

Scientific and Clinical Advances Advisory Committee Paper

Paper Title:	Prioritisation of issues identified through the horizon scanning process
Paper Number:	SCAAC(02/14)02
Meeting Date:	5 February 2014
Agenda Item:	5
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For information or decision?	Decision
Resource Implications:	This will depend on the number of issues which the Committee agrees to be high priority. This will be fed into the business planning process.
Implementation	SCAAC's advice will be immediately fed into the work planning process for 2014/15.
Communication	SCAAC's views on work priorities will be communicated to the Head of Business planning, who will feed this information into the business planning process where necessary.
Organisational Risk	Medium
Recommendation to the Committee:	<p>Members are asked to:</p> <ul style="list-style-type: none"> • Note all issues identified through the horizon scanning process (Annex A) and the priority suggested by the Executive • Consider the high priority issues and work recommendations • Consider whether advice from additional external advisers will be helpful for any of the areas of work identified and, if so, to identify relevant experts

Evaluation	N/A
Annexes	Annex A: Issues identified through the horizon scanning process Annex B: Briefings on high priority issues

1. Background

- 1.1. The HFEA established a horizon scanning function in 2004, the purpose of which is to identify issues that could have an impact on the field of assisted reproduction or embryo research. By identifying these issues, we can be aware of potential licence applications and prepared, if necessary, with an Authority policy or position.
- 1.2. Issues are identified from journal articles, conference attendance and contact with experts such as members of the HFEA Horizon Scanning Panel. The Horizon Scanning Panel is an international panel of experts who meet annually and are contacted via email throughout the year.
- 1.3. The horizon scanning process is an annual cycle that feeds into the business planning for the Executive, the Scientific and Clinical Advances Advisory Committee (SCAAC) and the Ethics and Standards Committee (ESC). The issues identified in this cycle of the horizon scanning process will be incorporated into the 2014/15 business plan and work plan for the Executive, SCAAC, and ESC.

2. Prioritisation process

- 2.1. A full list of all issues identified since February 2013 can be found in Annex A of this paper. They are grouped into relevant topics.
- 2.2. To help with the business planning process, it is important for the Executive to know which issues members consider to be of high priority. New techniques which have been identified this year have been categorised as low, medium or high priority using the following criteria:
 - Within HFEA's remit
 - Timescale for likely introduction (within 2-3 years)
 - High patient demand/clinical use if it were to be introduced
 - Technically feasible
 - Ethical issues raised or public interest
- 2.3. New techniques are considered to be high priority if they meet at least three of these criteria and medium if they meet at least two. Low priority issues are unlikely to impact on research or treatment in the near future.
- 2.4. High priority is also given to established techniques or issues which fall within the HFEA's remit and require ongoing monitoring eg, in vitro derived gametes or the use of vitrification.

3. High priority issues

- 3.1. The Executive considers the following topics to be of high priority and these topics are therefore recommended for consideration in 2014/15:
 - Frozen embryo transfer "freeze-all cycles"
 - Fertility Preservation - oocyte cryopreservation and IVM of oocytes

- Safety of embryo biopsy

3.2. Briefings about these issues can be found at Annex B. Briefings have not been written for the remaining high priority areas (listed below) as these are ongoing topics that have recently been considered by SCAAC and are monitored annually.

- Embryo culture media (ongoing)
- Alternative methods for the creation of ES or ES-like cells (ongoing)

3.3. Following discussion of the briefings, and their priority status, we ask members to put these issues into a priority list to assist the business planning process. Members may think that some of the medium priority issues should be considered by SCAAC and therefore should be made high priority, or vice versa.

4. Other work areas

4.1. In addition to areas of work identified through the horizon scanning process, SCAAC will need to advise on any other issues they feel should be prioritised and also be aware that a number of issues related to project work during the year may be areas identified by the Authority. For example:

- Update on blastocyst transfer and multiple births data (depending on capacity for analysis)
- In vitro derived gametes

5. Recommendations

5.1. Members are asked to:

- Note all issues identified through the horizon scanning process (Annex A) and the priority suggested by the Executive
- Consider the high priority issues and work recommendations
- Consider whether advice from additional external advisers will be helpful for any of the areas of work identified and, if so, to identify relevant experts.

6. Next steps

6.1. Following SCAAC's discussion, the prioritised issues, plus the other work areas, will be used to formulate a SCAAC work plan for 2014/15. Any areas of work which are likely to go beyond SCAAC's scope, and may impact on the work of other HFEA committees, will be considered for inclusion in the business plan for 2014/15.

1. Frozen Embryo Transfer – ‘freeze-all’ cycles

Background

- 1.1 Currently treatment may involve a combination of fresh and frozen transfer of embryos. However over recent years it has been suggested that freezing all embryos, from a stimulated cycle, for later transfer (in a natural cycle) might improve implantation and pregnancy rates. It is purported that ‘freeze-all’ cycles would mean that, if the first transfer takes place using a frozen embryo women would not be undergoing ovarian stimulation, and therefore the endometrium would be more receptive and the risk of ovarian hyperstimulation syndrome (OHSS) at the time of transfer, would be mitigated.
- 1.2 However, currently there is a lack of systematic studies to demonstrate whether the cryopreservation of all viable embryos with subsequent frozen embryo transfer (FET) results in better outcomes than fresh embryo transfers.

Summary of Developments

- 1.3 The first meta-analysis on this subject was presented at European Society of Human Reproduction and Embryology (EHSRE) annual conference in 2012 by Roque et al. The work addressed the question of whether *“the cryopreservation of all viable embryos and posterior FET is associated with improvements in ART outcomes when comparing to fresh embryo transfer”*. The article that followed (Roque et al 2013) reported that the chance of a clinical pregnancy is around 30% higher when all embryos are frozen for later transfer than with fresh embryo transfer. The study included three trials accounting for 633 cycles in women aged 27–33 years. The data demonstrated that the cryopreservation and FET may improve the outcomes of ART cycles and provides a rationale for conducting further randomised clinical trials assessing the consequences of ‘freeze-all’ cycles.
- 1.4 In 2013 Imudia et al tested a similar hypothesis, in a small cohort of patients who underwent elective cryopreservation of all embryos, due to risk of OHSS showing that they will be less likely to have small for gestational age (SGA) infants and preeclampsia as compared with patients who undergo fresh embryo transfer (ET). After adjusting for confounders the patients who elected for cryopreservation of all embryos and subsequent cryothaw ET were statistically significantly less likely to deliver SGA infants as compared with the patients who had fresh ET in patients showing indicators of OHSS. This preliminary

study suggests that elective cryopreservation of all embryos in patients with OHSS indicators for subsequent cryothaw ET in cycles with a more stable physiologic hormonal response reduce the odds of SGA in IVF singleton deliveries.

- 1.5 Wennerholm et al (2013) recently reported on a Nordic Cohort study exploring the risks of adverse outcomes in singletons born after FET. The study showed that singletons born after FET have a better perinatal outcome compared with singletons born after fresh IVF and ICSI with reference to low birthweight and preterm birth, but a worse perinatal outcome compared with singletons born after spontaneous conception. As in all observational studies, the possible role of residual confounding factors and bias should be considered. The study acknowledges that they were unable to control for confounding factors, such as BMI, smoking and reason for, or length of, infertility.
- 1.6 A study by Veleva et al (2013) explores which clinical and laboratory factors affect live birth rates (LBR) after FET. Top quality embryo characteristics, endometrial preparation protocol, number of embryos transferred and BMI affected independently the LBR in FET. The study noted that FET is an important part of present-day IVF/ICSI treatment but there is limited understanding of the factors affecting success rates after FET. They found that the presence of ≥ 1 top quality embryo at any step of the freezing and thawing process increases the chance of pregnancy. The data do not support the freezing of all embryos for transfer in order to improve the outcome.

Impact

- 1.7 The potential benefits of a 'freeze-all' cycle revolve around the eliminating the risks associated with fresh transfer following a stimulated cycle. By waiting a month (or more) through freezing of embryos the uterus is allowed time to return to a more natural and potentially receptive state, thus increasing the chance of successful implantation and reducing the risks associated with stimulation (OHSS).

Level of work recommendation

- 1.8 The benefits of 'freeze-all' cycles needs to be understood through a thorough analysis of the current research in this area and the correct advise for patients and the sector will need to be formulated by the Executive with guidance from SCAAC. It will also be important to consider how freeze all cycles are reported to HFEA and how success rate data is presented on CAFC.

References

- Imudia, AN. (2013) Elective cryopreservation of all embryos with subsequent cryothaw embryo transfer in patients at risk for ovarian hyperstimulation syndrome reduces the risk of adverse obstetric outcomes: a preliminary study. *Fertility and Sterility* 99 (1) 1615-1621.e10
- Roque et al (2012) Fresh embryo transfer versus frozen-thawed embryo transfer in assisted reproduction technique cycles: a systematic review and meta-analysis. EHSRE 2012 Proceedings: <http://www.eshre.eu/~media/emagic%20files/Press%20room/Annual%20meeting/Istanbul/Checa%20abstract.pdf>
- Ulla-Britt Wennerholm (2013) Perinatal outcomes of children born after frozen-thawed embryo transfer: a Nordic cohort study from the CoNARTaS group. *Hum. Reprod.* (2013) 28 (9): 2545-2553.
- Veleva Z. (2013) Factors affecting the outcome of frozen–thawed embryo transfer. *Hum. Reprod.* (2013) 28 (9): 2425-2431.

2. Female fertility preservation

Background

- 2.2** The two main methods of fertility preservation for women are cryopreservation of oocytes or embryos and cryopreservation of ovarian tissue/whole ovary, followed by transplantation back into the person it was removed from. The latter methods are, to a greater degree than oocytes and embryo cryopreservation, still at the research stage and have recently been considered by the Authority.

Tissue transplantation

- 2.3** The Authority has been working with the Human Tissue Authority (HTA) to reduce the regulatory overlap regarding the storage of ovarian and testicular tissue, and ensure appropriate regulation according to the intended use of the tissue. This has resulted in the re-interpretation of the requirements of the Act. As a result ovarian or testicular tissue which is intended for transplantation, can now be stored solely under the auspices of an HTA licence. An HFEA licence is no longer needed.

- 2.4** HFEA-licensed clinics currently storing ovarian or testicular tissue can continue to do so without an HTA licence until the tissue is to be used. At time of use, if a patient's own tissue is to be transplanted (autologous transplant) it must then be transferred to an HTA-licensed facility for processing and/or distribution to the transplant facility. An HTA licence is not needed to store ovarian or testicular tissue intended for fertility treatment (e.g. in vitro maturation of gametes). HFEA centres licensed to store gametes can store, process and use ovarian or testicular tissue to extract gametes for patients' own use in licensed fertility treatment, subject to the same conditions that apply to the use of sperm and oocytes.

- 2.5** It should be noted that research in this area is progressing and a number of studies relating to the use of ovarian and testicular tissue have been identified in Annex A.

Cryopreservation of gametes

- 2.6** Embryo cryopreservation represents the most traditional method of female fertility preservation, although the cryopreservation of oocytes are becoming increasingly common as techniques improve. Compared to embryos, oocytes have several characteristics that make their cryopreservation more difficult (e.g. the plasma membrane of an oocyte is less permeable and so cryoprotectants are less able to diffuse into the oocytes), practice in this area is developing with the

improvement of freezing methods using vitrification.

2.7 In addition there have been developments in in vitro maturation (IVM) of oocytes (Grynberg et al 2013). Immature oocyte retrieval from ovaries without ovarian stimulation followed by in vitro maturation and vitrification is a promising fertility preservation option for women who cannot undergo ovarian stimulation or cannot delay their gonadotoxic cancer treatment.

2.8 SCAAC considered female fertility preservation in February 2011. The Committee recommended that the Authority should provide information about the following on its website; non-gonadotoxic chemotherapy, links to information on cancer, funding options, which centres offered storage facilities and fertility preservation techniques that may be available in the future. The Committee also considered research into the cryopreservation of oocytes, however they did not specifically explore developments in IVM. The summary of developments below, presents recent findings relating to oocyte cryopreservation and IVM of oocytes.

Summary of Developments

Cryopreservation

2.9 A review by Cobo et al (2013) provides current knowledge on oocyte cryopreservation, with special emphasis on vitrification as a means to preserve fertility in different indications. Major advancements have been achieved in the past few years and this review presents general experiences on fertility preservation for age-related fertility decline as well as in oncologic patients, suggesting that “*oocyte vitrification is a standardized, simple, reproducible, and efficient option*”.

2.10 Cobo et al (2013) also conducted work evaluating the outcome of frozen embryo transfer of embryos developed from vitrified oocytes. Overall survival rates were 97.2%. The Delivery rates (DR) per warming cycle were 33.8% (group 1) and 30.9% (group 2). Double vitrification had no effect on DR and confounding factors did not modify the effect of double vitrification on DR. Vitrification at early cleavage or blastocyst stage of embryos obtained from previously vitrified oocytes were shown to have no effect on DR/warming cycle.

2.11 Nikiforaki, et al (2013) studied patterns of calcium oscillations during the fertilisation of human oocytes matured either *in vivo* or *in vitro* or aged *in vitro* to explore the effect of cryopreservation. The study suggested that oscillations in cytoplasmic calcium concentration are crucial for oocyte activation and further embryonic development. While several studies have described in detail the calcium oscillation pattern

during fertilisation in animal models, studies with human oocytes are scarce. This study showed that “*slow freezing differentially affects the calcium oscillation pattern of in vitro matured and in vitro aged oocytes*”. The study concluded that the analysis of calcium oscillations could be used as an oocyte quality indicator to evaluate *in vitro* culture and cryopreservation techniques of human oocytes.

In Vitro Maturation of oocytes

- 2.12** A recent study by Lee et al (2013) evaluated the maturation and post-thaw survival rates of immature oocytes to determine whether *in vitro* maturation (IVM) should be attempted prior to or after cryopreservation. Fresh IVM had a significantly higher maturation rate than post-thaw IVM. The authors concluded that superior maturation rate of GV and MI oocytes in the fresh versus post-thaw groups provides strong evidence for maturing oocytes to the MII stage before cryopreservation.
- 2.13** An article by Fadani et al (2013) reviewed the scientific literature concerning the application of oocyte IVM as a treatment for normally ovulating women. The article highlighted that maturation rates *in vitro* are suboptimal and influenced by several factors. In IVM cycles implantation and pregnancy rates are lower compared with controlled ovarian stimulation treatments, but accurate patient selection can improve IVM clinical outcome. In normal responders, IVM does not reach success rates similar to conventional ovarian stimulation regimens. The article concluded by proposing that IVM may represent a milder approach to assisted reproduction treatment and an alternative intervention for specific conditions.
- 2.14** Telfer et al (2013) explore the full potential of tissue to restore fertility, by the development of *in vitro* systems that support oocyte development from immature stages to maturation. The article examines the challenges of developing a complete culture system that would support human oocyte development, detailing the approaches being taken by several groups using tissue from women and non-human primate models to support each of the stages of oocyte development. The article also discusses the techniques involving IVM which is being developed with human tissue and primate tissues.

Impact

- 2.15** The Authority will need to consider mechanisms for regulation if donor ovarian tissue/ovary transplantation is thought to be viable. Furthermore, patients may consider oocyte cryopreservation as a more feasible method of fertility preservation and may therefore seek advice from the HFEA about this process.

Level of work recommendation

- 2.16** The viability of these techniques, and resulting success rates, need to be understood through a thorough analysis of the current research and consideration of presentations of any relevant experts in the field. Up to date advice for patients and the sector will need to be formulated by the Executive with guidance from SCAAC.

References

- Chian RC. (2013) In vitro maturation of human immature oocytes for fertility preservation. *Fertility and Sterility* 99(5):1173-1181
- Cobo A. (2013) Is vitrification of oocytes useful for fertility preservation for age-related fertility decline and in cancer patients? *Fertility and Sterility* 99 (6) 1485-1495
- Cobo A. (2013) Outcome of cryotransfer of embryos developed from vitrified oocytes: double vitrification has no impact on delivery rates. *Fertility and Sterility* 99 (6) 1623-1630.e7
- Fadini R. (2013) Oocyte in vitro maturation in normo-ovulatory women. *Fertility and Sterility* 99 (5)1162-1169
- Grynberg M. (2013) In vitro maturation of oocytes: uncommon indications. *Fertility and Sterility* 99 (5) Pages 1182-1188
- Nikiforaki, D. (2013) Oocyte cryopreservation and in vitro culture affect calcium signalling during human fertilization. *Hum. Reprod.* (2014) 29 (1): 29-40
- Telfer, E. Ovarian follicle culture: advances and challenges for human and nonhuman primates. *Fertility and Sterility* 99 (6) 1523-1533
- Zelinski MB. (2013) Ovarian follicle culture: advances and challenges for human and nonhuman primates. *Fertility and Sterility* 99 (6) 1523-1533

3. Safety of embryo biopsy

Background

- 3.1** Patients sometimes require their embryos to be genetically tested before transfer to avoid passing on a serious inherited condition to their child, to screen for problems with the genetic material in an embryo or because they already have a child with a very serious condition and want to have a sibling who could provide a potentially life-saving tissue transplant. The HFEA tightly regulates genetic testing of embryos for specific medical purposes.
- 3.2** Scientists are able to remove one or two cells from an embryo created by IVF when it is a few days old. They genetically test these cells, whilst the remaining embryos still have the potential to develop normally and lead to pregnancies.
- 3.3** However it is important to monitor the safety of this process to make sure that removing these cells does not have any adverse effects on the children born and the optimal process is defined. Researchers have examined the health, growth and development of these children, compared to children conceived by assisted reproduction without genetic testing and to naturally-conceived children.
- 3.4** SCAAC considered the safety of embryo biopsy in 2010 and the results of studies then were reassuring. For single children (ie, those not born as twins/triplets), there was no evidence that removing these cells puts the children born under increased health risks compared to children conceived by other assisted reproduction techniques. In addition, their growth and development at two years is the same as children conceived naturally. The evidence showed biopsy does not harm the child's health and it is therefore reasonable to allow embryo biopsy, even where there was no direct benefit to the subsequent child born. The Committee also agreed it did not wish to update its advice to the Authority regarding the use of embryo biopsy.
- 3.5** The Committee also asked the Executive to continue to keep under review research into the effect of embryo biopsy on subsequent child health. The Committee highlighted the need to consider other techniques such as polar body (PB) biopsy, trophoctoderm biopsy and vitrification post-biopsy. Whilst PB biopsy has known restrictions because only the female part can be investigated, trophoctoderm biopsy uncovers both the maternal and the paternal inheritance. All techniques should be monitored as viable alternatives.

Summary of developments

- 3.6** In 2011 the ESHRE PGD Consortium/Embryology Special Interest Group created best practice guidelines for polar body and embryo biopsy for preimplantation genetic diagnosis/screening (PGD/PGS). The document provides guidance for uses of embryo biopsy, laboratory issues relating to biopsy, timing of biopsy, biopsy procedure and cryopreserving biopsied embryos.

Studies showing no increased risk after biopsy

- 3.7** A study by Desmyttere et al (2012) examined whether embryo biopsy, as performed in PGD, has an impact on the health of infants up to two months old. A cohort of 995 children (live born after embryo biopsy between 1994–2009) was monitored, with a control group of 1507 children born after ICSI with embryo transfer on day 5. No differences regarding mean term, prematurity, mean birthweight, very low birthweight, perinatal death, major malformations and neonatal hospitalisations in singletons and multiples born following PGD versus ICSI were observed. This suggests that biopsy for PGD does not introduce extra risk to the overall medical condition of newborn children. Multiples born following embryo biopsy appear to be at lower risk for low birthweight compared with multiples born following ICSI.

Studies showing potential increased risk after biopsy

- 3.8** Kirkegaard et al (2013) looked at human embryonic development after blastomere removal using a time-lapse analysis. Embryos in the PGD group started hatching at the same time-point as the control group, but had a smaller diameter and a thicker zona pellucida when hatching. Time-lapse analysis revealed that in the control group, expansion of the blastocyst caused continuous thinning of zona pellucida until the blastocyst hatched, whereas in the PGD group the blastocyst hatched through the opening in zona pellucida artificially introduced prior to the biopsy. The study therefore concluded that blastomere biopsy prolongs the biopsied cell-stage, possibly caused by a delayed compaction and therefore alters the mechanism of hatching.
- 3.9** Montag et al (2013) provides a review of polar body biopsy combined with array comparative genomic hybridization techniques (a method of molecular DNA analysis) which allows detection of maternal chromosomal mutations. The review concludes that although it has limitations in terms of not being about to detect postmeiotic aneuploidies, it can be seen as an alternative to blastomere and trophectoderm biopsy for the diagnosis of structural and numeric chromosome abnormalities in oocytes.

3.10 A recent study by Scott et al (2013) examined the optimal time to perform biopsy for preimplantation genetic testing. The authors conclude that polar body biopsy does not identify approximately 40% of genetic errors when doing aneuploidy screening, and the resulting probability that the results are not an accurate reflection of the actual chromosomal constitution of the embryo can be up to 45%. Blastomere biopsy at the cleavage stage was said to significantly reduce the reproductive potential of the embryo by approximately 40%. They concluded by suggesting that currently, biopsies necessary for PGD are best obtained through trophectoderm biopsy at the blastocyst stage.

Level of work recommendation

3.11 Members are asked to:

- consider whether there are any further studies or developments in this area and:
- review evidence collated by the Executive in this summary on the safety of embryo biopsy in light of the recently published follow-up studies, and decide whether they wish to make any recommendations to the Authority regarding the use of embryo biopsy for tissue typing, PGD or PGS.

References

- Harton GL. et al (2011) ESHRE PGD Consortium/Embryology Special Interest Group—best practice guidelines for polar body and embryo biopsy for preimplantation genetic diagnosis/screening (PGD/PGS). *Hum. Reprod.* (2011) 26 (1): 41-46.
- Kirkegaard K. (2013) Human embryonic development after blastomere removal: a time-lapse analysis. *Hum. Reprod.* (2012) 27 (1): 97-105.
- Scott K. (2013) Selecting the optimal time to perform biopsy for preimplantation genetic testing. *Fertility and Sterility* 100 (3)
- Montag et al (2013) Polar body biopsy. *Fertility and Sterility* 100 (3) Pages 603-607
- Desmyttere S. (2013) Neonatal follow-up of 995 consecutively born children after embryo biopsy for PGD. *Hum. Reprod.* (2012) 27 (1): 288-293.