

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 6

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Output:

For information or decision? For information

Recommendation Member are asked to:

- Advise the Executive if they are aware of any other recent developments.
- 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 HFEA makes available to patients

Resource implications N/A

Implementation date N/A

Communication(s) N/A

Organisational risk Low Medium High

Annexes None

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 congenital malformations 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 June 2017](#). At this meeting the committee advised that there was no information on the HFEA website about birthweight, however, no specific action was recommended by the committee.
- 1.3.** 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 congenital malformations*
 - 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*
- 1.4.** Information for patients on the HFEA's [website](#) provides some information about the risks of congenital malformations and longer-term health issues associated with ART and states that research in this area is ongoing and a direct causal link is yet to be conclusively agreed.
- 1.5.** This paper summarises key research findings between June 2017 and December 2019.
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2. Research

Studies comparing the outcome of fresh and frozen embryo transfers

- 2.1.** A retrospective data analysis by Spijkers et al. (2017) compared the perinatal outcomes of children conceived by either fresh embryo transfer (fresh ET) (n=1,261) or frozen embryo transfer (FET) (n=2,519), with spontaneously conceived children as a control. There was a statistically significant difference in birth weight between FET and fresh ET children (3,512 ± 589 g vs 3,368 ± 616 g, p <0.001). FET children had an increased risk of high birth weight (HBW) (aOR 2.92; 1.503-3.482) and being large for gestational age (LGA) (AOR 1.47; 1.210-1.787) compared to fresh ET children, as well as higher birth weights compared to natural conceived children (3,443 ± 727 g vs 3,251 ± 797 g, p = 0.003).
- 2.2.** Maheshwari et al. (2018) conducted a systematic review and meta-analysis of 26 studies. FET children were at a lower risk of preterm birth (PTB) (RR 0.90; 95% CI 0.84–0.97), low birth weight (LBW) (0.72; 95% CI 0.67–0.77) and being small for gestational age (SGA) (0.61; 95% CI 0.56–0.67) compared to fresh ET children, but faced an increased risk of being LGA (RR 1.54; 95% CI 1.48–1.61) and HBW (RR 1.85; 95% CI 1.46–2.33). There was no difference in the risk of congenital anomalies and perinatal mortality between the two groups.

- 2.3.** Laval et al. (2019) studied the perinatal outcomes from 708 singleton live births after either FET or fresh ET. Children born after FET were on average 165.2g (95% CI 92.96–237.51) heavier than those born after fresh ET. No difference was found in gestation length.
- 2.4.** Beltran Anzola et al. (2019) compared the perinatal outcomes for babies conceived through FET (n=366), fresh ET (n=1961) and natural conception (n=6981). They found no significant difference between the SGA rate of babies conceived through fresh ET or natural conception (6.9% vs. 6.8%). However, they did find that SGA rate was influenced by maternal factors, such as multiparity, advanced maternal age, maternal underweight, maternal smoking or cessation during pregnancy, pre-existing hypertension and pregnancy induced hypertension. There was a significant difference between the LGA rate of babies conceived through FET and natural conception (6.6% vs. 3.2%) but this was also influenced by high maternal weight.
- 2.5.** Litzky et al. (2018) conducted a large retrospective cohort study in the USA to compare the birthweight babies conceived through either FET (n=55,898) or fresh ET (n=124,286). FET babies were 142g heavier ($P < 0.001$) than babies born from fresh ET, with a larger effect being found on male babies by 16g ($P < 0.0001$). FET babies were at a higher risk of macrosomia (RR 1.70, 95% CI 1.64-1.76), but a lower risk of LBW (RR 0.52, 95% CI 0.48-0.56) compared to fresh ET babies.
- 2.6.** Maris et al. (2019) conducted a retrospective cohort study of the perinatal outcomes in both FET children (n=371), using a closed vitrification system, and fresh ET children (n=127). The birth weight of FET children was 205 g heavier than fresh ET children (3368 g vs. 3163 g, $P < 0.001$).
- 2.7.** A multicentre cohort study by Anav et al. (2019) investigated the effect of FET on birth weight in siblings conceived using the same egg/embryo provider. The first cohort included an older sibling that were conceived after fresh ET (n = 158) and younger siblings after FET (n = 158). The second cohort included older and younger siblings that were both conceived using FET. In the first cohort the mean birth weight of the FET group was significantly higher than that of the fresh ET group (3508.9 ± 452.4 g vs 3237.7 ± 463.3 g; $p < 0.01$). In the second cohort the mean birth weight was higher for the younger siblings by 93.1 g, but this difference is not significant (3430.2 ± 347.6 g vs 3337.1 ± 391.9 g; $p = 0.3789$).
- 2.8.** Zhang et al. (2018) conducted a retrospective cohort study of children born after fresh ET (n = 2059) or FET (n = 2053). The mean birthweight of FET children was significantly higher than fresh ET children (3468.7 ± 475.3 vs. 3386.7 ± 448.1). The frequencies of LBW and SGA after FET were significantly lower than those after fresh ET (1.7% vs. 3.0 and 4.4% vs. 6.7%). FET resulted in higher frequencies of macrosomia and LGA (15.1% vs 10.2 and 22.8% vs. 17.5%) than fresh ET. Furthermore, the incidence of congenital malformations was not different between the two groups (1.2% vs. 0.9%).
- 2.9.** Ainsworth et al. (2019) conducted a retrospective cohort study of women who underwent fresh ET (n=87) or FET (n=49) at the Mayo Clinic from 2010 to 2014. Birth length (50.4 ± 3.1 cm v 51.5 ± 2.7 cm) and head circumference (34.0 ± 1.6 cm vs 34.8 ± 1.6 cm) were significantly different in infants delivered after fresh ET vs FET. There was a statistically significant difference in birth weight between infants born after fresh ET compared to FET ($3,066.9 \pm 857.8$ g vs $3,341.7 \pm 761.6$ g). However, this difference did not persist when adjusted for gestational age, sex, and maternal factors. Childhood growth measurements including age- and sex-specific weight, and body mass index percentiles were not significantly different between groups.

- 2.10.** A retrospective study by Hwang et al. (2019) looked at the perinatal outcomes of children conceived by either fresh ET or FET between 2004 and 2013. FET children were less likely to be SGA (aOR 0.56; 95% CI, 0.44–0.70) and LBW (aOR = 0.72; 95% CI, 0.59–0.88) than fresh ET children but more likely to be LGA (AOR = 1.47; 95% CI, 1.26–1.70) and experienced greater odds of infectious disease (aOR = 1.46; 95% CI, 1.03–2.06), respiratory (aOR = 1.23; 95% CI, 1.07–1.41), and neurologic (aOR = 1.32; 95% CI, 1.04–1.68) conditions.
- 2.11.** A retrospective study by Tsuji et al. (2017) looked at the birth weight of children born after FET (n=2415) and fresh ET (n=323) in a single facility. The mean birth weight of FET children was significantly higher than that of fresh ET children (3118.0 ± 374.9 g vs 3031.9 ± 369.3 g).
- 2.12.** A retrospective cohort study by Shavit et al. (2019) looked at of twin pregnancies conceived by either FET (n=614) or fresh ET (n=159). The FET children had a significantly higher birthweight (p=0.002), and lower rates of SGA (p=0.003), LBW (p=0.003) and very LBW (p=0.006). No significant difference was found between groups regarding gestational age at delivery, term birth (after 37 weeks of gestation), twin discordancy rate, fetal major malformation rate, and hospitalisation duration.
- 2.13.** Using data from the HFEA anonymised register, Kamath et al. (2018) analysed perinatal outcomes of live births resulting from fresh ET (n=95,779) and FET (n=18,005) cycles between 1991 and 2011. Fresh ET children had a significantly higher risk of PTB (aOR 2.70, CI 2.37–3.05) and LBW (aOR 2.76, CI 2.44–3.13) in singletons with initial multiple gestational sacs but there was no significant difference in the risk of PTB (aOR 1.08, CI 1.00–1.16) or LBW (aOR 1.08, CI 1.00–1.16) in singletons with an initial single gestational sac following transfer of ≥2 embryos compared to those following single embryo transfer. In frozen cycles, there was a significantly higher risk of PTB (aOR 2.13, CI: 1.55–2.93) and LBW (aOR 2.61, CI: 1.87–3.64) in singletons with initial multiple gestational sacs but there was no significant difference in the risk of PTB (aOR 1.02, CI: 0.88–1.18) or LBW (aOR 0.91, CI: 0.77–1.07) in the singletons with an initial single gestational sac following transfer of ≥2 embryos compared to those following single embryo transfer.

Studies comparing different IVF methodologies

Comparing IVF protocols

- 2.14.** In a randomised control trial conducted by Tomás et al. (2019) perinatal outcomes for children conceived using either a gonadotrophin-releasing hormone (GnRH) antagonist or long GnRH agonist protocol were compared. 1050 Women were randomised in a ratio 1:1 resulting in 521 confirmed clinical pregnancies. Similar perinatal outcomes were found after both protocols. Fresh ET children had a mean birthweight of 3264 ± 662 g in the antagonist and 3341 ± 562 g in the agonist group (P = 0.37). LBW was found in 12.4% versus 7% (P = 0.19) and very LBW in 2.9% versus 1% (P = 0.34). In FET cycles, the perinatal outcomes were similar. SGA and LGA rates were similar in both protocols for fresh and FET.
- 2.15.** A retrospective study by Ginström Ernstad et al. (2019) analysed the perinatal outcomes for different protocols used in FET. There was no significant difference in PTB or LBW between the different protocols. However, programmed frozen cycles, when compared to both natural and stimulated frozen cycles, were associated with a higher risk of post term birth (RR. 1.59, 95% CI 1.27–2.01 and RR 1.98, 95% CI 1.47–2.68) and macrosomia (RR 1.62, 95% CI 1.26–2.09 and RR 1.40, 95% CI 1.03–1.90).

2.16. Kamath et al. (2018) performed a systematic review and meta-analysis of 4 studies to determine differences in perinatal outcomes between stimulated IVF and natural or modified natural cycles of IVF. The analysis included 96,996 live births after stimulated of IVF and 704 after natural or modified natural cycle IVF. The risk of PTB (RR 1.27, 95% CI 1.03 to 1.58) and LBW (RR 1.95, 95% CI 1.03 to 3.67) were significantly higher after stimulated compared with natural or modified natural cycle IVF. One study included data on SGA, LGA and congenital abnormalities but found no statistically significant difference between the different IVF procedures.

In vitro maturation

2.17. A retrospective observational study by Mostinckx et al. (2019) looked into the obstetric and neonatal outcomes of women with PCOS who required IVF to conceive and either underwent in vitro maturation (IVM) (n=164) or controlled ovarian stimulation (n=229). Children born after IVM and controlled ovarian stimulation had a similar birthweight (0.51 ± 0.94 vs 0.33 ± 1.05 , $P = 0.19$) and similar rate of PTB. The total malformation rate was 4.1% in singletons after IVM and 2.4% in singletons after controlled ovarian stimulation.

2.18. Roesner et al. (2017) conducted a prospective controlled single-blinded study to investigate the mental development of children conceived using IVM (n=21) compared to IVF (n=21) and ICSI (n=21). The study included 63 pregnancies, with 70 live births. IVM children did not show differences in their neuropsychiatric development at the age of 2 compared IVF and ICSI children (Bayley score 91.3 ± 21.0 vs 96.8 ± 13.2 vs 103.9 ± 13.1). There was also no difference between IVM children, and the control group of children conceived spontaneously (96.6 ± 16.4 vs 103.2 ± 9.4).

Cleavage vs blastocysts stage embryo transfer

2.19. Alviggi et al. (2017) conducted a systematic review and meta-analysis of 14 studies to compare perinatal outcomes of singleton pregnancies conceived using either cleavage or blastocyst stage embryo transfer. There were significantly higher rates of PTB (11 studies, n = 106 629 participants; RR, 1.15 (95% CI, 1.05 – 1.25); $P = 0.002$) and very preterm birth (VPTB) (7 studies, n = 103 742; RR, 1.16 (95% CI, 1.02–1.31); $P = 0.03$) after blastocyst stage embryo transfers compared to cleavage stage embryo transfers in fresh cycles. The risk of PTB and VPTB was similar after blastocyst and cleavage stage transfers in frozen and fresh plus frozen cycles. There were fewer SGA deliveries after blastocyst compared with cleavage stage transfer in fresh cycles but a similar number in frozen cycles. Conversely, there was an increased number of LGA children after blastocyst compared with cleavage-stage transfer in frozen cycles (2 studies, n = 39 044; RR, 1.18 (95% CI, 1.09–1.27); $P < 0.0001$) and no differences between the two groups in fresh cycles (four studies, n = 42 982; RR, 1.14 (95% CI, 0.97–1.35); $P = 0.11$). There were no differences with respect to LBW, very low birth weight (VLBW) or congenital anomalies between blastocyst and cleavage stage transfers irrespective of the cryopreservation method employed.

2.20. Marconi et al. (2019) used data from the HFEA anonymised register, from 1999 to 2011, to compare the perinatal outcomes of children conceived using either fresh blastocysts stage embryo transfer (n=11,152) or fresh cleavage stage embryo transfer (n=55,995). There was no significant difference between the blastocysts and cleavage stage embryo transfer children in regards to PTB (aRR, 1.00; 99.5% CI, 0.79–1.25), very-PTB (aRR, 1.00; 99.5% CI, 0.63–1.54), very-low birth weight (aRR, 0.84; 99.5% CI, 0.53–1.34), low birth weight (aRR, 0.92; 99.5% CI, 0.73–1.16), HBW (aRR, 0.94; 99.5% CI, 0.75–1.18) and very-HBW (aRR, 1.05; 99.5% CI, 0.66–1.65). The risk of congenital anomaly was 16% higher in the blastocyst-stage group than in the cleavage-stage

group, but this was not statistically significant (aRR, 1.16; 99.5% CI, 0.90–1.49). The chance of having a healthy baby (born at term, with a normal birth weight and no congenital anomalies) was not altered by extended culture (aRR, 1.00; 99.5% CI, 0.93–1.07). In the sub-group analysis, the risk of congenital anomalies was significantly higher after blastocyst-stage embryo transfer (aRR, 1.42; 95% CI, 1.12–1.81).

Egg vs embryo cryopreservation

- 2.21.** Ho et al. (2017) conducted a retrospective cohort study comparing pregnancy and perinatal outcomes for children born after either egg (n=68) and embryo cryopreservation (n=446). There were no differences in perinatal outcomes between the two groups. The mean gestational age at delivery was 39.1 vs 38.6 weeks, mean birth weight 3284.2 vs 3161.1 g, PTB rate 5.9 vs 13.4%, and multiple gestation rate 5.9 vs 11.6%.

Studies of outcomes after embryo testing

- 2.22.** In a randomised controlled trial by Kuiper et al. (2018) 408 women were randomly assigned to IVF either with or without preimplantation genetic screening (PGS) on day 3. This led to 59 live births in the PGS group and 85 in the control group. These children were followed up at the age of 9 with 43 PGS children and 56 control children taking part in the study. There was no statistically significant difference in the neurological optimality score (NOS) between the PGS and control children (51.5, 95% CI 49.3-53.7 vs 53.1, 95% CI, 50.5 - 55.7). The prevalence of adverse neurological outcomes did not differ between the groups (40% vs 34%), although the prevalence of complex minor neurological dysfunction in both groups was rather high. Intelligence quotient (IQ) scores of the two groups were not significantly different and the behaviour, blood pressure and anthropometrics of both groups did not differ. Mean blood pressures of both groups were above the 60th percentile.
- 2.23.** Belva et al. (2018) studied the effects of day 3 embryo biopsy for pre-implantation genetic testing for monogenic (PGT-M) and structural chromosomal aberrations (PGT-SR) on body composition and blood pressure at 6-year olds compared to ICSI conceived children. There was no significant difference between the PGT-M, PGT-SR and ICSI conceived children in their anthropometry (including weight, height, BMI, skinfold thickness, waist and mid-upper arm circumference) and blood pressure.
- 2.24.** Heijlgers et al. (2019) conducted an observational cohort study investigating the growth, health and motor development health of children conceived after preimplantation genetic diagnosis (PGD) (n=103) compared to those conceived after IVF/ICSI (n=90) or natural conception (n=58). At 5 years old, the mean height, weight, and body mass index were comparable for all groups. The rate of acute and chronic illnesses was similar in all groups. Motor milestones were achieved on time, but the IVF/ICSI group had a slightly younger mean sitting age. None of the children had severe neurological problems. Congenital abnormalities were found in 5.8% of PGD children compared to 4.4% in IVF/ICSI and 8.6% in spontaneously conceived children.
- 2.25.** A study by Heijlgers et al. (2018) looked into the congenital malformation rate in children conceived following PGD between 1995 and 2014. The study included 364 children resulting from a live birth, 2.5% had major malformations, which is consistent with other PGD cohorts and comparable to the prevalence reported by the European Surveillance of Congenital Anomalies (EUROCAT). 20% of the children were born premature (< 37 weeks) and less than 15% had a LBW.

Studies of birthweight and weight in early childhood of ART children

- 2.26.** A large-scale cohort study by Hann et al. (2018) linked HFEA register data to data from the Scottish maternity and child health databases. The study compared the outcomes for 5,200 children conceived using ART to 20,800 spontaneously conceived children. Fresh ET babies weighed on average 93.7g less (95% CI, 76.6- 110.6g) than spontaneously conceived babies. FET babies weighed 57.5g more (95% CI, 30.7 - 86.5g) than spontaneously conceived babies. Fresh ET babies grew faster but were still 171g lighter at 6-8 weeks than spontaneously conceived babies and 133g lighter than FET babies. FET and spontaneously conceived babies were comparable by this stage. At 4-7 years old, both fresh ET and FET were comparable to naturally conceived children.
- 2.27.** In a retrospective study of HFEA register data by Castillo et al. (2019), the birth weight of children conceived through IVF for one publicly funded tertiary care centre were compared between 1991 to 2015. The study included singleton births conceived using the mother's own eggs. There was an increase in birth weight of 7.4g per year; an increase of 180g across the 25-year period. Fresh and FET babies showed a similar increase in birth weight. FET babies were on average 53g heavier than fresh ET babies (P= 0.035).

Studies of congenital abnormalities in ART children

- 2.28.** A meta-analysis of 30 papers by Hoorsan et al. (2017) compared the rate of congenital malformations in children conceived through ART (n=315,402) and spontaneous conception (n=5,154,779). The odds ratio for LBW 1.89 (95% CI, 1.36 to 2.62), PTB 1.79 (95% CI, 1.21 to 2.63), cardiac abnormalities 1.43 (95% CI, 1.27 to 1.62), central nervous system abnormalities 1.36 (95% CI, 1.10 to 1.70), urogenital system abnormalities 1.58 (95% CI, 1.28 to 1.94) and musculoskeletal disorders 1.35 (95% CI, 1.12 to 1.64) were all statistically significant. The odds ratio for chromosomal abnormalities was not statistically significant 1.14 (95% CI, 0.90 to 1.44).
- 2.29.** Zhao et al. (2018) conducted a systematic review and meta-analysis of 46 studies. They found that there was an increased risk of congenital malformations in ART conceived children compared with spontaneous conception (RR 1.40; 95% CI 1.31–1.49). When looking at ART treatments in more detail, the study also suggested that IVF (20 studies) and ICSI (15 studies) increased the risk of congenital malformations in children when compared to spontaneous conception (IVF: RR 1.25; 95% CI 1.12–1.40; ICSI: RR 1.29; 95% CI 1.14–1.45). When considering the effect of plurality, the study suggested that singleton births (22 studies) and twin births (15 studies) the risk ratios were 1.41 (95% CI 1.30–1.52) and 1.18 (95% CI 0.98–1.42), respectively.
- 2.30.** A large-scale retrospective cohort study by Shechter-Maor et al. (2018) compared the outcomes of ART conceived children (n=71,050) and spontaneous conception (11,791,730) to investigate any association with congenital malformations. ART conceived children had a greater risk of congenital malformations than those conceived spontaneously (OR 2.14, 95% CI 1.94–2.35). The malformations most commonly associated with ART were cyanotic heart defects (OR 2.74, 95% CI 2.42–3.09), cleft lip and/or palate (OR 1.47, 95% CI 1.14–1.89), and hypospadias (OR 1.77, 95% CI 1.42–2.19). There were no differences in risk of omphalocele or neural tube defects between the two groups.
- 2.31.** Zhang et al. (2017) investigate the effect of different methods of ovarian stimulation on the risk of congenital abnormalities in children conceived through ART in a cohort of 4596 children. The study found that a human menopausal gonadotrophin and medroxyprogesterone acetate regimen did

not significantly increase the risk of congenital malformations compared with short protocol and mild ovarian stimulation, with adjusted odds ratio of 1.22 (95% CI 0.61–2.44) and 1.38 (95% CI 0.65–2.93), respectively, after adjusting for confounding factors.

- 2.32.** Zhu et al. (2018) investigated the risk of congenital malformations in children conceived through ART using either vitrified blastocyst transfer, vitrified cleavage stage transfer or fresh cleavage stage transfer of embryos. There was no difference in the risk of congenital malformations between children born after vitrified blastocyst transfers or vitrified cleavage transfers. For children born after cleavage embryo transfers at day 3, there was no difference in the risk of congenital malformations between fresh ETs and FETs.
- 2.33.** Henningsen et al. (2018) conducted a cohort study of children conceived through ART (n=90,201) or natural conception (n=482,552) over a 20-year period to determine if the risk of congenital malformation in ART children had changed over time. The participants were divided into 4 groups dependant on the year of their birth (1988–1992, 1993–1997, 1998–2002 and 2003–2007). The absolute risk for ART singletons being born with a major malformation was 3.4% vs. 2.9% among spontaneously conceived children. The relative risk of a major congenital malformation between all ART children and spontaneous children was similar through all four time periods ($p = 0.39$).

2.34. Studies of risk in cancer in ART children

Studies indicating elevated risk of adverse outcomes

- 2.35.** A retrospective study by Hargreave et al. (2019) investigated the association between different types of fertility treatments and cancer risk in a cohort of 1,085,172 children born in Denmark between 1996 and 2012. FET was associated with an elevated risk of paediatric cancer compared to natural conception with a hazard ratio of 2.43 (95% CI, 1.44 to 4.11) and an incidence rate difference of 26.9 per 100 000 (95% CI, 2.8 to 51). This difference was mainly due to an increased risk of leukaemia (14.4 per 100,000, hazard ratio of 2.87 (95% CI, 1.19 to 6.93)) and sympathetic nervous system tumours (10.1 per 100,000, hazard ratio, 7.82 (95% CI, 2.47 to 24.70)). There were no statistically significant associations with the use of the other types of fertility treatment examined.
- 2.36.** A retrospective cohort study conducted by Spector et al. (2019) looked at the incidence of childhood cancers among children born between 2004 and 2013 in the USA. The study included 275,686 children conceived using IVF and a cohort of 2,266,847 children conceived naturally (10 randomly selected children for every 1 child conceived via IVF). The overall hazard ratio between the IVF and naturally conceived children was 1.17 (95% CI, 1.00-1.36). The rate of hepatic tumours was higher among the IVF group than the non-IVF group (18.1 vs 5.7; hazard ratio, 2.46; 95% CI, 1.29-4.70) but the rates of other cancers did not differ between the two groups. There were no associations with specific IVF treatment modalities or indication for IVF.
- 2.37.** Wang et al. (2018) performed a systematic review and meta-analysis of 16 cohort studies and three case-control studies investigating a possible association between fertility treatment and childhood cancer risk. Children conceived using ART had a significantly increased risk for developing overall cancer (RR 1.16, 95% CI 1.01, 1.32), haematological malignancies (RR 1.39, 95% CI, 1.21 1.60) and other solid tumours (RR 1.57, 95% CI 1.14, 2.16). For specific cancers, ART children were associated with a significantly increased risk of leukaemia (RR 1.31, 95% CI 1.09, 1.57) and hepatic tumours (RR 2.26, 95% CI 1.32, 3.85).

2.38. Chiavarini et al. (2019) conducted a meta-analysis of 18 cohort studies and 15 case control studies to investigate the association between medically assisted reproduction and childhood cancer. The overall cancer risk was significantly increased in children conceived by medically assisted reproduction, ART, and IVF. The risk of haematological tumours, hepatic tumours, and sarcomas were increased in medically assisted reproduction (OR 1.54; 95% CI 1.18–2.02) and ART (OR 1.92; 95% CI 1.34–2.74). Medically assisted reproduction increased acute myeloid leukemia risk (OR 1.41; 95% CI 1.02–1.95) and ART increased neural cancer risk (OR 1.21; 95% CI 1.01–1.46).

Studies indicating no risk of adverse outcomes

2.39. In a study by Gilboa et al. (2019) ART children born in Israel who were members of Maccabi Health Services (MHS) between 1999 and 2016 were linked to the Israeli Registry of Childhood Cancer (IGS) to identify those with cancer diagnosed before 16 years of age. The risk for paediatric cancer after ART in general was 0.95 (95% CI, 0.76–1.19). The risk of paediatric cancers after IVF specifically was 1.09 (95% CI, 0.79–1.48). A further meta-analysis of 13 cohort studies did not reveal increased risk for paediatric cancers (RR 0.99; 95% CI, 0.85–1.15).

2.40. Spaan et al. (2019) conducted a cohort study with prospective follow-up (median 21 years), including 47,690 children; 24,269 conceived through ART, 13,761 conceived naturally and 9,660 conceived either naturally or using fertility drugs in subfertile women (but not ART). Overall cancer risk was not increased in ART children, neither compared with spontaneous conception in subfertile women (HR: 1.00, 95% CI 0.72–1.38) nor compared with spontaneous conception in the general population (SIR = 1.11, 95% CI: 0.90–1.36). From 18 years of age onwards, the hazard ratio of cancer in ART conceived vs naturally conceived individuals was 1.25 (95% CI: 0.73–2.13). Slightly but non-significantly increased risks were observed in children conceived by ICSI or cryopreservation (HR = 1.52, 95% CI: 0.81–2.85; 1.80, 95% CI: 0.65–4.95, respectively). Risks of lymphoblastic leukemia (HR = 2.44, 95% CI: 0.81–7.37) and melanoma (HR = 1.86, 95% CI: 0.66–5.27) were non-significantly increased for ART-conceived compared with naturally conceived children.

Studies of mental, social and cognitive development in ART children

2.41. Heineman et al. (2019) conducted a longitudinal study to assess the effect of ovarian stimulation on cognitive development and behaviour at nine years old. The study included singletons born following IVF or ICSI with ovarian stimulation (n=57), modified natural cycle IVF/ICSI (n = 46) and born after spontaneous conception to subfertile couples (n = 66). There was no significant difference in total IQ scores between the children conceived through ovarian stimulation (114.8), modified natural cycles (114.0), or subfertility spontaneous conception (115.4). There was also no significant difference between the verbal IQ or performance IQ of the three groups. There was no significant difference between the groups found using NEPSY (a measure of specific domains of neuropsychological development (in this study, attention and executive functions, memory and learning and social cognition)). Behaviour was assessed using CBCL (questionnaire on behaviour completed by the parent) and TRF (questionnaire on behaviour completed by the teacher) and there was no significant difference in the scores for each of the three groups.

2.42. A longitudinal cohort study by Barbuscia et al. (2017) examined the cognitive development of children conceived through ART (n=150-180) or spontaneous conception (n=10,496–11,955) at the ages of three, five, seven and 11. At age three and five years, ART children had higher verbal

cognitive abilities than spontaneously conceived children ($P < 0.001$) but this difference consistently decreases over time and diminishes by age 11 years.

- 2.43.** Norrman et al. (2018) conducted a retrospective cohort study of school performance at primary school of children conceived with ART ($n=8,323$) or spontaneous conception ($n=1,499,667$) at nine years old. There was no significant difference between ART and spontaneously conceived children in the crude analysis of mean total score of 16 subjects (using percentiles). After adjustments for several confounders ART children had a lower mean total score compare to spontaneously conceived children (-0.72 , 95% CI -1.31 to -0.12 ; $P = 0.018$). There was also no significant difference between ART children and spontaneously conceived children in qualifying for secondary school (aOR 1.05; 95% CI 0.95–1.17, $P = 0.35$) or in poor school performance (AOR 0.98; 95% CI, 0.89–1.09, $P = 0.73$).
- 2.44.** Drenth Olivares et al. (2019) investigated the neurological condition at nine years of singletons born after controlled ovarian hyperstimulation IVF ($n=57$), modified natural cycle IVF ($n=46$) and born to subfertile parents after spontaneous conception ($n=66$). All groups were compared to a control of spontaneously conceived children ($n=282$). The Minor Neurological Dysfunction (MND) examination was used to create a NOS and identify the prevalence of the clinically relevant complex MND. The neurological condition of the three subfertile groups did not differ significantly. However, the NOS was lower and the prevalence of complex MND higher in children born to subfertile couples than in children of fertile couples (5.13, 95% CI 2.60–10.16).
- 2.45.** Diop et al. (2019) compared the prevalence of autism spectrum disorders (ASDs) in singleton babies conceived through ART ($n=10,147$) with those conceived spontaneously to subfertile women ($n=8072$) and those conceived to women with no indicators of subfertility ($n=441,898$). The risk of ASDs were not statistically higher in the ART (.07; 95% CI 0.88–1.30), subfertile (1.11; 95% CI 0.89–1.38), IVF (0.91; 95% CI 0.68–1.22), or ICSI (1.13; 95% CI 0.84–1.51) groups, even if the rate of PTB was the same across all groups.
- 2.46.** Aoki et al. (2018) investigate developmental outcomes of a cohort of 1085 children born after ART, compared to spontaneous conception, at ages two and three. At the age of two, no significant difference was found between children born through ART and those conceived spontaneously in development in any domain. At three years ART children were found to have a significant higher development in receptive language, expressive language and language concept than spontaneously conceived children.
- 2.47.** A study was conducted by Spangmose et al. (2018) to assess the academic performance of children at the age of 15-16 that were conceived by either FET ($n=423$) or fresh ET ($n=6072$) in Danish cohorts born from 1995 to 2001. The children were assessed according to their mean overall test score and test scores in Danish, mathematics, English, and physics/chemistry. There was no significant difference in the test scores between the FET and fresh ET conceived children, with an adjusted mean difference in the overall test score of +0.12 (95% CI -0.09 ; 0.34).
- 2.48.** Rumbold et al. (2017) conducted a systematic review of 35 studies, seven of which were considered high quality by the authors, to determine the effect of different IVF treatment types of cognitive development of ART conceived children. The studies deemed high quality showed no difference in cognitive outcomes between ART and spontaneously conceived children. There were inconsistent findings among studies that looked into the difference between ICSI and spontaneously conceived children. One study reported lower IQ among ICSI children whereas the remaining two high-quality studies reported no difference between groups. The three high-quality

studies comparing ICSI children with conventional IVF, one reported a significant increase in the risk of mental retardation, one reported a small difference in IQ and one no difference at all. There were scant studies examining exposure to embryo freezing, or less invasive treatments such as ovulation induction without IVF/ICSI.

Studies of physical development in ART children

- 2.49.** Reut Shiloh et al. (2018) studied the long-term cardiovascular disease risk in children born following IVF (n=2,603) and ovulation induction (n=1,721) compared to spontaneous pregnancies (n=237,863). They found no significant increase in risk in cardiovascular disease hospitalisations before the age of 18 between spontaneous pregnancies and IVF (1.05, 95% CI 0.63-1.74) or ovulation induction (0.97, 95% CI 0.55-1.71).
- 2.50.** Merino et al. (2019) conducted a multicentre study looking into the ovarian function of adolescents born from ART compared to those that were conceived naturally. ART adolescents had an older age of menarche than those that were naturally conceived. ART adolescence had lower incidence of ovulation (P=0.021) and higher luteinizing hormone serum levels (P=0.01). The incidence of oligomenorrhea and the cycle length were similar between ART adolescences and naturally conceived adolescence. ART adolescence had levels of anti-Müllerian hormone, inhibin B, follicle-stimulating hormone, oestradiol, and androgens similar to those that were naturally conceived. The ovarian morphology, ovarian volume, and follicle counts were similar in both groups.
- 2.51.** Goldsmith et al. (2018) conducted a cohort study to investigate the prevalence and clinical outcomes of cerebral palsy after ART (n=2914) compared with spontaneous conception (n=208,746). The prevalence of cerebral palsy (CP) was higher in ART children (7.2/1000 live births compared with naturally conceived births, 2.5/1000). Odds of CP were doubled for singletons; when stratified by gestational age odds were only increased in the under 32-week group. Prevalence of CP was increased in ART (9.9/1000 live births) and naturally conceived twins (8.4/1000 live births). Clinical outcomes were similar between ART and naturally conceived children.
- 2.52.** Meister et al. (2018) conducted a study to determine whether ART adolescence (n=54) had vascular alternations and premature vascular aging compared to age and sex matched controls (n=43). ART adolescences had a roughly 25% impairment of flow-mediated dilation of the brachial artery ($p < 0.001$) and increased pulse-wave velocity and carotid intima-media thickness. Most importantly, ambulatory blood pressure monitor (ABPM) values and blood pressure variability were markedly higher in ART adolescence than in control subjects. Eight of the 52 ART participants, but only one of the 43 control participants ($p = 0.041$ ART vs. controls) fulfilled ABPM criteria of arterial hypertension ($>130/80$ mm Hg and/or >95 th percentile).

Studies of donor conceived children

- 2.53.** A study by Kamath et al. (2017) used HFEA register data to compare the perinatal outcomes for children conceived using either donor eggs (n=5929) and autologous eggs (n=127,856) followed by fresh ET. In singleton births, the risk of PTB (aOR 1.56, 99.5% CI 1.34 to 1.80) and LBW (aOR 1.43, 99.5% CI 1.24 to 1.66) was increased in children conceived using donor eggs compared to autologous eggs. The risk of PTB was also increased (aOR 1.21, 99.5% CI 1.02 to 1.43) after egg donation compared with autologous IVF in multiple births.
- 2.54.** A study by Schwartz et al. (2019) investigated perinatal outcomes in singleton pregnancies using donor eggs (n=2105) compared to those using autologous eggs (n=69 615). They found an

increased risk of PTB (RR 1.39; CI 1.20–1.61) and LBW (RR 1.34; CI 1.16–1.55) in children conceived using donor eggs compared to those conceived using autologous eggs. Fresh ET using embryo created through donor eggs was associated with an increased risk for stillbirth compared to embryos created using autologous eggs (RR 3.73; CI 1.96–7.11), this association was not found when comparing FET (RR 1.15; CI 0.59–2.25).

- 2.55.** A retrospective cohort study conducted by Williams et al. (2018) looked at 12,137 children born after donor ART and found no overall increased risk of cancer, with a RR of 0.83 (95% CI 0.43–1.45). There was a small, significant increased risk of hepatoblastoma, but the numbers and absolute risks were small (<5 cases observed; RR 10.28; 95% CI 1.25–37.14). This increased hepatoblastoma risk was associated with low birthweight.
- 2.56.** Woo et al. (2017) investigate the differences in perinatal outcomes between singleton live births resulting from commissioned and spontaneously conceived embryos carried by the same surrogate. The outcomes of 124 surrogates, who achieved a total of 494 pregnancies, were analysed. Children conceived using IVF had a higher rate of PTB (10.7% vs. 3.1%) and higher rates of low birth rate (7.8% vs. 2.4%) with the average IVF conceived neonate weighing 105g lower than those that were spontaneously conceived.
- 2.57.** Using HFEA register data, Sunkara et al. (2017) investigated the perinatal outcomes of children born through surrogacy using donor eggs (gestational surrogacy) (n=224), mothers using autologous eggs and fresh ET (n=87,571) and mothers using autologous eggs and FET (n=15,345). There was no difference found in the risk of PTB (aOR 0.90, 95% CI 0.56 to 1.42) and LBW (aOR 0.90, 95% CI 0.57 to 1.43) after gestational surrogacy compared with autologous fresh ET. There was also no difference found in risk of PTB (aOR 0.96, 95% CI 0.58 to 1.60) and LBW (aOR 1.16, 95% CI 0.69 to 1.96) between gestational surrogacy and FET. The incidence of HBW was significantly higher after gestational surrogacy compared with fresh ET (aOR 1.94, 95% CI 1.38 to 2.75) but no difference was found in HBW between gestational surrogacy and autologous FET.

3. Conclusions

- 3.1.** This paper outlines research looking at health outcomes in children conceived using ART, published between June 2017 and December 2019. Since SCAAC last considered health outcomes in children conceived by ART, there has been an increase in the number of studies investigating the effects of fresh and frozen embryo transfer on perinatal outcomes. However, as with the paper considered by SCAAC in June 2017, studies looking at longer term developmental outcomes still appear to generally have small sample sizes compared to studies that focus on birth outcomes.

4. Recommendations

- 4.1.** Members are asked to:

- Advise the Executive if they are aware of any other recent developments.
- Consider areas of development in further detail and advise the HFEA on issues that should be particularly monitored
- Review whether any outputs from HFEA are required addressing health outcomes in children born following ART

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Annex A

Glossary of terms

ABPM	Ambulatory blood pressure monitoring
aOR	Adjusted odds ratio
aRR	Adjusted risk ratio
ART	Assisted reproductive technology
ASD	Autism spectrum disorder
EUROCAT	European surveillance of congenital anomalies
FET	Frozen embryo transfer
Fresh ET	Fresh embryo transfer
GnRH	Gonadotrophin-releasing hormone
HBW	High birth weight
HR	Hazard ratio
ICSI	Intracytoplasmic sperm injection
IQ	Intelligence quotient
IVF	In vitro fertilisation
IVM	In vitro maturation
LBW	Low birth weight
LGA	Large for gestational age
MND	Minor neurological dysfunction
NOS	Neurological optimality score
OR	Odds ratio
PGD	Preimplantation genetic diagnosis
PGS	Preimplantation genetic screening
PGT-M	Pre-implantation genetic testing for monogenic
PGT-SR	Pre-implantation genetic testing for structural chromosomal aberrations
PTB	Preterm birth
RR	Risk ratio
SCAAC	Scientific and Clinical Advances Advisory Committee
SGA	Small for gestation age

SIR	Standardised infection ratio
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VLBW	Very low birth weight
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VPTB	Very preterm birth
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