HUMAN FERTILISATION AND EMBRYOLOGY AUTHORITY
MINUTES OF THE SCIENTIFIC AND CLINICAL ADVANCES ADVISORY COMMITTEE

Meeting held at Etc. venues 120 Moorgate, Moorgate, London EC2M 6UR on
Wednesday 4 February 2015

1. Welcome, apologies and declarations of interest
1.1 The Chair welcomed Committee members to the meeting and introduced Kate
Brian as a new Authority and Committee member. Helen Picton and Yacoub Khalaf
were welcomed as guest speaker and observer, respectively.
1.2 The Chair conveyed apologies on behalf of Debbie Barber and Alan Thornhill.
1.3 In relation to the meeting agenda, interests were declared by Daniel Brison.

2. Matters arising
2.1 Minutes of the meeting held on 22 October 2014 were agreed remotely prior to the
meeting. Matters arising from previous minutes were noted and agreed.

3. Chair’s business
3.1 It was highlighted that points raised by the Committee in its annual review have
been taken on board: the length of meetings have been extended to enable more
thorough discussions; and invited speakers have been given a thorough briefing of
how their presentation fits into the Committee’s work plan.
3.2 The Chair updated the Committee on the recruitment of new external advisors;
particularly, the recruitment of an embryologist, andrologist and epigeneticist.

4. Prioritisation of issues identified through the horizon scanning process
[SCAAC(02/15)05]
4.1 The Secretary to the Committee introduced a paper on the prioritisation of issues
identified through the horizon scanning process. Members were reminded that:
- the process is an annual cycle to identify issues that could have an impact on the field of assisted reproduction or embryo research; and
- the issues identified in this cycle of the process will be incorporated into the work plans of the Executive, the Committee and the Authority.

4.2 Issues were largely identified from journal articles, conference attendance and contact with experts, including the Authority’s Horizon Scanning Panel. A full list of identified issues categorised according to level of priority can be found at Annex A to the relevant paper.

4.3 To aid the business planning process, a number of topics that were recognised as high priority via horizon scanning were presented to the Committee for their consideration. Summary briefings on these issues, based on horizon scanning findings, can be found at Annex B to the relevant paper. Committee discussions on each of these topics are noted as follows:

**Freeze-all cycles**

4.4 The Committee was asked to consider whether a thorough analysis of the research regarding freeze-all cycles is required, and whether patient and sector advice on this issue needs to be revised and/or introduced.

4.5 The Committee agreed that freeze-all cycles is a high priority issue and that a detailed analysis of research from previous years to date would be beneficial due to conflicting research in the area. While the Committee was aware of an elective freeze-all ‘EFREEZE’ clinical trial taking place in the United Kingdom, it was brought to the Committee’s attention that another multicentre trial is taking place in South East Asia and that its progress should be monitored. It was suggested that the Executive may like to invite an expert in this area to present to the Committee.

4.6 It was noted that patient information on this area should address potential questions such as the reason(s) for a delay between egg collection and embryo transfer, and should note that this is a fast-evolving area of assisted reproduction.

**Mitochondria**

4.7 The Committee was asked to consider the relevant literature and/or techniques, its applicability to clinical practice, and whether the area should be further explored or monitored as part of their work plan.

4.8 The Committee discussed a review by Schatten et al (2014) that highlighted the ‘augment technique’ which is based on the theory that mitochondria age and mtDNA accumulates mutations in old oocytes. The method involves injecting a preparation of cytoplasm containing mitochondria from putative egg precursor cells that have been grown in vitro from an ovary biopsy into mature eggs from the same patient. This has been proposed by the originators of the method (Jonathan Tilly
and collaborators) to restore optimal mitochondrial function. However the Committee noted that women carrying oocytes with abnormal mtDNA, such that their children are at risk of developing mitochondrial disease, do not have fertility problems, and that this is at odds with the idea that older, potentially more mutated mitochondrial would lead to infertility. It was also noted that the purpose of the technique is not to avoid disease transmission and concern was raised regarding mitochondrial overload in the mature egg; particularly, as the normal range of mitochondria numbers and mtDNA copies per cell is not currently known. It was agreed that research in this area should be monitored and that the Executive may like to invite an expert to discuss the technique in further detail with the Committee. It was also noted that consideration needs to be given to whether eggs and embryos subject to this technique would fall under the legal definition of ‘permitted’ for use in treatment.

4.9 Additional studies within the briefing note that explored the use of mitochondria as non-invasive assays of embryo health were considered of interest. Although not at the level of being introduced into clinical practice, it was agreed that studies in this area should continue to be monitored as part of the horizon scanning process.

New technologies in embryo testing

4.10 The Committee was asked to consider the latest research into new technologies in embryo testing and the notion that these technologies have the potential to generate additional genetic information. The Executive highlighted that it will be presenting a paper to the Authority – as part of an ongoing piece of work initiated by the Committee – on the legal boundaries for testing embryos for genetic conditions and chromosomal abnormalities using these technologies. In turn, the Executive will advise centres and formulate up-to-date patient advice on the area, with guidance from the Committee.

4.11 It was agreed that this area continues to be of high priority and should remain on the Committee work plan. The Executive highlighted that its paper would be put to the Authority in May 2015 – before the next Committee meeting – and it was therefore agreed that a sub-group of the Committee would convene for a one-off focus meeting (April 2015) so that their thoughts could be conveyed in the Authority paper. The Authority’s recommendations/decisions will be conveyed to the Committee in June 2015.

Safety of embryo biopsy

4.12 The Committee was asked to consider whether there are any additional studies or developments in embryo biopsy; whether they wish to make any recommendations
to the Authority; and whether the Committee should continue to monitor research into the effect of embryo biopsy on children born as a result of the technique.

4.13 While the Committee was not aware of any additional studies regarding embryo biopsy, the concept and effect of two cryopreservation and two thawing procedures on outcomes – effectively, the re-freezing of embryos – by Taylor et al (2014) was of particular interest to the Committee. It was noted that this should be explored as part of the freeze-all cycle area of work and that professional bodies may wish to address this area in its guidelines.

4.14 It was highlighted that the overall safety of embryo culture, as well as its associated risks, should continue to be monitored as part of the horizon scanning process. It was agreed that follow-up studies on children born from assisted reproductive techniques should be also be monitored and incorporated into the Committee’s work plan.

Ongoing areas of high priority

4.15 The Committee agreed that the longstanding areas of high priority – embryo culture media and alternative methods for the creation of ES or ES-like cells – should continue to be monitored on an annual basis and remain on the work plan.

4.16 Regarding culture media in particular, it was noted that the European Society of Human Reproduction and Embryology working group on this area will be producing a position statement this year.

Horizon scanning: overall process

4.17 The Committee was asked to reflect on the modified approach to the horizon scanning process, which included extended time for the Committee to have early sight of the issues identified via the process and an opportunity to flag further relevant studies for the Executive to include in briefing notes.

4.18 It was noted that the process was comprehensive and useful. Moving forward, it was proposed that feedback could be formalised, with set criteria for the Committee to comment against and the Executive could ask for comments on draft briefing notes (time permitting) and note journal impact factors. The Committee agreed to highlight papers from groups that are an extension of previous work, to demonstrate continuity.

5. Committee work plan

5.1 The Committee evaluated its work plan for the previous year and confirmed the following priorities for upcoming meetings:

- Freeze-all cycles
- In vitro maturation
Fertility preservation
- New technologies in embryo testing
- Mitochondrial techniques (excluding mitochondrial replacement techniques)
- Follow-up studies of children born from assisted reproductive techniques
- Embryo culture media (ongoing priority)
- Alternative methods to ES and ES-like cells (ongoing priority)

5.2 It was highlighted that a literature review will be released by the Association of Clinical Embryologists (ACE) and the British Fertility Society (BFS) to address the use of ICSI for non-male factor infertility. It was agreed that the Committee should be updated on its outcomes at a meeting this year.

6. Fertility preservation
6.1 In February 2014, the Committee identified fertility preservation as a high priority area via the horizon scanning process and recommended that a more detailed analysis would be beneficial as:
   - the Authority would need to consider mechanisms for regulation if donor ovarian tissue/ovary transplantation is thought to be viable; and
   - patients may consider egg cryopreservation as a feasible method of fertility preservation for social reasons and may seek advice from the HFEA about this process as a result.

6.2 Helen Picton (University of Leeds) was invited to discuss fertility preservation further and to update the Committee on any relevant additional information; particularly, recent developments in the cryopreservation of eggs and sperm, in tissue transplantation, and up-and-coming research.

6.3 Helen Picton highlighted from the outset that research into testicular tissue preservation is increasing across Europe and is currently in a similar position to that of ovarian tissue preservation around 10 years past; therefore, the focus of the presentation is in reference to the latter. However, regardless of the tissue type, it was noted that research should address the reason and/or need for egg and sperm preservation, the ideal stage of development to cryopreserve tissue and the optimum methods of cryopreservation.

   Egg freezing

6.4 There are multiple strategies for preserving female fertility, including the banking of eggs at the immature (germinal vesicle) and mature (metaphase II) stages. Immature eggs must be preserved with the surrounding cumulus cells that are required for egg maturation, or can be matured in vitro prior to cryopreservation.
6.5 It was explained that the optimal cryopreservation methods are dependent on the tissue type; therefore, optimum freezing for immature eggs and the surrounding cumulus cells differs. With regards to mature eggs, however, it was explained that slow freezing can be inefficient as the meiotic spindles are temperature sensitive and mitochondrial function is compromised. As a result, efficiency is around 5-6% babies born per egg thawed, compared to clinical research that indicates vitrification is the optimum method for freezing mature eggs with success at 12-15% babies born per egg thawed. It was highlighted, however, that there is natural variation in the effects of egg freezing among women.

Ovarian tissue banking

6.6 Recent developments in ovarian tissue banking were explained as follows:

- There is an increased understanding of the mechanisms involved in ovarian tissue damage and follicular loss in the human ovary
- Slow freezing appears to be the optimum method for ovarian tissue freezing
  - Research is moving towards the use of vitrification; however, there are varying degrees of success in large animal models
- There are varying degrees of success in restoring fertility
  - Methods include injecting or attaching strips of frozen ovarian tissue to the ovaries; approximately 40 children have been born as a result
- There are two strategies for treating oncology patients
  - Option 1: cryopreserve ovarian tissue after diagnosis, prior to the first round of treatment. This preserves a higher amount of ovarian reserve, although there is a chance that malignant cells will survive post-thaw.
  - Option 2: cryopreserve ovarian tissue after diagnosis, following the second round of treatment. This potentially reduces the risk of malignant cell survival; however, depletes ovarian reserve
- Research into whole ovarian tissue banking using animal models has shown no transgenerational affect

Future research and practice

6.7 It was explained that the risk of reintroducing malignant cells may be reduced by growing primordial cells to mature eggs. This may be possible through advances in in vitro growth (IVG; in situ culture, isolated follicle culture and somatic cell differentiation) and in vitro maturation (IVM), however, for this to occur several questions need to be addressed:

- Establishing the developmental time frames in vitro to develop primordial follicles into full-sized eggs
• Whether eggs are fertile and developmentally competent after IVG and IVM
• Whether egg and embryo genetics/epigenetic health/gene imprinting status are compromised after cryopreservation, IVG and/or IVM

6.8 Helen Picton highlighted that the ‘Augment’ technique (see Section 4.8) has been considered suitable by certain professionals in the context of fertility preservation for oncology patients. It was explained that in this context, primordial germ cells within ovarian tissue preserved from youth could be used to safeguard fertility following oncology treatment. During discussions it was noted that not all mitochondria may be active; if those that are active produce an excessive level of energy, this will lead to an increase in reactive oxygen species and can lead to damage. As such, it was highlighted that the question of ‘how many is too many?’ remains to be answered and whether the levels of mitochondria change with age. Up-and-coming research may also address whether medical therapies can be used to protect the ovary from oncology treatment.

6.9 In conclusion, Helen Picton highlighted that fertility preservation is a balancing act and while there has been significant advances in the area, multiple factors need be taken into consideration when treating a patient.

6.10 The aim of the patient information provided on the HFEA website is to provide a fair, balanced and accurate picture on current progress regarding fertility preservation to assist people who are seeking to make decisions/gather treatment about the process. It was voiced that this may be conveyed to greater effect if patients are given success rates using the appropriate statistic (babies born per egg thawed). Additionally, clinic staff should complete appropriate training in order to understand the impact of cryopreservation techniques and the differences if preserving differing tissue types.

Actions

6.11 The Chair invited Helen Picton and the Committee to review HFEA website content regarding fertility preservation and highlight the most important messages to convey. A formal paper will also be presented to the Committee detailed the results to date and the points raised by Helen Picton.

7. Preimplantation genetic screening [SCAAC(02/15)07]

7.1 The Scientific Policy Manager updated the Committee on technological advances in preimplantation genetic screening (PGS) – a technique that aims to identify aneuploid embryos, allowing the choice of aneuploidy-free embryos from being transferred, thereby increasing the likelihood of pregnancy and reducing miscarriage rates.
7.2 It was presented that recent research and literature demonstrates that considerable progress has been made in the technologies available for use in PGS; however, controversy exists surrounding its practice in assisted reproduction and there is a need for a greater number of well-designed randomised controlled trials.

7.3 The Committee was asked to review the recent literature in this area; to consider proposed amendments to the patient information available on the HFEA website; and whether guidance in the Code of Practice, particularly regarding information clinics should provide to patients about PGS, should be amended.

7.4 The Committee agreed that patient information regarding PGS should be updated to provide a fair, balanced and accurate picture on current progress to assist those who are seeking to make decisions about fertility treatment. It was noted that discussions at the focus meeting (see 4.11) will feed into this area of work and it should continue to be a part of the work plan. It was brought to the Committee’s attention that two professional body guideline papers are due to be released this year that refer to PGS.

Actions

7.5 The Committee agreed to review HFEA website content regarding PGS and highlight the most important messages to convey. Amendments and outcomes of the April focused meeting on embryo testing will be presented at the next Committee meeting.

8. Reproductive immunology

8.1 In June 2014, the Committee revisited the topic of reproductive immunology by considering paper [SCAAC(06/14)02]. Discussions raised further questions; particularly, whether patients should be given steroids in the first trimester as a safety concern and whether blood tests predict miscarriage or the population of uterine natural killer cells.

8.2 In October 2014, Siobhan Quenby was invited to discuss these areas further and to update the Committee on any relevant additional information with regards to reproductive immunology. It was agreed that the Committee would review HFEA website content regarding reproductive immunology and highlight the most important areas to convey.

8.3 The Scientific Policy Manager presented the latest literature in this area, and asked the Committee to consider any safety and efficacy issues and review the draft website information on reproductive immunology. It was noted that the amendments conveyed up-to-date information; however, the information could be presented in a more simplistic format for patients from the outset, allowing them to explore the
The Committee agreed to review the patient information outside of the meeting setting.

**Actions**

8.4 The Committee agreed to finalise HFEA website content regarding reproductive immunology outside of the meeting setting.

**9. Any other business**

**Mitochondrial replacement techniques**

9.1 The Committee was informed that Parliament had voted in favour of legalising mitochondrial donation that means it will be possible for clinics to apply to the HFEA for approval to use these techniques, for the avoidance of serious mitochondrial disease from 29 October 2015. Members highlighted the importance of clear patient information on these techniques.

**10. Meeting summary and close**

10.1 The Chair thanked the Committee, Helen Picton and its observers for their time and for a productive meeting.

**Next meeting: Wednesday 10 June 2015**

I confirm this to be a true and accurate record of the Meeting.

Signature: ...................................................

Name: ..........................................................

Position: Committee Chair

Date: ..........................................................