Annex B

1. Health outcomes of ART children

Background

1.1. Assisted reproductive technology (ART) includes techniques such as egg freezing, *in vitro* fertilisation, and intra-cytoplasmic sperm injection. Some research suggests that these techniques may be associated with an increased risk of birth defects in the children born. However, whether there is a direct causal link is yet to be shown conclusively. The possibility remains that the association is due to other reasons and compounding factors, such as underlying subfertility in patients, or a bias because infants conceived as a result of ART are more rigorously monitored.

1.2. The HFEA's Scientific and Clinical Advances Advisory Committee (SCAAC) last discussed birth defects following ART in 2009. At this time it concluded that there was no substantial evidence to suggest that ART affects the risk of resulting infants developing cancer, suffering from impairments in neurological development, or damaging their psychosocial wellbeing.

1.3. However, SCAAC did suggest there was some evidence to show that infants born as a result of ART have an increased risk of the imprinting conditions Angelman Syndrome and Beckwith-Wiedemann Syndrome. More recently SCAAC considered a study by Davies *et al* (2012) that looked at reproductive technologies and birth defects. Finally, it should be noted that 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.

Summary of developments

1.4. A study examining an children born from IVF, for imprinted and genome-wide DNA methylation abnormalities at four imprinted gene loci (H19, SNRPN, KCNQ1OT1 and IGF2) and satellite 2 using methylation-sensitive quantitative polymerase chain

reaction followed by bisulphite sequencing at showed low-level imprinting errors are not common in the IVF population (Oliver *et al* 2012).

1.5. The risk for congenital heart defects (CHDs) associated with ARTs has been evaluated as a whole; however, there is limited information on the risks for specific CHDs. A study by Tarabit *et al* (2012) showed that children born as a result of ART was higher for cases of CHD than controls, and was associated with a 40% increase in the maternal age, socioeconomic factors and year of birth-adjusted odds of CHD without chromosomal abnormalities. ARTs were specifically associated with significant increases in the odds of malformations of the outflow tracts and ventriculoarterial connections and of cardiac neural crest defects and double outlet right ventricle. In general, the study found specific associations between methods of ART and subcategories of CHD. However the study could not rule out compounding factors such as underlying infertility.

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

1.7. Wen *et al* (2012) conducted a meta-analysis of studies assessing the effect of IVF and intracytoplasmic sperm injection (ICSI) on birth defects. They identified all studies published by September 2011 with data related to birth defects in children conceived by IVF and/or ICSI compared with spontaneously conceived children, or birth defects in the children conceived by IVF compared with those by ICSI. The analysis concluded that children conceived by IVF and by ICSI are at significantly increased risk for birth defects, and there is

no risk difference between children conceived by IVF and those conceived by ICSI.

1.8. Fedder *et al* (2012) explored whether neonatal outcome including congenital malformations in children born after ICSI with epididymal and testicular sperm [testicular sperm extraction (TESE)/percutaneous epididymal sperm aspiration (PESA)/testicular sperm aspiration (TESA) (TPT)] differ from neonatal outcome in children born after ICSI with ejaculated sperm, IVF and natural conception. Children born after TPT have similar neonatal outcome, including total malformation rates, as have children born after ICSI and IVF with ejaculated sperm. Testing for variance over the four groups may indicate smaller differences in specific malformation rates, with TPT as the highest risk group. Accumulating data show that TPT treatment is as equally safe as conventional ICSI and IVF treatment, and as natural conception with regard to neonatal outcome including congenital malformation.

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

1.10. Finally, research linking the HFEA data and that of the Congenital Abnormalities System and the Childhood Cancer Registry is currently being carried out. Sutcliffe et al are currently investigating whether children born after assisted reproductive treatment (ART), such as in vitro fertilisation (IVF), have a higher risk of developing cancer than other children. The researchers also aim to assess whether different types of infertility or different fertility treatments might be associated with different types of childhood cancer.

Impact

1.11. If it is agreed that further understanding of the risk of birth defects has developed, then information given to patients seeking assisted reproductive technologies may need to cover the risks of multiple birth, perinatal

outcomes, congenital abnormalities and neurological development.

Level of work recommendation

1.12. Members are asked to consider whether they require a more detailed review of current research in order to put forward their views about whether the Authority should review guidance for clinics (outlined in the Code of Practice), regarding the information they are required to make available to patients, and the information the HFEA makes available to patients through its website.

References

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

Background

2.1 In recent years transplantation of cryopreserved ovarian tissue has been carried out by many research groups around the world. This technology can restore fertility after treatment that may have been impaired. Success

in animal models has been demonstrated, such as in sheep (Gosden *et al*, 1994) and more recently in humans (Donnez *et al*, 2005; Donnez *et al*, 2008; Rosendhal et al 2011) showing some level of success in terms of reintegration of tissue and subsequent live births.

2.2 SCAAC considered the progress of research in this area in November 2008. SCAAC further considered this topic in 2011, as part of a wider discussion on female fertility preservation where the Committee concluded that transplantation did not currently represent a good method of fertility preservation due to it's low pregnancy rates. However research into these techniques continues apace, focusing on the grafting of cryopreserved human ovarian tissue. A summary of recent developments is outlined in Section 1.6.

Legislation/regulation

1.3. Upon commencement of the updated Human Fertilisation and Embryology Act in October 2009, the HFEA's remit expanded to include cells of the germ line at any stage of maturity. Therefore the storage and use of the ovarian tissue and immature gametes described in this paper is within the HFEA's remit as well as the remit of the Human Tissue Authority (HTA).[i]

1.4. HFEA licensed facilities are not required to process gametes for ART in an environment of Grade A air quality. Commission Directive 2006/86/EC recommends that an air quality with particle counts and microbial colony counts equivalent to those of Grade A, as defined in the European Guide to Good Manufacturing Practice, Annex 1 and Commission Directive 2003/94/EC (2), is generally required. However, the Directive recognises that air quality of this standard is not always indicated. The HFEA has determined that the processing of gametes for ART can safely be conducted in an environment of Grade C air quality and this is a standard condition of all HFEA licences. This air quality is not suitable for the processing of ovarian tissue for transplant and this means that a separate standard is applicable for the

processing of this tissue in HFEA licensed clinics (guidance at Code of Practice 17A and 17.10).

1.5. The technique described in this paper involves the autologous orthotopic reimplantation (transplantation of tissue into the same patient and site from which it was taken) of ovarian tissue or immature gametes into patients, which is distinct from techniques currently used in ART.

Summary of Developments

1.6. Donnez *et a*l (2012) reported on the restoration of ovarian function and pregnancy in a woman after bilateral oophorectomy for benign disease and autotransplantation of cryopreserved ovarian cortex. Restoration of ovarian function began at 20 weeks and was achieved 24 weeks after transplantation. One embryo (seven cells) was obtained and transferred, leading to a normal pregnancy. The patient had healthy baby at 38 weeks of gestation. The authors conclude that ovarian cortex cryopreservation can be performed at the time of surgery for benign diseases when fertility is impaired. The group reported the first pregnancy to occur after ovarian tissue cryopreservation for benign disease after bilateral oophorectomy.

1.7. Del Pozo *et al* (2012) considered ovarian tissue cryopreservation and the possibility of reintroducing metastatic cells within the reimplant. They highlighted that current data indicates that ovarian cortical grafting for fertility preservation is contraindicated in patients with leukaemia owing to the risk of reintroducing malignant cells. However they emphasised that there does not appear to be a risk for women with Hodgkin's disease, or those in the early stages of breast cancer.

1.8. Wallace *et al* (2012) examined the long-term (>7 years) duration of function of ovarian cortical tissue grafts in three patients who had several successful pregnancies. However, the success rate for ovarian cryopreservation is unclear as the denominator (the number of women in

whom frozen-thawed ovarian tissue has been re-implanted) is unknown.

Risks

1.9. Given that the technique is largely aimed at patients diagnosed with cancer, there is the risk that procurement of reproductive tissue for storage delays the patient starting treatment. Although it is important to note that the alternative of egg retrieval/ovarian stimulation may be a longer process with further exposure to hormone treatment that may hasten malignancy.

1.10. When used for cancer patients there is also the risk that malignant cells could be reintroduced by reimplantation of reproductive tissue to the patient.

1.11. It is important to note there is also ethical/public interest to consider. There is likely to be public interest as the technique could preserve the fertility of prepubescent female patients wishing to undergo chemotherapy and/or radio therapy treatment, or be used as a social fertility preservation technology.

Level of work recommendation

1.12. The viability of this technique needs to be understood through a thorough analysis of the current research in this area. It is also important that research addresses the risk of transmission of malignant cells in cancer patients.

1.13. The Committee is asked to consider whether they think a more extensive update on current research and progress in this area would be useful to ensure that the Executive is informed of any new developments, and how this should inform our patient information and current Code of Practice.

References

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[i] The HFEA and HTA are working together to try to remove this regulatory overlap and there is a possibility that future regulation of the storage of ovarian tissue for transplantation will fall solely within the remit of the HTA.