

Embryo culture media update

Strategic delivery: Safe, ethical, effective treatment Consistent outcomes and support Improving standards through intelligence

Details:

Meeting SCAAC

Agenda item 8

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Output:

For information or decision? For information

Recommendation Members are asked to:

- consider the progress of research (since June 2017) 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;
- identify 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 Medium High

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 outcome 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 on several previous occasions. At its meeting on 19 June 2017, SCAAC identified that there was a possible association between type of culture media and birthweight. Prior to that at a meeting in 2015, there was discussion on 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.

2. Current regulation

- 2.1.** In the UK, human embryo culture media use for treatment purposes are considered to be medical devices and must be CE marked by a Notified Body. The MHRA designate UK Notified Bodies to assess manufacturers for quality and safety, and these bodies are in turn audited by MHRA within the UK under the European Medical Devices Directive 93/42/EEC¹ to ensure certificates are issued appropriately and that the relevant standards are adhered to. It is therefore not within the remit of the HFEA to regulate the composition and safety of culture media.
- 2.2.** It is the responsibility of the manufacturer to determine the appropriate class of their product and the Notified Body to review and agree in line with MEDDEV (2.4/1)² before certification is issued. MEDDEV (2.4/1) contains guidance for the application of the classification rules for medical devices which is a 'risk based' system. Presently, embryo culture media with medicinal products are classified as Class III (generally regarded as high risk) and those with no medicinal products

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

² <http://ec.europa.eu/DocsRoom/documents/10337/attachments/1/translations/en/renditions/native>

as Class IIa (generally regarded as medium risk). Under the new EU regulations on medical devices all embryo culture media will be classified as Class III.

- 2.3.** Manufacturers are required to note and justify any changes to medical devices including changes in culture media composition in their technical documentation to Notified Bodies. Notified Bodies will request post-market surveillance/post-market clinical follow-up data as part of the ongoing certification process to monitor the long-term safety of embryo culture media. This post-market surveillance data would include a review of any customer complaints therefore it is important that customers do report incidents.

3. Research

- 3.1.** Kazdar et al carried out a prospective randomised study to determine how morphokinetic parameters are altered in embryos grown in sequential versus global culture media. Morphokinetics refers to time specific morphological changes during embryo development which provide dynamic information on a fertilised egg. Morphokinetic parameters of 160 single embryos transferred were analysed by time lapse imaging. The study found that the fading of the two pronuclei occurred earlier in global versus sequential media. Likewise, the first cleavage started earlier. Also, the first cytokinesis was shorter in global medium compared to sequential culture medium. They also observed a significant shortening in the duration of the 2-cell stage in sequential medium versus global medium which suggested a faster progression of the embryos through their first mitotic cell cycle. In conclusion, morphokinetic analysis of human embryos by time lapse imaging reveals significant differences in five kinetic variables according to culture medium. The study highlights the need to adapt morphokinetic analysis accordingly to the type of media used to best support early human embryo development.
- 3.2.** Sigalos et al carried out a randomised control trial with 236 patients to evaluate if the use of two different volumes (20-25 vs 40-45 µl) of media for embryo transfer affects the clinical outcomes in fresh IVF cycles. No statistically significant differences were observed in clinical pregnancy, implantation and ongoing pregnancy rates between the low and high volume groups.
- 3.3.** A study by Zandstra et al carried out an observational cohort study (MEDIUM-KIDS) for follow-up of 136 singletons after their ninth birthday, who were born after fresh embryo transfer of cleavage stage embryos resulting from an IVF or intracytoplasmic sperm injection (ICSI) treatment when two different culture media were used alternately (Vitrolife or Cook). Birthweight was higher in the Vitrolife group, furthermore, waist circumference was significantly higher in the Vitrolife group. Height and height corrected for age and gender were similar in both groups. The study concluded that the choice of culture medium for human embryos is associated with differences in body weight, BMI, truncal adiposity, waist circumference and waist/hip ratio at the age of 9, while no significant differences were observed in cardiovascular development. This study underlines the importance of structured follow-up of IVF/ICSI children to further elucidate possible long-term health effects. The study also highlights that small changes in culture conditions and culture medium composition for the early embryo can have long-term health effects.
- 3.4.** Zandstra et al then published a second study investigating whether culture media used during an IVF/ICSI treatment has an effect on cognitive development of 119 singleton IVF children at nine years of age. The study showed that cognitive development of children born after culture in the two different embryo culture media (Vitrolife or Cook) is comparable.

- 3.5.** A study by Petersen et al investigated randomised comparison of two embryo culture media (Cook and Vitrolife) for embryo culture after intracytoplasmic morphologic sperm injection (IMSI) on a cohort of 120 patients. The study concluded that both culture media used are equally effective for culturing embryos until day two, in the bench incubator at low O₂ concentration, in relation to fertilisation, embryo quality, pregnancy and implantation rates, and can be used depending on the ease and availability of acquisition.
- 3.6.** A prospective randomised study by Hardarson et al compared blastocyst development on the same cohort of oocytes using a single-step medium with or without three antioxidants (α -lipoic acid, acetyl L-carnitine and acetyl L-cysteine). The study found that there was a tendency towards a better pregnancy rate in the medium containing the antioxidants, indicating possible positive effects of this combination of antioxidants on embryo viability when cultured in-vitro.
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4. Conclusions

- 4.1.** Since SCAAC last considered embryo culture media in 2017, research in this area has continued to progress slowly with concerns being raised about the impact of changes in culture media composition for early embryo development and the long-term health effects.
- 4.2.** An association has been identified between the type of culture media used and birthweight, which has prompted some debate within the sector on whether manufacturers should be more transparent in reporting the composition of their culture media.
- 4.3.** Further research is required to further explore the relationship between embryo culture media and longer-term health outcomes in children born.
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5. Recommendations

- 5.1.** Members are asked to:
- consider the progress of research (since June 2017) 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;
 - identify what, if anything needs to be communicated to the MHRA
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6. References

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