



Scientific and Clinical Advances Advisory Committee - minutes

19 June 2017

Conwy Room 10 Spring Gardens, London SW1A 2BU

Any other information required

Authority members	Present	Yacoub Khalaf Sally Cheshire Andy Greenfield Anne Lampe	
	Apologies	Tony Rutherford	
Members of the Executive		Anna Quinn (lead) Rasheda Begum (secretary) Hannah Verdin Peter Thompson Erin Barton	Catherine Drennan
External advisors		Gudrun Moore Joyce Harper Melanie Davies Raj Mathur Robin Lovell-Badge	Daniel Brison Jane Blower Sheena Lewis
Observers		Steve Pugh (DH)	

1. Welcome, apologies and declarations of interest

- 1.1.** The Chair welcomed Committee members to the meeting and introduced Rasheda Begum as the new Scientific Policy Officer at the HFEA and also welcomed Hannah Verdin who had returned to her post as Head of Regulatory Policy. Apologies were conveyed on behalf of Tony Rutherford, Jane Blower and Sheena Lewis.
- 1.2.** In relation to the meeting agenda, interests were declared by Daniel Brison who is an IVF Director and has research interests in culture media and Yacoub Khalaf who runs an IVF unit. Interests were also declared by Melanie Davies who has a research interest in health outcomes in children conceived using assisted reproductive technologies. No commercial interests were declared.

2. Matters arising

- 2.1.** Minutes of the meeting held on 6 February were agreed remotely prior to the meeting.
- 2.2.** The Scientific Policy Manager updated the Committee on matters arising. Genome editing has been added as a topic of interest to the horizon scanning process. Genome editing will be an item on the agenda for the next SCAAC meeting in October. Patient information about clinical trials as well as treatment add ons has been drafted and will be published on the HFEA website. The format of the horizon scanning spreadsheet will be modified and the Committee will be able to review the new layout in time for this year's horizon scanning process.
- 2.3.** A Committee member queried when information on treatment add ons will be published. The Chief Executive mentioned that the HFEA hopes to announce a date at the next Authority meeting.
- 2.4.** A Committee member is a member of the Nuffield Council on Bioethics working party for genome editing, which is currently working on its recommendations and the draft report is expected in November. The Committee member will aim to give an update on this at the next SCAAC meeting in October.

3. Use of ICSI

- 3.1.** The Scientific Policy Manager presented a paper on the use of ICSI. Research on the use of ICSI and health outcomes has been monitored by the Committee. The HFEA Code of Practice requires that patients are informed of the potential risks of ICSI. The following risks associated with ICSI are highlighted on the website: genetic and developmental defects, possibility of boys inheriting paternal infertility as well as low sperm count and increased risk of miscarriage. Two graphs produced using data from the HFEA register were provided, one looking at fertility treatments over time showing a steady rise in the use of ICSI. The other showed number of ICSI and IVF cycles carried out in individual clinics in NHS and private treatment.
- 3.2.** One Committee member had identified an additional relevant study prior to the meeting. The study by Zagadalov et al. looked at use of ICSI in different regions across the USA. Higher use of ICSI was not associated with frequency of male factor infertility within the regions and was not supported by corresponding improvement in ART outcomes. A full reference to this study is provided at Annex 1.

- 3.3.** Members noted that one NHS clinic carried out 100% ICSI. As this clinic does not offer private treatment, the Committee noted that the reason for their high ICSI usage could not be commercial interest. The cost of ICSI was said to be up to £1,000 (£1,500 in London) in addition to the cost of an IVF treatment cycle. The Chair suggested that high use of ICSI could be due to various reasons including clinics inability to discern when patients will benefit from ICSI, fear of failure of IVF and commercial interest due to the costs of ICSI.
- 3.4.** In response to the graphs presenting ICSI data, the Committee noted that the fact that the use of ICSI appears to have plateaued over recent years was reassuring. One member noted that PGD and PGS cycles were not included in the graph and this could lead to the true number of ICSI cycles being underestimated. There was general agreement that use of ICSI carries risks and should only be used when there is male factor infertility. One suggestion given for why ICSI is used more was higher fertilisation rates. The Chair responded that higher fertilisation is found per injected egg. Failure to fertilisation is twice as high in IVF compared to ICSI, although the rate is low for both treatment types.
- 3.5.** The Head of Regulatory Policy asked the Committee's thoughts on risks associated with ICSI occurring as a result of the procedure itself or underlying infertility. The Chair addressed the heterogeneity of the studies in the paper, and noted that they do not show causation of any defects associated with the use of ICSI.
- 3.6.** Further discussion on ICSI raised the following concerns:
- There are no clear diagnostic criteria for male factor subfertility that is sufficient to require ICSI, and we should not put too much focus on clinics with very high ICSI usage, as there are very few of them. It was asked whether use of ICSI is flagged during inspection. The Scientific Policy Manager confirmed that inspectors do look at use of ICSI.
 - Patient information should make it clear that there are studies that show ICSI does not have benefit unless you have male factor infertility. The Committee agreed patient information should be updated to include information on research showing ICSI is not more effective than IVF without male factor infertility and information on risks of ICSI.
 - The Committee considered whether the data still shows that ICSI leads to increase in miscarriage. The Chair referred to register data which found no increase in miscarriage in ICSI for male factor infertility.
 - Suggested reasons for why clinics perform ICSI included male factor infertility or a previous failed cycle. Clinics should have a strategy for identifying which patients may benefit from ICSI rather than IVF alone.
 - The Committee discussed diagnosis of male factor infertility. At the consultation stage, if a man has a sperm test and the results in any parameters are below the expected criteria, this will be labelled as male factor infertility. However, patients whose sperm tests are normal may then still be diagnosed with male factor infertility if there is poor sperm preparation. In cases where there is no clear cause of infertility, this is labelled as unexplained. Some countries, such as in the Middle East, carry out 100% ICSI. It was highlighted that potential risks of ICSI are theoretical, and that prevention of ICSI should focus on the invasive nature of the procedure and the high costs. In terms of what the HFEA can do, the Committee agreed that patient information should be strengthened, it was also suggested that inspections should be more clinically focused.

- The Chief Executive agreed that there are no clear criteria for use of ICSI and that there needs to be a consensus from professionals about what good practice looks like. A Committee member mentioned that there is a desire for a BFS and ACE guideline. It was agreed that such a guideline would be useful.
- IVF clinics may be offering ICSI because of profit, although rise of ICSI could also be a result of patients who had low fertilisation in previous cycles requesting ICSI. Also, clinics may have a tendency to want couples to feel like they have tried all options in their treatment.

-

3.7. The Chair suggested that the SCAAC paper could be submitted to a journal. This would be beneficial as it would be peer reviewed and provide a source of information for patients. The Chair requested that the Committee look at the literature review and convey feedback to the Scientific Policy Manager. Options for further work to explore the use of ICSI in the UK were discussed, the Executive will consider how best to progress with this work.

Actions

3.8. The Scientific Policy Manager will draft patient information on ICSI and will send to Committee members for feedback.

3.9. The Scientific Policy Manager will circulate a word file of the ICSI literature review to the Committee with a view to editing the paper for publication in a scientific journal.

4. Health Outcomes

4.1. The Scientific Policy Officer presented a literature review of research carried out on health outcomes after ART since October 2015. 37 studies were included in the review, which covered fresh and frozen embryo transfer, studies comparing siblings, risk of cancer, weight in early childhood, and mental, social and cognitive development. The SCAAC members were asked to discuss areas of work that they wanted the HFEA to consider or monitor and if the information given to patients by clinics and the website should be reviewed.

4.2. The Committee discussed low birth weight studies which were considered to be important, and it was mentioned that the E-Freeze trial will provide data on the effect of frozen embryo transfer on birthweight. There was a suggestion that comparing fresh transfer and frozen transfer is not valid because frozen embryo transfer will be from good prognosis patients. The Committee then considered whether high or low birthweight is necessarily a bad outcome, where one member highlighted that high and low birthweight could lead to long term risk of disease such as cardiovascular disease and diabetes. It was questioned whether low birthweight is a result of the embryo being frozen or the uterine environment. The descriptive evidence of studies was considered strong however members agreed randomised controlled trials are needed to confirm their findings.

4.3. The Committee discussed what should go into patient information, with particular focus on defined very low and high birthweight. The Committee pointed out that very high and low birthweight outcomes needed to be controlled for gestational age.

4.4. When asked about general trends in birthweights, one member described work in their centre that looked at IVF birthweights over 25 years. They found that birthweight has increased by 350g over

25 years and this is independent of patient factors. In the general population, birthweight is not increasing even though maternal BMI is increasing.

- 4.5.** One member noted that women who have IVF in the UK should be expected to have heavy babies because they are generally non-smokers and well nourished, so results should be analysed in terms of social factors and ethnicity. Another member added that increased BMI is inversely related to birthweight where larger women have small babies.
- 4.6.** The Scientific Policy Manager informed the Committee that there is currently no information on the HFEA website about birthweight and asked if this information should be added. There were suggestions that because of the evidence in the paper and publicity around the E Freeze trial, lower birthweight following fresh embryo transfer compared with frozen embryo transfer should be flagged.
- 4.7.** The Committee discussed what could be done to facilitate future research and noted the 2017-2020 HFEA strategy includes an aim to enable high quality research. Following this SCAAC meeting, a paper on embryo research was presented to the Authority.

5. Embryo culture medium update

- 5.1.** The Scientific Policy Manager presented a paper providing an update on embryo culture media. In studies looking at sequential media and single step media, most found development was not affected by type of culture media. However, one of the studies found delivery rate was lower in single step media and children in this group were more likely to have developmental problems. Another study provided the first evidence that culture media could influence birthweight. Committee members were asked to consider research since October 2015, advise the Executive whether they are aware of any other research and reflect on their views to date on any information that should be communicated to the MHRA. The Committee was also asked whether culture media should remain as a standing item for SCAAC or if it should be included in the horizon scanning process.
- 5.2.** Committee members expressed concern that the composition of culture media is not clearly known. Culture media acts as a surrogate for maternal nutrition for the first few days, therefore it would be important to know concentration of nutrients such as glucose and amino acids in the media. There was also concern that non-CE marked products were being added to culture media.
- 5.3.** One member noted that if the HFEA register collected information on culture media, this could facilitate long term follow up studies. The Committee was keen to liaise with the MHRA to discuss regulation of embryo culture media which is regulated as a medical device. The Committee agreed that a letter will be sent from the Chair and the HFEA Chief Executive to the MHRA setting out the Committee's concerns and inviting them to discuss this further at a meeting.
- 5.4.** Following the meeting one member provided references of further studies relevant to discussions about embryo culture media. References to these studies are provided at Annex 1.

6. Emerging technologies in embryo research

- 6.1.** The Scientific Policy Manager explained that the aim of this item is for the Committee to have a broad discussion about upcoming techniques and technologies in embryo research. There have been significant developments in the field of embryo research in recent years, including the

granting of a licence to carry out genome editing in human embryos, culturing of an embryo up to the 14-day limit and a recent study that reported mouse embryonic stem cells when cultured alongside trophectoderm stem cells in an extracellular matrix grow into a structure similar to a post implantation mouse embryo. The Committee was asked to reflect on the research that has been carried out, advise on how recent techniques could be used on human embryonic stem cells, and advise of any other research that should be taken into account.

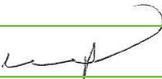
- 6.2.** One member noted that in the recent study using mouse embryonic stem cells, there was poor efficiency of the technique. The analysis was incomplete, there was no evidence of endoderm production and no evidence of patterning in the neuroectoderm. Members agreed the structures were not embryos.
- 6.3.** One member referred to a paper by George Church who referred to structures as “synthetic human entities with embryo-like features” or “SHEEFs”. The paper proposed an evaluation of what embryo-like structures are, taking into account their features and how they are relevant to regulation of human embryos.
- 6.4.** It was noted that the definition of an embryo in the HFE Act 1990 (as amended) is broad and allows for embryos to have different origins, i.e. for an entity to be classed as an embryo it does not necessarily need to be created as a result of fertilisation: ““Embryo” means a live embryo, including an egg that is in the process of fertilisation or is undergoing any other process capable of resulting in an embryo.”
- 6.5.** The Committee made reference and comparisons to previous discussions about outgrown embryos/embryoid bodies, which are produced from human embryonic stem cells and plated out (at which point they lose their ability to be organised structures) to form precursors of different cell types. The embryos in the Harrison et al. paper do have 3D organisation to some extent.
- 6.6.** It was agreed that it is too soon to consider this research in detail and the research needs to be reproduced.

7. Any other business

- 7.1.** The Committee was informed that the annual horizon scanning panel meeting will take place on 3 July at ESHRE and topics for discussion, many of which have been suggested by the panel members, include: the 14 day limit, measuring success in ART, PGS use in frozen embryos, mitochondrial donation for repeated failed implantation, culture media and measuring mitochondrial load.

Next meeting:

Monday 16 October 2017, 10 Spring Gardens, London SW1A 2BU.

Signature 

Name Yacoub Khalaf

Committee chair

Date 16/08/2017

8. Annex 1: References provided by Committee members

Use of ICSI

Zagadailov P, Hsu A, Seifer DB, Stern JE. Differences in utilization of Intracytoplasmic sperm injection (ICSI) within human services (HHS) regions and metropolitan megaregions in the US. *Reproductive Biology and Endocrinology*. 2017 Jun 12;15(1):45.

Embryo culture media

Morbeck DE, Baumann NA, Oglesbee D. Composition of single-step media used for human embryo culture. *Fertility and Sterility*. 2017 Apr 30;107(4):1055-60.

Biggers JD. Ethical issues and the commercialization of embryo culture media. *Reproductive biomedicine online*. 2000 Jan 1;1(3):74-6.