental, and cognitive impacts of treatment on the children born. Studies looking at longer term developmental outcomes generally appear to have small sample sizes compared to studies that focus on birth outcomes. More systematic reviews need to be conducted to gain better understanding of the effects of ART on mental, social and cognitive development.

- 3.2.** There were some studies that compared siblings born either from ART or from spontaneous conception included in this paper. These studies can have value as it would be easier to distinguish where maternal characteristics may have influence, as opposed to the IVF treatment itself.

4. Recommendations

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

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