Scientific and Clinical Advances Advisory Committee (SCAAC) - agenda

Monday 08 February 2020, 11:00am – 1:00pm
Virtual

Agenda item	Time
1. Welcome, apologies, declarations of interest	11:00am (5')
2. Committee effectiveness review Paula Robinson (HFEA)	11:05am (20')
3. Matters arising Matthew Mudford (HFEA)	11:25am (5')
4. Updates from Fertility 2021 All	11:30am (10')
5. Monitoring the effects of COVID on fertility, assisted conception and early pregnancy All	11:40am (5')
Break	*11:45am (15')*
6. Prioritisation of issues identified through the horizon scanning process and the Committee work plan Victoria Askew (HFEA)	12:00pm (20')
7. Embryo culture media Dina Halai (HFEA)	12:20pm (20')
8. Any other business	12:40pm (10')
9. Meeting summary and close	12:50pm (10')

Scientific and Clinical Advances Advisory Committee (SCAAC) – matters arising

Monday 8th February 2021

Date and item	Action	Responsibility	Due date	Progress to date
19/10/2020 3.3	The Committee will continue to monitor and share relevant literature on COVID-19.	All SCAAC members	Ongoing	The Committee were reminded to highlight relevant papers ahead of the meeting. An agenda item will be scheduled at SCAAC meetings for this discussion.
19/10/2020 3.3	The Executive to present on early pregnancy data and live birth rates at the next SCAAC to see the effect of treatment cessation and delay caused by COVID-19	Dina Halai, Policy Manager	Ongoing	It is too early for the HFEA to say anything about pregnancy and live birth rate outcomes based on HFEA register data. Typically, there is a two-year delay in reporting outcomes, so this would be expected in 2022. In the interim, it might be useful for the SCAAC to see this publication in Human Reproduction using the HFEA register data.
19/10/2020 5.9	The Executive to share summary of the results of the patient survey results on the treatment add-ons website update with SCAAC.	Victoria Askew, Policy Manager	Completed	This patient survey was discussed during the November 2020 Authority meeting. A summary of the results is available in Annex 1 of agenda item 7 (pg. 105 of paper set).
19/10/2020 6.29	The Executive will review the HFEA website information on reproductive	Matthew Mudford, Policy Officer	Ongoing	These updates will be live on the HFEA website by mid-February 2021. An

	immunology along with the survey findings.			associated Clinic Focus article will be circulated to inform the sector about the update.
19/10/2020 6.34	The Executive to consider how information about safety is presented within the HFEA's treatment add-ons information on the HFEA website along with the survey findings.	Victoria Askew, Policy Manager	Ongoing	Treatment add-on traffic light ratings no longer reflect the safety considerations of each treatment. Safety will be commented on for each treatment but outside of the traffic light ratings. These updates will be live on the HFEA website by mid-February 2021.

Prioritisation of issues identified through the horizon scanning process

Details about this paper

Area(s) of strategy this paper relates to:	Shaping the future
Meeting:	Scientific and Clinical Advances Advisory Committee (SCAAC)
Agenda item:	6
Paper number:	HFEA (08/02/2021) 006
Meeting date:	08 February 2021
Author:	Victoria Askew, Policy Manager
Annexes	Annex 1: Briefings on key issues that have been identified as high priority through the horizon scanning process Annex 2: Spreadsheet of papers identified through horizon scanning

Output from this paper

For information or recommendation?	For recommendation
Recommendation:	Members are asked to: • note the issues identified as high and medium priority through the horizon scanning process; • consider the high and medium priority issues and work recommendations; and • consider whether advice from additional external advisors would help in achieving the work recommendations.
Resource implications:	Dependant on the number of issues the Committee recommend to be high priority
Implementation date:	The Committee work plan for 2021/2022

Communication(s):	None
Organisational risk:	Low

1. Background

1.1. The Authority 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, the Authority can be aware of potential licence applications and prepare, if necessary, a policy of position or relevant patient information.

1.2. Issues are identified from journal articles, conferences and contact with experts who are invited to the Authority's Annual Horizon Scanning meetings. 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 of the Executive, the Scientific and Clinical Advances Advisory Committee (SCAAC) and the Authority's consideration of scientific and ethical issues and standards.

2. Prioritisation process

2.1. A full list of papers identified since January 2020 can be found in Annex 2 to this paper.

2.2. To help with the business planning process, it is important for the Executive to be fully aware of which issues members consider to be high priority. New issues which have been identified this year have been categorised as high, medium or low priority using the following criteria:

a) Within the HFEA's remit
b) Timescale for likely introduction (2-3 years)
c) High patient demand/clinical use if it were to be introduced
d) Technically feasible
e) Ethical issues raised or public interest

2.3. New issues are high priority if they are within the HFEA's remit and meet at least two other criteria. New issues are medium if they are within the HFEA's remit and meet one other criterion or are outside of HFEA remit but meet at least two other criteria. Whilst low priority issues are those outside of HFEA's remit and unlikely to impact on research or treatment in the near future, published studies in these areas will continue to be collected and considered as part of the horizon scanning process.

2.4. High priority is also given to established techniques or issues which fall within the HFEA's remit and require ongoing monitoring or provision of patient information.

3. High priority issues

3.1. The Executive considers the following topics to be high priority for consideration in 2021/22. These topics are displayed in the priority order outlined by the Committee at the February 2020 meeting.

a) Treatment add-ons (expanded on in Annex A)
b) Health outcomes in children conceived by ART
c) New technologies in embryo testing (including embryo biopsy and noninvasive methods for PGT-M and PGT-A)

d) Genome editing (expanded on in Annex A)
e) Mitochondrial donation (expanded on in Annex A)
f) Alternative methods to derive embryonic and embryonic-like stem cells
g) Synthetic human entities with embryo like features, “SHEEFs”
h) Artificial intelligence (AI)

3.2. Based on this years’ horizon scanning findings, key developments on some of these high priority issues can be found at Annex A. Briefings have not been written for all prioritised issues, as these topics are either standing items that are considered by the committee every year, or they have already been considered by the Committee recently.

3.3. It was noted during the horizon scanning process that much of the literature relevant to ‘Health outcomes in children conceived by ART’ was, by its nature, in paediatric journals. These journals are not currently recommended by the SCAAC and so were not included in the findings. The Executive suggests that the list of recommended journals be expanded for that topic to include some of the leading paediatric publications.

Annual review of treatment add-ons

3.4. The evidence for treatments add-ons is reviewed annually by an expert in systematic reviews and evidence assessment to carry out an independent assessment of the quality of evidence (using the GRADE methodology1) for each treatment add-on. At their October meetings, the SCAAC are then asked to consider the quality of new evidence for each treatment add-on based on the findings from the independent assessor and recommend updates to the HFEA’s treatment add-ons information**.** The Executive have therefore not carried out horizon scanning for new research on existing treatment add-ons for this meeting.

3.5. As part of this horizon scanning process, the Executive have identified research investigating treatments that claim to increase live birth rate that are not currently part of the HFEA’s treatment add-ons information, a briefing on these can be found at Annex A. Medical professionals, academics or patient organisations can apply to propose a treatment for inclusion in the HFEA’s traffic-light rated list of add-ons

4. Medium priority issues

4.1. The Executive considers the following topics to be medium priority for consideration in 2021/22 because they are outside of the HFEA’s remit but meet at least two other criteria and the HFEA are keen to continue their awareness of these issues.

a) The impact of the microbiome on fertility and fertility treatment outcomes
b) The impact of stress on fertility treatment outcomes
c) Embryo culture media
d) COVID-19 (expanded on in Annex A)

Review of COVID-19 research

4.2. SCAAC’s role is to consider advances in science and clinical practice which are relevant to the Authority's work. At the June 2020 SCAAC meeting the committee agreed to monitor research into the effects of COVID-19 on reproduction or early pregnancy and to discuss this research in

a standing agenda item. This monitoring process will take place outside of the annual horizon scanning discussed in this paper.

4.3. The Executive suggests that COVID-19 meets the criteria to be classified as a medium priority item. Although COVID-19 does not fall within the HFEA remit of being a new treatment or technology that is likely to be introduced to the fertility sector in a traditional sense, it seems to meet the two criteria of timescale for likely introduction (2-3 years), as infection that appeared quickly and spread amongst all populations including those seeking fertility treatment, and an ethical issues raised or public interest.

4.4. The relevant research that has been highlighted since June 2020 are included as part of Appendix A to this paper.

5. Recommendations

5.1. Members are asked to:

- note the issues identified as high and medium priority through the horizon scanning process;
- consider expanding the list of recommended journals to include certain paediatric journals when scanning for articles related to ‘Health outcomes in children conceived by ART’;
- consider the high and medium priority issues and work recommendations; and
- consider whether advice from additional external advisors would help in achieving the work recommendations.

Annex A

Briefings on new issues that have been identified as high priority through the horizon scanning process

6. Treatment add-ons – Potential future treatment add-ons identified through horizon scanning

Background

6.1. Treatment add-ons are optional additional treatments that may be offered on top of routine fertility treatment, often at an additional cost. Evidence on whether these treatment add-ons are safe and/or effective at increasing live birth rates are often of low quality or absent. For this reason the HFEA has undertaken a large piece of work around treatment add-ons including publishing a traffic light rating system for add-ons that meet the criteria laid out by the Authority.

6.2. The evidence base for each of the treatment add-ons currently included in the HFEA's traffic light rated list of add-ons is reviewed on an annual basis. Over time it is expected that additional treatments will be identified as meeting the criteria of a treatment add-on. For this reason, the HFEA have developed an application process for medical professionals, academics and patients organisations to highlight to the HFEA treatments that they feel would benefit from being part of the annual evidence review.

6.3. The horizon scanning process has highlighted that there are a number of treatments available to patients that may fit the criteria to be included in the HFEA's traffic light rated list of treatment add-ons. These treatments have been outlined below for discussion by the Committee and we would ask the Committee if they could highlight any further treatments they feel might qualify as a treatment add-on that is not currently included in the list.

Summary of developments

6.4. The use of techniques, tests and treatments without male factor infertility

a) **Sperm aneuploidy testing (SAT)** – This test is used to determine the percentage of sperm within a sample that have chromosomal abnormalities. It is suggested that men with increased numbers of aneuploidy sperm may be more likely to experience recurrent implantation failure, recurrent miscarriage, have abnormal semen parameters or have a pregnancy with chromosomal abnormalities. SAT tests sperm for abnormalities in chromosomes 13, 18, 21, X and Y. It is suggested that men who are identified to have a high aneuploidy rate are then recommended to undergo PGT-A during their IVF or ICSI cycle.

b) **Microfluidic sperm sorting** – This sperm selection technique is thought to allow for the separation of motile and morphologically normal sperm within a semen sample. The chip uses microchannels which are thought to mimic the female reproductive track and allow 'healthy' sperm to travel from the input to the output holes whilst 'unhealthy' sperm remain within the channels. It is suggested that microfluidic sperm sorting has benefits of being 'gentler' and chemical free when compared to other sperm section techniques, such as centrifuge. It is thought that this technique aids the selection of sperm for use in ICSI.

c) **Treatments for high DNA fragment rate** - High DNA fragmentation rates in ejaculated sperm have been linked to a reduction in successful ART outcomes. A suggested treatment is to use surgical sperm retrieval (SSR) to aspirate testicular sperm for use in ICSI. It is thought that using testicular sperm avoids the DNA fragmentation caused by oxidative stress during the sperms journey through the epididymis.

d) **ICSI for non-male factor infertility** – ICSI is often used for patients that have no male factor infertility. This comes with an additional cost and risks for patients and research suggests that there is no benefit for use in these patients.

6.5. **Endometrial Receptivity Array (ERA)** – this test uses genetic analysis on a biopsy of the endometrium during a mock embryo transfer cycle to determine a specific embryo transfer date to be in line with a woman's window of implantation (WOI). Women are classified as either pre-receptive (WOI is earlier in the cycle than expected), receptive (WOI is when you would expect in the cycle) or post-receptive (WOI is later in the cycle than expected). It is suggested that with this information a patient's embryo transfer can be personalised to be in line with their WOI. It is likely that if a patient WOI is earlier or later than would be expected they would be required to undergo a frozen embryo transfer. This allows the embryo to be in the correct developmental stage for embryo transfer regardless of where the patient is in their cycle when embryo transfer takes place.

6.6. **PGT-A using non-invasive techniques** - In December 2020 a legal case was brought against an Australian fertility clinic, Monash IVF, by a group of patients who had received a non-invasive technique for pre-implantation genetic testing for aneuploidy. The technique used DNA collected from the spent culture media instead of conducting an embryo biopsy. The patient that originally pursued the lawsuit felt that they had not been informed that PGT-A using non-invasive techniques could return false positive results and this had effect their ability to make an informed choice about the use of their embryos. Monash IVF has since suspended the use of non-invasive PGT-A.

Level of work recommendation

6.7. Committee members, as well as the Executive, medical professionals, academics or patient organisations, are able to apply for these treatments to be considered for inclusion in the HFEA's traffic light rated list of treatment add-ons. If accepted, the evidence base for that treatment would then be reviewed in line with the annual review of treatment add-ons conducted by the executive and the Committee, discussed further in the paper above.

7. Mitochondrial donation

Background

7.1. In 2015 the UK parliament made the decision to legalise mitochondrial donation for use in treatment. Mitochondrial donation treatment can only be used by people with severe mitochondrial disease who have a very high risk of passing a serious mitochondrial disease onto their children. Currently, only Newcastle Fertility Centre at Life has a licence to conduct research and treat patients using mitochondrial donation techniques.

7.2. Through horizon scanning papers have been identified that are investigating the use of mitochondrial donation or supplementation for indications other than mitochondrial disease.

Summary of developments

7.3. Costa-Borges et al. (2020) summarised that oocyte cytoplasmic dysfunction, including mitochondria function, had been identified as a potential cause of poor-quality embryos either failing to fertalise or arresting during culture. The group hypothesised that as maternal spindle transfer (MST) allows replacement of the entire cytoplasm of an affected oocyte, it holds promise for the enhancement of embryonic development. The pilot study, conducted in Greece, recruited 25 participants with previous failed cycles of IVF due to embryo development arrest. MST was applied successfully in 113 of 123 oocytes. Normal fertilisation was confirmed in 76.1% of injected oocytes and 60.5% of these developed into good quality blastocysts. Single blastocyst transfers were performed in 9 patients, resulting in 6 clinical pregnancies. Two patients have delivered a healthy child and 3 more pregnancies are ongoing. Genetic analyses of the biopsied cells, amniotic fluid and samples collected after birth confirmed the parentage of the children and the origin of the donated mtDNA. Follow-up studies are being performed on the children born.

7.4. A preliminary study conducted by Kile et al. (2020) hypothesised that poor-quality oocytes in patients of advanced maternal age is in part due to mitochondrial dysfunction. The group did not suggest mitochondrial donation as a treatment for this and instead wanted to determine the effect of supplementing mitochondrially targeted antioxidants (MTQ) during embryo culture for women of advanced maternal age (>35 years old). The study included 11 participants with, after the use of ICSI, 143 presumptive zygotes places into a control medium and 66 placed in a medium containing the MTQ. There were no differences between control and MTQ treatment in day 5 good quality blastocysts (control, 18%; MTQ, 20%). To date, four euploid blastocysts from the control treatment and one from the MTQ treatment have been transferred individually to a total of 5 patients, all resulting in ongoing pregnancies with fetal heartbeat. The group summarised that the use of MTQ in culture media did not seem to improve good quality or euploid blastocyst development.

7.5. Ferreira et al. (2020) produced a systematic review of the clinical/biological outcomes of mitochondrial supplementation, aiming to improve oocyte competence or explore the safety of this technique, until September 2019. Clinical pregnancy was not improved in the only randomised controlled trial published, although an increase was demonstrated in other non-randomised studies. Fertilisation rate and embryo development were not different from control groups in the majority of studies, although performed in different contexts and using diverse sources of mitochondria. The safety of mitochondria transfer is still a concern, however, the euploid rate and the absence of reported congenital malformation from the clinical studies are reassuring. In summary, mitochondrial supplementation does not seem to cause harm although the benefit of improving oocyte competence is still unclear due to the diversity of methodological approaches and low-quality of the data available.

Level of work recommendation

7.6. The committee will be asked to monitor any further developments in the scientific and clinical literature relating to mitochondrial donation techniques or uses. In order to aid discussions on this topic, the committee is asked if they would like to invite any specialist speakers to present at the relevant meeting and take part in a discussion with the committee. The Executive will update the committee on the analysis of any follow up data they receive on children born using MST or pronuclear transfer (PNT). These discussions will help the Executive in their monitoring of mitochondrial donation and highlight any possible issues with the techniques which may impact on their clinical use.

References

- Costa-Borges N,Nikitos E, Spath K, Rink K, Kostaras K, Zervomanolakis I, Kontopoulos G, Polyzos P, Grigorakis S, Prokopakis T, Vasilopoulos Y, Vlahos N, de Ziegler D, Wells D, Psathas P, Calderón G. First registered pilot trial to validate the safety and effectiveness of maternal spindle transfer to overcome infertility associate with poor oocyte quality. Fert and Ster. 2020 Sept 1;114(3):E71-E72. doi.org/10.1016/j.fertnstert.2020.08.220.
- Ferreira AF, Soares M, Almeida Reis S, Ramalho-Santos J, Sousa AP, Almeida-Santos T. Does supplementation with mitochondria improve oocyte competence? A systematic review. Reproduction. 2020 Dec 1:REP-20-0351.R1. doi: 10.1530/REP-20-0351.
- Song WH, Ballard JW, Yi YJ, Sutovsky P. Regulation of mitochondrial genome inheritance by autophagy and ubiquitin-proteasome system: implications for health, fitness, and fertility. Biomed Res Int. 2014;2014:981867. doi: 10.1155/2014/981867.

8. Genome editing

Background

8.1. There are thousands of pathogenic genetic variants that have been identified in humans. Genome editing methods using nucleases and base editors have the potential to correct only a minority of those variants and have seemingly reached a limit to their efficiency and precision owing to the tools' reliance on complex and competing cellular processes. A new technology called prime editing has greater precision and efficiency, potentially being able to correct many more disease-causing genetic variants.

Summary of Developments

8.2. In 2019, Anzalone et al. announced a new approach to genome editing known as 'prime editing. Prime editing differs from previous genome-editing systems in that it can "search and replace", using RNA to direct the insertion of new DNA sequences in human cells.

8.3. The prime editing system involves coupling a Cas9 enzyme to reverse transcriptase to form a fusion protein known as the prime editor. It uses one strand of the target DNA site to "prime," or initiate, the direct writing of edited genetic information into the genome.

8.4. The other important component of the system is new type of engineered RNA, called a pegRNA, which has the function of both a guide and a template. First it directs the prime editor to its target site, where it cuts one strand of the DNA. The pegRNA also contains additional RNA nucleotides encoding the new edited sequence. To transfer this information, the reverse transcriptase element reads the RNA extension and writes the corresponding DNA nucleotides into the target spot.

8.5. Prime editing achieves successful edits with a lower rate of undesired "off-target" changes when compared to previous approaches that require making nearby breaks on each DNA strand. Prime editing can also make precise single-nucleotide changes in target sequences that could previously not be accessed.

8.6. Anzalone was able to prime editing in human cells to correct, efficiently and with few byproducts, the primary genetic causes of sickle cell disease (requiring a transversion in HBB) and Tay-Sachs disease (requiring a deletion in HEXA).

8.7. The technology is still new and so original research using the technique using it has not yet been published but many papers have explored the significant potential, notably Marzec et al.

(2020) in Trends in Cell Biology. They described how prime editing overcomes many of the challenges of genome editing and demonstrates the potential to perform insertions, deletions, and all putative 12 types of base-to-base conversions in human cells.

Level of work recommendation

8.8. The Executive will keep abreast of the progress of research in this area to ensure that developments are monitored. The Committee is, therefore, asked to consider whether there are any further studies or developments in the area and identify particular concerns or issues that should be highlighted.

References

- Anzalone AV, Randolph PB, Davis JR, Sousa AA, Koblan LW, Levy JM, Chen PJ, Wilson C, Newby GA, Raguram A, Liu DR. Search-and-replace genome editing without double-strand breaks or donor DNA. Nature. 2019 Dec;576(7785):149-157. doi: 10.1038/s41586-019-1711-4.
- Anzalone AV, Koblan LW, Liu DR. Genome editing with CRISPR-Cas nucleases, base editors, transposases and prime editors. Nat Biotechnol. 2020 Jul;38(7):824-844. doi: 10.1038/s41587-020-0561-9.
- Marzec M, Brąszewska-Zalewska A, Hensel G. Prime Editing: A New Way for Genome Editing. Trends in Cell Biology. 2020 Apr 01;30(4):257-259. doi: 10.1016/j.tcb.2020.01.004
- Urnov FD. Prime Time for Genome Editing? N Engl J Med. 2020 Jan 30;382(5):481-484. doi: 10.1056/NEJMcibr1914271.
- Yan J, Cirincione A, Adamson B. Prime Editing: Precision Genome Editing by Reverse Transcription. Mol Cell. 2020 Jan 16;77(2):210-212. doi: 10.1016/j.molcel.2019.12.016.

9. COVID-19

Background

9.1. SCAAC's role is to consider advances in science and clinical practice which are relevant to the Authority's work. At the June 2020 SCAAC meeting the committee agreed to monitor research into the effects of COVID-19 on fertility, conception and early. This monitoring process will take place outside of the annual horizon scanning discussed in this paper.

Summary of developments

9.2. As outlined in this paper, SCAAC's role is to consider advances in science and clinical practice which are relevant to the Authority's work. At the June 2020 SCAAC meeting the committee agreed to monitor research into the effects of COVID-19 on reproduction or early pregnancy and to discuss this research in a standing agenda item. The papers outlined under this review to date are listed in the reference of this section.

Level of work recommendation

9.3. The Committee will be asked to continue to monitor any further developments in scientific and clinical literature relating to the effects of COVID-19 on reproduction and early pregnancy. These developments will be discussed as a standing agenda item at SCAAC meetings

References

- Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, Debenham L, Llavall AC, Dixit A, Zhou D, Balaji R, Lee SI, Qiu X, Yuan M, Coomar D, van Wely M, van Leeuwen E, Kostova E,

Kunst H, Khalil A, Tiberi S, Brizuela V, Broutet N, Kara E, Kim CR, Thorson A, Oladapo OT, Mofenson L, Zamora J, Thangaratinam S; for PregCOV-19 Living Systematic Review Consortium. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ. 2020 Sep 1;370:m3320. doi: 10.1136/bmj.m3320.

- Royal College of Obstetricians and Gynaecologists and Royal College of Midwives. Coronavirus (COVID-19) Infection in Pregnancy, version 12. Available at 2020-10-14-coronavirus-covid-19-infection-in-pregnancy-v12.pdf (rcog.org.uk)
- Smith ADAC, Gromski PS, Rashid KA, Tilling K, Lawlor DA, Nelson SM. Population implications of cessation of IVF during the COVID-19 pandemic. Reprod Biomed Online. 2020 Sep;41(3):428-430. doi: 10.1016/j.rbmo.2020.07.002.
- The Association of Reproductive and Clinical Scientists (ARCS) and British Fertility Society (BFS) U.K. best practice guidelines for fertility clinics during the COVID-19 pandemic, version 3. Available from: https://www.britishfertilitysociety.org.uk/wp-content/uploads/2020/09/ARCS-BFS-guideline-Covid-19-version-3-30-September-2020.pdf
- Tian Y, Zhou LQ. Evaluating the Impact of COVID-19 on Male Reproduction. Reproduction. 2020 Nov 1:REP-20-0523.R1. doi: 10.1530/REP-20-0523.
- Weatherbee BAT, Glover DM, Zernicka-Goetz M. Expression of SARS-CoV-2 receptor *ACE2* and the protease *TMPRSS2* suggests susceptibility of the human embryo in the first trimester. Open Biol. 2020 Aug;10(8):200162. doi: 10.1098/rsob.200162.

Committee work plan 2021/2022

Priority topic	Item	Possible speaker(s)	Meeting
Synthetic embryo-like entities	Literature review	Internal	June 2021
Mitochondrial donation	Literature review and external speaker	Newcastle Fertility Centre	June 2021
Review treatment add-ons	Literature review and external speaker	Expert reviewer	October 2021
Alternative methods to derive embryonic and embryonic-like stem cells	Literature review	Internal	February 2022
Artificial intelligence (AI)	Literature review and an external speaker	Academic	February 2022
The impact of stress	Literature review	Internal	June 2022
The impact of the microbiome	Literature review	Internal	June 2022

Human Fertilisation & Embryology Authority

Embryo culture media update

Details about this paper

Area(s) of strategy this paper relates to:	The best care – effective and ethical care for everyone
Meeting:	Scientific and Clinical Advances Advisory Committee (SCAAC)
Agenda item:	7
Paper number:	HFEA (08/02/2021) 007
Meeting date:	08 February 2021
Author:	Dina Halai, Scientific Policy Manager
Annexes	None

Output from this paper

For information or recommendation?	For recommendation
Recommendation:	Members are asked to: • consider the progress of research (since June 2019) into the effects of components in culture media used for IVF treatment; • advise the Executive if they are aware of any other recent developments and; • advise what, if anything, needs to be communicated to the MHRA who are responsible for regulating the composition and safety of culture media used in the UK
Resource implications:	None
Implementation date:	N/A
Communication(s):	None
Organisational risk:	Low

1. Introduction

1.1. Clinical in vitro fertilisation (IVF) systems aim to imitate the conditions an embryo would encounter in vivo. This means it is important to optimise the culture environment of embryos during IVF treatment. The components of embryo culture media, therefore, require scrutiny to ensure that risks are minimised, embryo stress is avoided, and embryo health is maintained.

1.2. Although generally considered to be safe based on past and current experience, uncertainties remain about the effects of embryo culture media. The concentrations of components such as growth factors, amino acids, energy substrates and antibiotics could impact fertilisation rate, early embryo development and clinical outcomes for children conceived by assisted reproduction. Different media can influence many outcomes including fertilisation rate and clinical outcome.

1.3. Concerns about the components of embryo culture media, how they are regulated, and their potential effects have been discussed by the SCAAC previously. At its meeting in:

1.3.1. June 2019, SCAAC noted that one study found no difference in cardiovascular development in 9-year-old children, who were born following IVF or intracytoplasmic sperm injection (ICSI) treatment when two different culture media were used. SCAAC also commented that the use of using data driven technologies in IVF would be difficult if the contents of embryo culture are still largely unknown.

1.3.2. In June 2017, SCAAC discussed research questioning a possible association between type of culture media and birthweight

1.3.3. Also, in 2017, SCAAC discussed the possible association between culture media and imprinting disorders based on mice studies. This is particularly concerning as the precise composition of culture media is not disclosed by the manufacturers to those purchasing and using the product.

1.4. 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.

1.5. New research in this area is monitored periodically to inform members of the potential impact of culture media composition on embryonic development and SCAAC's discussions on this research are passed on to the Medicines and Healthcare Products Regulatory Agency (MHRA) for information. The research highlighted in this paper has been published between June 2019 and January 2021.

2. Current regulation

2.1. Since 1 January 2021, in response to the end of the transition period after EU Exit, there have been several changes, introduced through secondary legislation, to how medical devices are placed on the market in Great Britain (England, Wales and Scotland). In the UK, all medical devices, including human embryo culture media used for treatment purposes, placed on the Great Britain market need to be registered with the MHRA and be approved by UK Approved Bodies. Following assessment, the approved body will issue relevant certification allowing manufacturers to place UKCA marking on their products and to place them on the market in Great Britain. It is not within the remit of the HFEA to regulate the composition and safety of culture media.

2.2. Prior to this, human embryo culture media used for treatment purposes had to be CE marked by a UK Notified Body recognised by the EU. The MHRA designated UK Notified Bodies to assess manufacturers for quality and safety, and these bodies were audited by MHRA within the UK under the European Medical Devices Directive 93/42/EEC[1]. Although the UKCA mark will be available for use in Great Britain from 1 January 2021, CE marking will continue to be needed for devices placed on the Northern Ireland market and EU rules will need to be met. CE marked devices will also be accepted on the Great Britain market until 30 June 2023.

2.3. From January 2021 for Great Britain, activities that can be undertaken by an approved body to assess whether manufacturers and their medical devices meet the requirements were set out in the Medical Devices Regulations 2002 , these include:

2.3.1. an assessment of the manufacturer's quality system, including design

2.3.2. assess the full design dossier relating to each type of product to ensure that they meet the requirements

2.3.3. assess the full technical information relating to each type of product and carry out appropriate testing of a representative sample of production to ensure that it meets the requirements

2.3.4. either test every unit or every batch of product to ensure that they are meeting the requirements before the manufacturer can place them onto the market

2.3.5. production and product quality assurance

2.3.6. unannounced audits of manufacturers

3. Research

Culture media comparisons

3.1. Reed et al investigated the viscosities of media used for human embryo transfer and the possible effect of viscosity as it relates to interactions between transfer media and uterine fluid. The study observed a relatively narrow distribution of viscosities across several transfer media (G1-Plus, G2-Plus, G-TL, 1-Step, Global Total, Global Total HEPES, and Sperm Wash Medium) despite the various commercial or in-house modifications. The data did however demonstrate the difference between the viscosities of embryo transfer media and the assumed viscosity of uterine fluid. The authors highlighted that embryo transfer media may be well-suited for IVF, but additional evaluation of all variables, e.g. media viscosity in the context of embryo transfer, adds to the knowledge base that should be available to practitioners.

3.2. A cross sectional study by Castillo et al surveyed 46 UK IVF clinics. Information regarding culture medium type, incubator type, and oxygen level used in ART between January 2011 and December 2013 was collated. The survey responses were merged with recorded treatment and outcome data held in the HFEA Register up to the end of 2014. There were statistically significant differences in live birth weight (LBR) between the eight culture media systems analysed; however, none of the embryo culture factors showed statistically significant associations with birth weight.

[1] https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=%20CONSLEG:1993L0042:20071011:en:PDF

The study did note a very strong effect of clinic site on both LBR and birth weight, therefore treatment practices and clinic site may have masked the effect of culture conditions.

3.3. A multi-centre randomised controlled trial (RCT) in the Netherlands carried out by Mulder et al investigated if there is a difference in DNA methylation status of imprinted genes in human placenta derived from IVF conceptions exposed to human tubal fluid (HTF) (n=43) versus G5 culture (n=54) medium. Placenta samples from 69 naturally conceived live births were collected during 2008-2013 in the Netherlands as reference material. Results showed no statistically significant differences in the mean DNA methylation status of any of the 34 imprinted differentially methylated regions in placentas derived from IVF conceptions cultured in HTF or G5 culture medium. It has often been postulated, but has yet to be rigorously tested, that there is an association between culture media and imprinted genes which brings about the effects on pregnancy, birth, and child development in humans. Since the study did not detect any statistically significant effects of embryo culture conditions on methylation status of imprinted genes in the placenta, this suggests that other unexplored mechanisms may underlie these effects.

3.4. A randomised control trial by Rose et al investigated if Embryogen®/BlastGen™ culture medium improved live birth rates compared with standard Cleavage/Blastocyst sequential culture medium for women undergoing IVF and ICSI with poor prognosis. A total of 100 couples undergoing IVF/ICSI were included in the study. A significant reduction in day-5 embryo outcome parameters was found using Embryogen®/BlastGen™ compared with standard medium, and insufficient evidence of a difference in pregnancy outcomes. Taking into consideration the small samples size, study limitations and strict inclusion criteria of this single-centre study, they found that further research is needed to determine the efficacy of Embryogen®/BlastGen™ medium in couples undergoing IVF/ICSI.

3.5. Fabozzi et al randomised sibling oocytes for culture in the novel Geri-medium (n = 631 oocytes) or continuous single culture medium (CSCM, n = 643 oocytes) to investigate the difference in blastulation rate per cohort of inseminated oocytes. They found that blastulation rate among cohorts of sibling oocytes cultured in the same incubator is a fast, reliable and comprehensive performance indicator to validate novel commercially available culture medium. The media tested were considered similarly efficient. They found that differences in blastocyst morphology and developmental timings warrant further investigation, although euploidy and ongoing implantation rates were similar.

3.6. A multicentre cohort study by Castillo et al studied whether IVF treatment and laboratory factors affect singleton birthweight (BW). They reported that BWs of IVF-conceived singleton babies are increasing with time, but could not identify the specific treatment factors responsible. The study reports that no significant associations of birth outcomes with IVF embryo culture parameters were seen independent of clinic or time, including embryo culture medium, incubator type or oxygen level, although small differences cannot be ruled out.

3.7. Desai et al published a prospective randomised study which evaluated the efficacy of two different IVF culture media for blastocyst development, pregnancy, and live birth rate on 10,768 sibling pronucleate embryos. Global (GB) medium (used without refreshment) and G-TL medium (designed specifically for culture in time-lapse incubators) were compared. The study concluded that uninterrupted culture in a time-lapse incubator without medium refreshment was well supported by both media tested. Differences in morphokinetics did not necessarily dictate the superiority of one media over the other. Both pregnancy and LBR were not significantly influenced

by choice of culture medium. No difference was noted in blastocyst euploidy rates between the two media: GB 34.7% (275/793) and G-TL 33.3% (209/627).

3.8. A study by Barberet et al compared the epigenetic profiles of 57 children, aged between seven and eight years old, according to the mode of conception (ie ART compared with naturally), the type of embryo culture medium used (ie global medium (LifeGlobal) and single step medium (Irvine Scientific)) and the mode of in vitro fertilisation (ie IVF versus ICSI). The study concluded that significant differences in the DNA methylation of imprinted genes or transposon families were reported between ART and naturally conceived children, but there was no difference between culture media.

3.9. Togola et al assessed 17 plastic consumables and 18 cell culture and ART media for the presence of bisphenols (BPS) which has already been reported to impair oocyte quality at nanomolar concentrations. The study found that while the plastic consumables did not release BPS under routine conditions, 16 of the 18 cell culture and ART media assessed contained BPS. Six media exhibited BPS concentrations higher than 1 nM and reached up to 6.7 nM (1693 ng/l). The study highlighted that a wider implication of the findings is that the presence of BPS in ART media, at a similar concentration range, could contribute to a decrease in the ART success rate.

Self-spent culture medium versus fresh medium

3.10. To explore the role of autocrine factors in embryo self-spent culture media, a study by Wu et al prospectively compared embryo transfers with self-spent culture medium and fresh medium on clinical pregnancy outcomes. A total of 318 fresh IVF/ICSI cycles were randomly allocated into two subgroups based on their transfer media. The study found that implantation rates, clinical pregnancy rates and live birth rates in the transfer group using self-spent medium instead of new pre-equilibrated culture medium were slightly improved but without statistical significance. In addition, biochemical pregnancy rate was found to be significantly decreased after transfer using self-spent medium for day 3 embryos compared with new pre-equilibrated culture media. The authors acknowledged that large sample size studies are still needed to confirm these observations.

Sequential versus single media

3.11. Stimpfel et al published a retrospective study which analysed the outcome of IVF/ICSI cycles (n=172) with regard to different types of culture media used to culture embryos, namely sequential and two types of single step continuous embryo culture media. Results indicated that continuous media can be equivalent to sequential media and could help lower the workload in busy IVF labs without impairing the clinical results. However, the authors stated that caution is needed because this study is limited by its retrospective design. To confirm the results, especially in terms of live birth rates and perinatal outcome, a prospective study is needed with a higher number of included couples.

Effects of supplementation

3.12. Gardner et al carried out a study to investigate if the inclusion of three antioxidants (A3), acetyl-l-carnitine (ALC), N-acetyl-l-cysteine (NAC) and alpha-lipoic acid (ALA) improve human embryo development and pregnancy potential. A total of 1563 metaphase II oocytes from 133 patients in two IVF centres were included and day 3 embryos and day 5/6 blastocysts quality were assessed. The study concluded that the presence of antioxidants during IVF and embryo culture for patients aged 35-40 years resulted in a significant increase in implantation and pregnancy rate. Supplementation of antioxidants to IVF and culture media may therefore improve the viability of human embryos in assisted reproductive technologies, plausibly through the reduction of oxidative stress.

3.13. Armstrong et al assessed the available evidence from RCTs on the effectiveness and safety of granulocyte macrophage colony-stimulating factor (GM-CSF) supplemented culture media, in women or couples undergoing assisted reproduction. Due to the very low to low quality of the evidence, the author's concluded that claims from marketing information that GM-CSF has a positive effect on pregnancy rates are not supported by the available evidence; further well-designed, properly powered RCTs are needed to lend certainty to the evidence.

3.14. Heymann et al published an update of a Cochrane Review first published in the Cochrane Library (2010, Issue 7) to determine whether adding adherence compounds such as hyaluronic acid (HA) to embryo transfer media could improve pregnancy outcomes, including improving LBR and decreasing miscarriage, in women undergoing assisted reproduction. The authors concluded that moderate-quality evidence shows improved clinical pregnancy and LBRs with the addition of HA as an adherence compound in embryo transfer media. Low-quality evidence suggests that adding HA may slightly decrease miscarriage rates when only studies at low risk of bias were included in the analysis, but the results were inconclusive. HA had no clear effect on the rate of total adverse events.

3.15. An RCT by Fawzy et al evaluated the influence of integration of granulocyte-macrophage colony-stimulating factor, heparin-binding epidermal growth factor-like growth factor, and leukaemia inhibitory factor into culture media on human embryo development after ICSI. The study, which included 443 ICSI cycles, concluded that inclusion of cytokines into human embryo culture media showed improvement in embryological and clinical outcomes after ICSI. However, they found the long-term effect of cytokine enrichment of a medium is still unclear and warrants further studies with longitudinal follow-up.

3.16. Hernández et al investigated whether culture media enriched in 4-OH-E2 could improve the quality and implantation rate of embryos obtained in vitro, using both in vitro and in vivo models. They also analysed its effects on the epidermal growth factor-binding (EGF-binding) capability of the embryos. Results showed that the presence of 4-OH-E2 in the culture media of embryos during the morula to blastocyst transition increases embryo quality and attachment to endometrial cells in vitro. Results also showed that 4-OH-E2 can improve viable pregnancy rates of mouse embryos produced in vitro, reaching success rates that are similar to those from embryos obtained directly from the uterus. 4-OH-E2 improved the embryos' ability to bind EGF, which could be responsible for the increased embryo implantation potential observed. Therefore, suggesting that 4-OH-E2 is a strong candidate molecule to supplement human IVF culture media in order to improve embryo implantation. However, they found that further research is required before these findings can be translated with efficacy and safety to fertility clinics.

3.17. Fujii et al carried out a proteome-wide analysis of distal tubal lavage specimens collected from 26 healthy women undergoing open microtubal anastomosis surgery to investigate if there are phase-specific changes in the early secretory (ES) phase human tubal lavage proteome that can inform and potentially optimise IVF culture media. Comparison of the ES and menstrual phase human tubal lavage proteomes revealed 74 differentially expressed proteins with enrichment of pathways and biological processes involved in the regulation of carbohydrate metabolism, oxidative stress and cell survival. The adapter-regulator protein 14-3-3 zeta was among the most significantly increased in the ES phase. Supplementation of embryo culture media with 14-3-3 zeta at concentrations tested did not significantly improve the murine blastocyst development.

4. Conclusions

4.1. Since SCAAC last considered embryo culture media in 2019, research in this area has continued to progress, however, the impact of changes in culture media composition for early embryo development and the long-term health effects of children conceived by ART remains unclear.

4.2. Possible associations have been identified between the type of culture media used and birthweight, imprinting disorders, pregnancy rate and LBR. This has prompted some debate within the sector on whether manufacturers should be more transparent in reporting the composition of their culture media.

4.3. Additional research is required to further explore the relationship between embryo culture media and LBR and longer-term health outcomes in children born from ART.

5. Recommendations

5.1. Members are asked to:

- consider the progress of research (since June 2019) into the effects of components in culture media used for IVF treatment;
- advise the Executive if they are aware of any other recent developments and;
- advise what, if anything, needs to be communicated to the MHRA

6. References

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